Public Comments for
Draft Guidance Documents for Coverage Evidence Development
April 7 – June 7, 2005

Organization: Abbott

Abbott is pleased to submit these comments in response to the CMS *Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development* (hereinafter, "Draft Guidance"). Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture, and marketing of pharmaceuticals and medical products

Abbott is a strong supporter of evidence-based medicine and believes that the best available evidence should inform all health care decisions. Good medicine is based on good evidence. We are concerned, however, that the Draft Guidance is vague and/or overly broad in certain respects, and therefore could be more finely tuned in order to provide proper direction to stakeholders. Abbott therefore requests CMS to consider the following comments and clarify certain outstanding issues.

We have organized these comments to address the following general topic areas considered by the Draft Guidance:

- Factors Considered in Applying CED
- Process for Deciding When and How to Apply CED
- Evidence Development Methods
- Process for Study Design and Implementation

I. Factors Considered in Applying CED

The Draft Guidance indicates that CMS will consider requiring data collection as a condition of coverage when additional information is needed to determine if an item or service is reasonable and necessary. Abbott urges CMS to consider the following broad principles when determining whether or not to apply CED:

Evidence-based medicine should not become a barrier to innovation. When properly understood and applied, evidence-based medicine benefits both patients and the health care system. However, evidence is not always perfect and more data can always be collected. The purpose of CMS coverage decisions should be to improve the quality of care and encourage appropriate medical practice and utilization. Therefore, while the quality of evidence is key with regard to assessing whether there is an improvement in net health outcomes, the desire for evidence should not serve as a barrier to innovation. Application of CED also should explicitly recognize the consequences of requirements to collect additional evidence, including both research costs and any limits to patient access to new technologies during the review process.

CED should not apply to the local coverage process. The Draft Guidance states that CED is not intended to reduce the frequency or importance of the local coverage process. CMS states further that it does not anticipate that CED would result in a net reduction in coverage available under existing local coverage policies. Abbott urges CMS to clarify that CED will only be applied as part of the national and not the local coverage process. It would be impractical and highly inefficient for local Medicare contractors to require regional data collection as part of the local coverage process. We request that CMS issue guidance to local contractors in this regard.

II. Process for Deciding When and How to Apply CED

The Draft Guidance states that CMS intends to apply CED to issues with the greatest potential benefit for Medicare beneficiaries and the Medicare program. CMS also states that it expects CED will be applied in specific cases where better evidence to support decision making by patients and clinicians is an essential part of reaching a conclusion that a treatment is reasonable and necessary. The agency asks for input regarding the process for requesting national coverage decisions with evidence development and whether any existing mechanisms and processes would serve as a useful model for obtaining public input to identify and prioritize topics for CED.

Abbott urges CMS to clarify the circumstances where CED will be applied. The Draft Guidance offers an initial lengthy list of circumstances in which coverage with data collection might be valuable. However, CMS does not offer any direction concerning how these various factors will be weighed or balanced when making decisions to require CED. Abbott urges CMS to clarify that CED will only be applied in very limited circumstances where additional evidence is required to answer essential scientific questions affecting the health of Medicare beneficiaries. CED should not be required, as CMS proposes, in situations where a therapy has demonstrated to improve health outcomes in a broad population of patients. Questions related to safety and effectiveness is the responsibility of FDA and generally should not be addressed through CED. Lastly, in deciding whether to apply CED, CMS should take into account any relevant existing and/or planned research in order to avoid duplication of efforts.

In addition to clarifying when CED will be applied, CMS should work with stakeholders to specify the following:

- The funding mechanisms for the data collection and analysis
- The methodology and process for ongoing evaluation of the data
- The relationship of data collection to a future coverage determination

Abbott believes that it is vital for CMS to maintain an open and ongoing dialogue with all relevant stakeholders, including manufacturers, providers, suppliers, physicians, and patient groups. Many issues cannot be addressed or resolved by a single set of decision-makers. By involving stakeholders early, CMS can help to ensure that adequate resources are provided for the successful realization and resolution of crucial issues, and that no undue burden has been placed on affected parties. Open forums, advisory meetings, and requests for comments all serve as beneficial vehicles for involving stakeholders in this process.

III. Evidence Development Methods

Abbott applauds CMS for recognizing that developing methods for conducting simple, inexpensive clinical studies is essential to optimizing CED. Abbott also supports the agency in its desire to avoid stipulating the use of a particular research design, since data collection protocols will vary according to the use of the item or service being provided, the purpose of the data collection, and the group of patients receiving the item or service. We note that privacy considerations may also be a factor in determining the most appropriate research design. Notably, where a covered entity conducts clinical research involving protected health information ("PHI"); physician-investigators need to understand the HIPAA Privacy Rule restrictions on the use and disclosure of PHI. In addition, other Federal and state privacy standards may be implicated and researchers need to be cognizant of the fact that they need to adhere to various standards for protecting the privacy of patients and clinical research subjects.

In considering the appropriate research design to study a particular question, we urge CMS to take into account limitations associated with various designs, including the following:

- While a well-designed registry can provide a depth and variety of information not readily available from any other source, even with the most careful quality control, bias can occur due to both known and unknown factors, which may affect the validity of the data. Registries are not randomized clinical trials, and conclusions based on registry data should not be confused with conclusions based on more sophisticated statistical work.

- Registries or prospective studies may experience loss of study subjects from non-participation or loss to follow up. Consequently, these conditions might affect the outcome of the study. Studies based on registry data should explicitly declare database biases.

- Registries and prospective studies can be expensive and time-consuming on the part of both sponsoring organizations and research staff. It will be necessary to consider whether the potential benefits of data collection outweigh the cost.

- Retrospective cohort studies can be accomplished relatively quickly, but only if suitable cohorts can be identified and if adequate data about them are available. Retrospective cohort studies, of course, cannot help evaluate new technologies that are approaching market.

- Randomized, blinded, controlled trials are not designed to address the extent to which patients will comply with a treatment, which in some cases may be the crucial issue for determining an item or service's benefit.

- Many diseases of interest are so rare that case control studies may be the only practical way to study certain interventions and outcomes. Thus, non-prospective, non-cohort studies may provide some value and insight.

- In many instances, the true benefit of an intervention can remain uncertain even after evidence has been collected.

Given such limitations, it is imperative that CMS not be wedded to a particular research method with regard to CED. Furthermore, Abbott believes that CMS should have a process to identify the research questions, goals, data elements, research design and time frames for CED. As mentioned, data collection can be difficult, time consuming and costly. Given the potential costs and other burdens associated with clinical research, it is essential for the agency to establish standards for deciding what should be researched, as well as why, how, and when it should be researched.

IV. Process for Study Design and Implementation

Abbott applauds CMS for asking what approaches to study design and implementation would be least costly and most efficient, and for requesting input on ways to minimize the resources required for conducting these studies. Oversight of data collection and efficient operating system issues most certainly depend upon factors mentioned in the Draft Guidance, such as patient safety, timeframes, training, and the data collection burden.

The appropriate approach to study design also may differ depending on whether drugs or medical devices are the topic of study. For example, medical device trials are often more expensive to execute than drug trials because device trials may require highly specialized surgical skills. Fewer physicians with such skills may limit the number of patients who can participate in the trials (smaller sample sizes), which may also limit the generalizability of the outcomes. In addition, the impact of devices may be more obvious, thus often making it difficult to conduct a blind device trial as it is harder to mask the effects of a device versus placebo (and in some cases, it may be unethical to do so). Finally, it may be more difficult to utilize CED for a device whose purpose is diagnostic rather than therapeutic. It may be far more complicated to conduct follow-up on patients who have received a diagnostic service than patients who have received a therapeutic service, because there are likely to be far fewer continuing contacts with a patient following a diagnostic procedure. These differences are therefore important for the agency to consider in applying CED.

V. Conclusions

Abbott agrees that use of CED is an important topic that needs further ongoing dialogue. Medicare coverage policy for new technologies can have profound implications for beneficiaries' access to medical advances, as well as for the Medicare program. The CMS Draft Guidance raises a number of questions that are of significant importance to the future of the Medicare Program and to patients, providers and manufacturers.

As a leading health care company, committed to developing new and innovative technologies, Abbott has tremendous experience in evidence development strategies, including designing appropriate inquiries and establishing relevant hypotheses. Abbott wishes to offer its expertise and resources to CMS as it continues to refine policy related to CED.

Organization: AdvaMed

(Comment on next page.)

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June 6, 2005

Via Electronic Mail and U.S. Mail

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Re: Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. McClellan:

The Advanced Medical Technology Association ("AdvaMed") appreciates the opportunity to provide you with comments to the draft guidance document regarding factors the Centers for Medicare and Medicaid Services ("CMS") considers in making a determination of coverage with evidence development ("CED") issued on April 7, 2005. Our industry strongly supports evidence-based medicine and the use of sound evidence to support medical practice. We appreciate CMS's efforts to promote evidence-based medicine to ensure patient access to important therapies and innovations and look forward to working with CMS on the development and implementation of CED in a manner that promotes, not deters, such access. Towards that end, we continue to believe that the collection of additional data through CED should be to inform – not dictate – clinical practice, specifically for patient and practitioner use. If properly done, data collected to improve quality of care and outcomes may provide decision-makers with important information on the impact of new technologies and procedures on the Medicare population.

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the $75 billion of health care technology products purchased annually in the United States, and more than

50 percent of the $175 billion purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. Nearly 70 percent of our members have less than $30 million in sales annually.

As we noted at both the February 14, 2005 and May 9, 2005 Open Door Forums, given the scope of our membership and the potential impact of CED, AdvaMed has and will continue to approach CED with great seriousness and the attention it warrants. In conjunction with AdvaMed's December 2004 Board of Directors meeting, our members created a CMS Coverage Response Task Force chaired by Sarah Wells, Director of Health Policy & Payment at Boston Scientific. The Task Force held a two-day meeting on January 31 and February 1, culminating in the adoption of principles related to CED at our March 2005 Board of Directors meeting. These principles were conveyed in a statement provided to CMS on March 15, 2005.[1] Shortly after the draft guidance was issued on April 7, 2005, the Task Force held another two-day meeting to analyze the guidance and deliberate on our comments to the draft guidance. We subsequently held a special meeting of the Payment and Healthcare Delivery Committee to the Board of Directors solely to address CED during which the comments included in this letter were approved. As such, the comments included in this letter represent the consensus of our membership.

In our comments set forth below, we will address (1) principles that AdvaMed believes are critical to the development and implementation of CED that CMS has incorporated into the draft guidance; (2) principles that require further clarification or reconsideration; and (3) our responses to specific questions set forth in the draft guidance.

Important Principles Incorporated by CMS

Given the need to clarify or resolve certain aspects of the guidance and the evolving nature of the national coverage process, we view this draft guidance as an important step in an ongoing process. ***We provide comments with the hope that CMS will issue a revised draft of the guidance with a further comment period***.

We are pleased to note that the draft guidance incorporates certain principles that we conveyed to CMS in our March 15, 2005 statement. These are certainly among the most important principles that are critical to the implementation of CED. Included among these are the following.

1) The objectives of CED include enhancing access to technologies and services that improve the health of beneficiaries.[2]

2) CED should only be used to answer specific evidence questions.[3]

[1] A copy of the AdvaMed March 15, 2005 statement is attached for your reference.
[2] Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development, April 7, 2005, at 2.
[3] *Id.* at 5, 6.

3) CED must be worth its cost.[4]

4) CED should not duplicate existing data collection efforts of the Food and Drug Administration ("FDA") or other public or private sector entities.[5]

5) CED should minimize financial and other resource burdens.[6]

6) CMS should maintain the local coverage process.[7]

7) CMS should limit the application of CED.[8]

In recent NCDs, CED (also known as coverage under protocol) has not appeared to embody these principles. For example, specific evidence questions have not been defined prior to requiring data collection and the expected costs and worth of evidence collection has not been assessed or compared prior to requiring data collection (*e.g.*, the NCD pertaining to implantable cardioverter defibrillators). Thus, AdvaMed commends CMS for including these principles in the draft guidance. As the development and implementation of CED continues, CMS should ensure that the CED process retains and adheres to these principles.

CMS Principles of Concern that Require Clarification and Reconsideration

The draft guidance contains several fundamental principles concerning the development and implementation of CED that are of concern to our industry. These pertain to: (1) the interpretation of reasonable and necessary, (2) the two general circumstances in which CMS intends to apply CED, (3) responsibility for monitoring safety: CMS vs. FDA, (4) the role of utilization and costs in coverage, (5) impact on the local coverage process, (6) CMS's anticipated use of the three broad types of coverage, and (7) potential infringement upon the principle of informed consent. We address each of these concerns below.

Definition of Reasonable and Necessary

CMS's use of "reasonable and necessary" in the draft guidance appears to be a departure from its previous interpretation of this phrase for making coverage decisions. Generally, this phrase has been interpreted to mean that, at the point an item or service is provided to a patient, it has to be "reasonable and necessary" *for that patient*. The draft guidance equates "reasonable and necessary" with the quality of available evidence on improvement in health outcomes. For example, the draft guidance states, "The primary purpose of obtaining additional evidence through CED is for the agency's use in making

[4] *Id.* at 5.
[5] *Id.*
[6] *Id.*
[7] *Id.* at 6.
[8] *Id.* at 2.

payment determinations, *i.e.*, that a treatment is reasonable and necessary."[9] The guidance continues, "the core consideration in determining whether an item or services is 'reasonable and necessary' is the quality of evidence available to assess whether it improves net health outcomes."[10] The guidance also states that, in some cases, "CMS will determine that an item or service is only reasonable and necessary when specific data collections accompany the provision of a service."[11]

We contend that it is inappropriate to base an *individual* patient care decision on the quality of available evidence pertaining to a *population*. Also, we question how it is that an otherwise reasonable and necessary service for a patient would no longer be reasonable and necessary by virtue of simply not accompanying the service with the collection of specific data. Similarly, we question whether it is appropriate to base an individual patient care decision on whether there is an expectation that current and future data collection may show that it improves net health outcomes. Furthermore, we contend that it is inappropriate to tie CED to determining "reasonable and necessary" to those interventions that are already "demonstrated to improve health outcomes in a broad population of patients."[12] (We refer to this potential circumstance for applying CED as "Type 1" and elaborate on this concept in the next section.) While we recognize CMS's interest in prospective data collection for subgroups, longitudinal data collection, etc., such studies are inconsistent with determining whether a proven intervention is reasonable and necessary for a given patient.

With regard to preventive, screening, or diagnostic technology (*i.e.*, technologies that are not therapies), we believe linking such technology to whether it "improves net health outcomes" may be impractical as it can be confounded by multiple intervening factors. In addition to being accurate and providing information that could change a physician's finding, such a standard would require that technologies result in changed physician treatment decisions and physician and patient compliance with an effective treatment that would ultimately show an improvement in net health outcomes. This may be an inappropriate coverage criterion for a preventive, screening, or diagnostic technology itself. For coverage purposes (including for determining reasonable and necessary under CED), there should be additional criteria (based on study designs and endpoints) appropriate for these types of technology. The FDG-PET example given in the draft guidance recognizes this distinction, noting, "Under these circumstances, FDG-PET has the potential to improve health outcomes by influencing patient management; and by helping physicians appropriately evaluate the PET scan results…"[13]

Two General Circumstances in which CMS Intends to Apply CED

The draft guidance describes "two general circumstances under which clinical care provided may only be considered reasonable and necessary in the context of

[9] *Id.*
[10] *Id*. at 3.
[11] *Id*. at 6.
[12] *Id.*
[13] *Id*. at 8.

protocol-driven data collection."[14] The first circumstance, which we will refer to as "Type 1," may occur when "a particular medical intervention may have been demonstrated to improve health outcomes in a broad population of patients … but the evidence would only be adequate, and the service therefore reasonable and necessary for the individual patient, when specific data is collected and reviewed by the provider at the time that the service is delivered."[15] The second circumstance, which we will refer to as "Type 2," may occur when "a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit…"[16] AdvaMed strongly contends that CED should not be applied to the Type 1 circumstance. When available evidence is "demonstrated to improve health outcomes in a broad population of patients," and FDA has given market clearance and approval, the evidence supporting the item or service intervention should be considered adequate for coverage and CED should not be applied.

Responsibility for Safety: CMS vs. FDA

The draft guidance refers to data collection on safety under CED in ways that appear to be FDA's responsibility. For example, the draft guidance states, "Conversely, support for post-coverage evidence development to achieve a reasonable and necessary determination may help address important questions of safety and effectiveness that otherwise would be very difficult to address in the pre-market setting or in the post-market setting in the absence of CMS support."[17] Furthermore, included in the list of circumstances in which CMS may apply CED are two additional references to the evaluation of safety. First, CMS may apply CED if "the item or service is likely to provide benefit, but there are substantial safety concerns…"[18] Second, CMS may apply CED when "new evidence development may help evaluate the safety and benefit of requested items and services for our beneficiaries."[19]

AdvaMed firmly contends that the evaluation of safety is clearly within the purview of the FDA and should not be linked to coverage decisions for Medicare. In general, post-market safety and effectiveness studies are the primary responsibility of the FDA and should not be considered as a condition for Medicare coverage. CED may be appropriate where CMS has a clinical basis for concluding that patient outcomes (including safety and effectiveness) in rigorous studies conducted for FDA approval are not generalizable to the Medicare population. However, even where existing safety data are not yet established, including for Type 2 interventions, CMS should be required to show why FDA post-marketing surveillance or other existing data are insufficient for capturing such safety data before requiring CED to obtain such data. As noted earlier,

[14] *Id*. at 6.
[15] *Id*.
[16] *Id*. at 7.
[17] *Id*. at 5.
[18] *Id*. at 9.
[19] *Id*. at 10.

CED should never be applied to Type 1 interventions, whether for safety, effectiveness, or other outcomes.

Role of Utilization and Costs in Coverage

The draft guidance provides that the absence of data on utilization and costs could prompt CED, and that utilization and costs are among the outcomes CMS believes would be studied under CED. For example, in listing the circumstances in which CED may be applied, the draft guidance indicates that CED may be applied where the "assessment of outcomes has not been evaluated in the available clinical studies. These outcomes may include… utilization, costs, and other real-world outcomes."[20] This list also includes circumstances in which the evidence "will assist doctors and patients in better understanding … the benefits and costs of alternative diagnostic and treatment options" and "will help doctors and patients get the most benefits at the lowest possible cost in our increasingly complex and individualized health care system."[21]

Until now, CMS has cited utilization and costs (particularly in the form of anticipated aggregate cost impact to the Medicare program) as being among the factors that might increase the priority for undertaking a NCD for a given technology. But CMS has not formally considered utilization and costs in the context of a NCD itself. AdvaMed contends that the absence of utilization and/or cost data alone is an insufficient reason to apply CED. Where multiple criteria are being considered, we recognize that utilization and/or cost data may be among the criteria for considering or setting priority among technologies for NCD. However, in the context of conducting a NCD for any particular technology, neither utilization nor costs should be considered in the coverage determination.

Local Coverage Process

We were encouraged to see that the draft guidance appears to protect the local coverage process in its statement, "it is not the intent of this approach to reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program."[22] However, the very next sentence raises questions regarding the relationship between national and local coverage processes under CED. This sentence indicates that CMS does "not anticipate circumstances under which CED would represent a net reduction in coverage available under existing local coverage policies."[23] It is critical that CMS clarify the distinction, including providing guidance, between local coverage determinations ("LCD") and NCD with CED and the data requirements that flow from this.

AdvaMed supports CMS's intent to issue guidance to carriers regarding the continuation of local coverage and informing them that CED should not result in a

[20] *Id*. at 9.
[21] *Id*. at 4.
[22] *Id*. at 6.
[23] *Id*.

reduction of coverage. In addition, we recommend that CMS include the following points in the revised guidance. First, local coverage should not require data collection as a condition of coverage. Second, if a LCD exists that extends broader coverage than a NCD with CED, and the NCD is not exclusionary, the portion of the LCD that is broader than the NCD should not be subject to CED. Third, as a general rule, data collection requirements should not be imposed on local contractors. Although not directly relevant to CED, AdvaMed retains its position that, with regard to local coverage, one director per state and one Carrier Advisory Committee ("CAC") per state (unless multiple CACs decide to share a director) should be maintained.

Anticipated Use of Three Broad Types of Coverage

The draft guidance describes "three broad types of possible coverage decisions:" (1) non-coverage where the evidence is not adequate; (2) coverage with conditions where the evidence is adequate only with specific clinical or demographic characteristics, with providers and/or facilities that meet specific criteria, and/or in the context of CED; and (3) coverage without conditions.[24]

We seek clarification regarding the second type of coverage, "coverage with conditions." It is not apparent whether the three sub-types of coverage with conditions are applicable as a group or individually. That is, are they linked by "ands" or "ors"?

With regard to the third type of coverage decision, "coverage without conditions," we note the statement that "CMS does not anticipate issuing additional decisions of this type."[25] AdvaMed encourages CMS not to exclude the possibility of issuing additional decisions of this type. Where a technology studied in a randomized clinical trial or other rigorous design appropriate for that technology is "demonstrated to improve health outcomes in a broad population of patients," coverage without conditions may indeed be appropriate.

CMS also should consider the circumstance in which it takes up an issue under the NCD process, but does not issue a policy (*i.e.*, one of the three broad types of coverage) because of insufficient evidence. In such instances, CMS should make clear that these issues can be addressed at the local level without nationally required evidence collection.

Finally, AdvaMed seeks clarification regarding whether two statements from the April 27 notice of the CMS Special Open Door Forum on May 9 are inconsistent. The first statement reads, "CED is intended to be limited to only those items or services that would normally be covered under the NCD process…" The second statement reads, "CED will only be used in those instances where a NCD has been opened and the evidence is less convincing and would have resulted in non-coverage."[26] Does the first

[24] *Id.* at 3.
[25] *Id.*
[26] Notice of May 9, 2005 CMS Special Open Door Forum on the Draft Guidance Document on Coverage with Evidence Development (CED), April 27, 2005.

statement actually refer to the types of items and services that fall into the benefit categories that are eligible for Medicare coverage? AdvaMed understands this to exclude LCD matters as noted earlier and other matters that would not be taken up at the level of a NCD.

Potential Infringement Upon Informed Consent

Among its important oversight issues, the draft guidance states, "Patient confidentiality and protection – All necessary measures should be taken to ensure patient privacy. When appropriate, there should be institutional review and informed consent."[27] We understand that CMS is already aware of concerns that conditioning Medicare reimbursement on a patient's consent to participate in medical research could potentially pose problems of coercion. We too are concerned that conditioning benefits in this way may conflict with basic elements of informed consent required by the Common Rule[28] and FDA human-subject protections,[29] if these regulations apply to the studies envisioned by the draft guidance. The current draft, however, does not address two points, without which it is impossible to assess how likely these regulations are to apply. Pending clarification of these points, we are not able to develop a full response to CMS's request for public comment on this issue, but we have the following concerns.

First, the draft guidance notes that CMS "would seek to use de-identified data for all analyses...".[30] It is true that research with de-identified data may not be subject to the Common Rule at all or may be eligible for an exemption.[31] However, FDA human-subject protections differ from the Common Rule, and research that uses or records de-identified data would ordinarily remain subject to FDA informed consent requirements and, hence, to concerns about potential coercion. Section II.C of the draft guidance cites examples of recent NCD decisions that covered FDA Category B IDE trials, either directly or because FDA-regulated trials are deemed to comply with CMS's Clinical Trial Policy.[32] We request clarification of CMS's basis for determining that coverage with evidence development, even if it involves de-identified data, is consistent with informed consent requirements for FDA-regulated trials.

Second, we believe that identified or coded data ultimately may be required to achieve the purposes outlined in Section II.B and Section V of the draft guidance. If so, the research may be subject to the Common Rule and require informed consent, unless it is eligible for an exemption. The exemption in 45 CFR §46.101(b)(5) appears potentially applicable; however, we have two concerns: First, the aims of the research outlined in the draft guidance potentially go beyond the four exempt purposes outlined in 45 CFR §46.101(b)(5). Second, the Office of Protection from Research Risks' ("OPRR") *Guidance on 45 CFR §46.101(b)(5): Exemption for Research and Demonstration*

[27] Draft Guidance at 14.
[28] 45 CFR §46.116(a)(8).
[29] 21 CFR §50.25(a)(8).
[30] Draft Guidance at 12.
[31] 45 CFR §46.102(f), 45 CFR §46.101(b)(4).
[32] National Coverage Determinations Manual § 310.1.

Projects on Public Benefit and Service Programs defines four criteria for applying this exemption. We believe two of these criteria (specific statutory authority for the research or demonstration project, and avoidance of significant physical invasions of the research subjects) may not be met. As such, we request that CMS address the following issues in revised draft guidance: (a) Can the research aims described in Section II.B. and Section V of the draft guidance be fully met using only de-identified data? (b) If identified or coded data may be required in certain instances, would coverage with evidence development be implemented in a way that meets requirements for exemption under §46.101(b)(5) of the Common Rule?

Responses to Selected Questions for the Public

Factors Considered in Applying CED

The draft guidance lists an initial set of nine circumstances in which data collection might be valuable. We discuss each separately.

1) *The item or service is likely to provide benefit, but there are substantial safety concerns or potential side effects that are inadequately described in the available clinical literature.*

   AdvaMed Response: This is not an appropriate circumstance for CED. As noted above, except in limited circumstances, safety evaluation is FDA's responsibility.

2) *Risks and benefits for off-label use of an item or service have not been adequately addressed in the available clinical literature, particularly when risks are common or potentially uncommon.*

   AdvaMed Response: CED is not appropriate for well-established off-label uses, however, it may be appropriate for less established, off-label uses when existing evidence has yet to conclusively demonstrate an improvement in health outcomes.

3) *The available clinical studies may not have adequately described risks and benefits in specific patient subgroups, or in patients with disease characteristics that exclude them from clinical trials, which make up a significant segment of the Medicare beneficiary population likely to receive the treatment if covered.*

   AdvaMed Response: CED is not appropriate for patient subgroups where available evidence is "demonstrated to improve health outcomes in a broad population of patients" (Type I circumstance). CED may be appropriate where patients are excluded from clinical trials and there are clear clinical reasons for concluding that the existing data are not generalizable to the Medicare population.

4) *Assessment of important outcomes has not been evaluated in the available clinical studies. These outcomes may include, but are not restricted to, long-term risks and benefits, quality of life, utilization, costs, and other real-world outcomes.*

AdvaMed Response: Although data on the outcomes listed above may help address certain important clinical and economic issues, collection of data on these outcomes should not be a condition of Medicare coverage.

5) *Risks and benefits of surgical procedures may not be extensively evaluated because limited information about benefits and risks has been developed for many categories of Medicare beneficiaries. For example, some non-invasive FDA-approved devices may be well characterized in terms of safety, but less well studied in terms of clinical effectiveness in a pre-market setting for certain Medicare beneficiaries under the FDA risk-based regulatory framework. The nature of device development and evolution, in which clinical experience leads to further product modifications that are expected to improve outcomes, often highlights the importance of post-market evidence development.*

AdvaMed Response: CMS's meaning with this circumstance is not clear. Is CMS referring to surgical procedures that are not subject to FDA approval? Is CMS making multiple points?

6) *Comprehensive evidence of effectiveness of treatments for rare diseases is not always available or feasible to develop in a pre-market setting. It may be beneficial to evaluate interventions for rare conditions such as orphan drugs and humanitarian use devices.*

AdvaMed Response: As noted above, NCDs with CEDs should not preclude local coverage. However, if a) Medicare patients are not included in a study for FDA approval and there are clear clinical reasons for concluding that the existing data are not generalizable to the Medicare population, or b) this type of item/service is being considered under NCD framework, or c) the clinical evidence available is minimal, CED may be appropriate.

7) *When the current evidence is not generalizable to providers/facilities or the Medicare population has not been included in the available clinical studies, new evidence development may help evaluate the safety and benefit of requested items and services for our beneficiaries.*

AdvaMed Response: Data collection for providers/facilities may be useful, but should not be addressed in the context of coverage decisions.

If CMS has a clear clinical basis for concluding that the existing data is not generalizable to the Medicare population, CED may be appropriate.

8) *There may remain questions about the comparative effectiveness of new items and services compared to existing alternatives or to usual care.*

AdvaMed Response: For items/services that have been "demonstrated to improve health outcomes in a broad population of patients" (Type 1 circumstance), CED should not be applied.

9) *The evidence to date shows statistically significant benefits but the clinical significance of the outcomes may not be well understood.*

AdvaMed Response: AdvaMed understands the distinction between statistical and clinical significance, but requests examples of how this distinction might arise in the context of CED.

Factors Considered in Applying CED - Selected Questions for the Public

The draft guidance includes several specific questions concerning the factors to be considered in applying CED. We provide a separate response to each.

1) *Are there situations listed above that would be unlikely to be constructively addressed through evidence collections linked to coverage decisions?*

AdvaMed Response: Yes. For each of the nine circumstances, we have noted above certain instances or reasons why CED would not be appropriate.

2) *How can formal "value of information analysis" be applied to help decide when to require data collection following coverage decisions?*

AdvaMed Response: The value of information ("VOI") expected to result from evidence collection should be assessed either before a pilot CED is conducted or as part of a pilot. CMS should have an outside independent organization develop a framework for assessing VOI and it should only be applied to items/services that are being considered for CED. In assessing VOI, CMS should take into consideration current clinical trends and guidelines and its information needs to make a coverage decision.

3) *Are there existing approaches to priority setting for clinical studies that could serve as a model for identifying priorities for CED?*

AdvaMed Response: Priority setting for clinical studies is a complex and important process that warrants attention from appropriate experts. Any models created for such priority setting must be developed in a transparent manner with ample opportunities for expert and stakeholder input. In general, AdvaMed contends that in setting priorities, CMS should always consider the impact on health outcomes for Medicare beneficiaries first.

4) *Should the focus of these activities be only on new technologies and services, or the entire spectrum of technologies and services?*

AdvaMed Response: These activities should only apply to those items/services subject to CED, and not to those "demonstrated to improve health outcomes in a broad population of patients" (Type 1 situations).

Process for Deciding When and How to Apply CED – Selected Questions for the Public

The draft guidance includes several specific questions concerning the process for deciding when and how to apply CED. We provide a separate response to each.

1) *What procedures and forums would be most effective for obtaining public input in this decision making process?*

AdvaMed Response: CMS should follow the FDA workshop approach and include opportunities for informal meetings between CMS and manufacturers.

2) Are there existing mechanisms and processes that would serve as a useful model for obtaining public input to identify and prioritize topic for CED?

AdvaMed Response: CMS should follow the FDA workshop approach.

3) Should there be a process for requesting national coverage decisions with evidence development, and how should such requests be prioritized?

AdvaMed Response: We believe the current process works, but would recommend that manufacturers be given additional opportunities for input into the process from beginning to end.

Evidence Development Methods – Selected Questions for the Public

The draft guidance includes several specific questions concerning evidence development methods. We address these questions collectively.

1) What type of questions is each study design best able to answer?

2) What are the limitations of each study design?

3) Under what circumstances should CMS require a database? A longitudinal data collection? A prospective study? A clinical trial?

4) What process should CMS use to evaluate the quality of a proposed study?

5) How should CMS determine whether the evidence collected suggests patients are either harmed or not benefited by the item or service?

AdvaMed Response: Conducting these types of studies in the context of coverage is a new area. AdvaMed contends that a key element in this process is the identification of the evidence CMS believes necessary to answer the coverage question that may prompt CED. An independent, properly qualified body should establish in a transparent manner a framework for study designs for purposes of informing coverage decisions, including relative strengths and weaknesses; ability to address particular types of evidence questions; tradeoffs involving internal and external validity, costs, duration, etc. In establishing such a framework, CMS should consult with interested stakeholders and appropriate experts. In addition, prior to considering any item or service for CED, it should be subject to designated inclusion/exclusion criteria as well as a VOI analysis. Furthermore, any proposed study design should be responsive to a prospectively determined set of specific evidence questions to inform specific coverage needs, rather than starting with a study design and then determining what types of questions it might answer. Any proposed study design should address, as appropriate, the methodological aspects listed in the draft guidance.

Process for Study Design and Implementation – Selected Questions for the Public

The draft guidance includes several specific questions concerning the process for study design and implementation. We provide a separate response to each question.

1) Who should participate in study oversight and implementation?

AdvaMed Response: Qualified investigators with disclosed interests, with support from other parties with relevant capabilities, as appropriate.

2) How should CMS determine when the data collection should end?

AdvaMed Response: Study duration and closure of data collection should be determined prospectively, consistent with requirements to answer specific evidence questions.

3) Who should have access to the data and in what form?

AdvaMed Response: This will depend on study design (*e.g.*, registries or clinical trials), including appropriate informed consent, and who is funding the data collection. In addition to CMS, those with access to the data should include, although not necessarily be limited to, manufacturers, investigators and other parties with relevant capabilities, and clinicians.

4) How will evidence collected through CED be disseminated?

AdvaMed Response: This will depend on who is funding the data collection. However, in general, evidence should ultimately be disseminated to the public when a final NCD is rendered.

5) How should the costs of study design, data collection, analysis and other activities associated with CED be fairly allocated to various stakeholders?

AdvaMed Response: CMS may consider expanding or creating a program similar to the Category B program that enables Medicare payment for certain devices with Investigational Device Exemptions ("IDEs"). In general, AdvaMed contends that providers should be given appropriate compensation for any additional costs they incur in collecting data as required by a NCD with CED.

Conclusion

AdvaMed greatly appreciates this opportunity to comment on CMS's draft guidance document regarding factors CMS considers in making a determination involving CED. We urge CMS to consider these comments and incorporate them into a revised draft of the guidance document and to allow the public an opportunity to comment on the revised draft as well.

We would be pleased to answer any questions regarding these comments. Please contact Jane Hyatt Thorpe, Associate Vice President, Payment and Policy, at 202/434-7218 if we can be of further assistance as you prepare the next draft of this guidance document.

Sincerely,

___ /s/_____
David Nexon
Senior Executive Vice President

cc: Steve Phurrough, M.D.
Barry Straube, M.D.

Organization: Albany Medical College

While I applaud CMS in their attempt to further our knowledge through post-NCD data collection, unless the collection of that data is done with the rigor of a scientific study, the conclusions from the pooled data will always be suspect. This will be the case particularly if the post-NCD data is at odds with multi-center study data collected before or after the NCD. I would urge CMS to cautiously use post-NCD data collections for very specific reasons and with very tight reporting requirements.

As we implement the post-NCD requirement for primary prevention ICD's in my institution, the guidelines for how that data is to be collected is too lose. Who should be the primary source of the data? The Electrophysiologist? A chart abstractor? The nurses in the EP Lab? When should the data be collected? Pre-procedure? Post? A combinations of pre and post? Who will review the data for accuracy? What are the required source documents? We have struggled to define these and other elements. I suspect each institution will do the same and settle on slightly different approaches that will influence the data.

Organization: Alliance of Dedicated Cancer Centers

(Comment on next page.)

The Alliance of Dedicated Cancer Centers
Arthur G. James Cancer Hospital and Richard J. Solove Research Institute
City of Hope National Medical Center
Dana-Farber Cancer Institute
Fox Chase Cancer Center
H. Lee Moffitt Cancer Center and Research Institute
M.D. Anderson Cancer Center
Memorial Sloan-Kettering Cancer Center
Roswell Park Cancer Institute
Seattle Cancer Care Alliance
Sylvester Comprehensive Cancer Center

June 6, 2005

By Electronic Mail

Rosemarie Hakim
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Room C1-12-28
7500 Security Blvd.
Baltimore, MD 21244

Re: Comments on CMS Draft Guidance: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Ms. Hakim:

On behalf of the Alliance of Dedicated Cancer Centers, I am writing to comment on the above-referenced draft guidance document on factors CMS will consider when determining whether to provide Medicare coverage in connection with the collection of data and other evidence development (the Draft Guidance). The Alliance is an association of ten comprehensive cancer centers, listed individually above, that focus exclusively on the care of cancer patients.

The practices and principles of evidence-based medicine are well understood and are deeply engrained in the daily work of the clinicians and scientists of our institutions, and we applaud CMS's interest in basing coverage decisions on these principles. The Alliance believes that, if properly implemented, the Coverage with Evidence Development (CED) initiative can offer a significant opportunity for expanding patient access to state-of-the-art treatments for cancer and other disease conditions. In order to ensure that this initiative can achieve its fullest potential, we urge CMS to consider the following recommendations, which are based on specific issue areas identified in the Draft Guidance:

I. Clinical Trials at NCI-Designated Comprehensive Cancer Centers Should Be Incorporated in the CED Process

The Alliance generally supports CMS's proposed use of clinical studies and trials to provide coverage to drugs and technologies while developing a base of evidence for broader coverage decisions. See Draft Guidance, at 12-13. Specifically, we believe CMS should extend coverage to all drugs and technologies provided in clinical trials conducted at NCI-designated comprehensive cancer centers, such as members of the Alliance, whenever these trials are used to collect data in connection with the CED initiative. Many, but not all, of these trials are funded by the National Institutes of Health and other government agencies. In 2000, CMS determined that Medicare would cover the routine patient care costs of certain approved clinical trials, and that trials conducted at NCI-designated cancer centers were "deemed" to qualify for such approval. See National Coverage Determination for Routine Costs in Clinical Trials (Sept. 19, 2000). Consistent with this precedent, we believe that the CED initiative should extend coverage to the drugs and technologies provided in these trials.

Further, as discussed in the Draft Guidance and at the recent CMS Open Door Forum, one goal of the CED initiative is to identify issues for future study. The trials conducted at NCI-designated cancer centers are often based on emerging clinical understanding and development of new drugs and, therefore, are testing concepts that lead to NCI-sponsored trials. Providing coverage for drugs and other technologies studied by these trials would augment the accrual of data, within the context of high-quality, state-of-the-art clinical trials, which could then be used to either establish broader coverage, or, where appropriate, design other clinical studies.

Additionally, providing coverage of the investigational item or service for trials conducted at NCI-designated cancer centers would advance CMS's goal of improved data collection by providing patient access to a larger number of trials. In contrast, the recent National Coverage Determination on colorectal cancer chemotherapy limited the number of trials subject to Medicare coverage to nine specifically listed studies, which will limit the number of participants in the trials and impede data collection. By expanding the number of clinical trials that can provide Medicare-covered investigational drugs and technologies, CMS will increase the number of trial participants, which in turn should increase the amount of data collected for study and evaluation.

Finally, while we firmly believe that clinical trials provide the most complete and useful data regarding the safety and efficacy of a particular drug or technology, we also recognize that, in some circumstances, clinical trials do not exist or are not available for certain patients. Consequently, we also support CMS's use of registries in the CED initiative to extend coverage to drugs and other therapies where clinical trials do not exist. One such scenario, rare orphan diseases, is discussed in greater detail below, and other situations exist where treatments may be available, but are not covered by Medicare and are not the subject of a clinical trial or study. In such circumstances, the Alliance believes that properly structured registries can provide expanded coverage to beneficiaries while still collecting data and ensuring patient safety through monitoring for potential adverse events. Therefore, we encourage CMS to continue exploring this option as a means to increase Medicare coverage of new drugs and technologies.

II. CMS Should Establish an Advisory Board Under CED to Evaluate Trials at Non-NCI-Designated Centers

For those cancer therapy trials that are not conducted at NCI-designated centers, the Alliance recommends that CMS establish an advisory board, comprised of respected members of the oncology community, to develop criteria for assessing whether such a trial should be approved for CED purposes. In conducting its evaluation, the advisory board should consider whether: 1) the nature of the disease is such that a traditional clinical trial is not feasible because of a lack of patients (e.g., rare diseases); 2) the therapy being studied has shown promise but has only been presented in an abstract; and 3) financial support is not otherwise available for conducting additional studies once efficacy has been demonstrated through a Phase II trial.

The advisory board could also serve as a resource for local Medicare contractors by maintaining a databank containing the data collected by CED trials. As you know, in making local coverage determinations regarding the off-label use of chemotherapy, contractors base such decisions on existing clinical evidence. A central resource of CED data, maintained by the aforementioned advisory board (or similar entity), would better enable contractors to determine whether a drug or technology should receive Medicare coverage.

Finally, the advisory board should advise CMS on when the burden of data collection outweighs the benefits of CED. The agency states that "[d]ata collection should only continue as long as important questions remain and it is determined that the effort and resources required to collect this data are justified by the potential value of the information that will be generated." Draft Guidance, at 5. The board should assess when it is appropriate to terminate data collection efforts that do not satisfy these criteria.

III. CED Should be Invoked for Rare "Orphan" Diseases Where Evidence of Effectiveness is Not Available or Feasible to Develop

We strongly support CMS's proposal that CED be used to provide coverage for drugs and technologies where comprehensive evidence of effectiveness of such items and services are not available or feasible to develop in pre-market settings, such as for rare "orphan" and other diseases that do not affect sufficiently large patient populations to attract industry funding. See id. at 10. Absent such coverage, patient access to these vital medicines would be severely restricted and would be dependent solely on the business imperatives of industry sponsors.

IV. CMS Should Ensure that the Results of CED are Rapidly Integrated into Broader Coverage Decisions

While we strongly support the expansion of coverage that CED may offer, we recommend that CMS take steps to ensure that the data collected through CED be rapidly incorporated into broad coverage decisions. To guarantee broad access to state-of-the-art therapies, the coverage decision process must be expedited based on information regarding efficacy and safety obtained through the CED initiative. Consequently, we urge CMS to revise its decision-making process to allow for coverage determinations to be promulgated upon receipt of CED data, without delaying such decisions until the

results of trials and studies are published. Because CMS will have previously approved the study or trial in question through the CED participation process, the agency will not need to wait for the quality assurance provided by publication in peer-reviewed journals. Therefore, CMS should be able to make much more expedited national coverage determinations as a result of the CED initiative.

Further, we urge CMS to expedite its coverage processes outside of the CED initiative. As you are aware, it is not uncommon for the media to cover a new therapy (e.g., based on abstracts or other publicly released information) long before Medicare covers the therapy. During this period, patients may ask their physician for the new treatment only to learn that the therapy is not covered because of the time required to publish the trial's results in approved journals. This process needs to be expedited for all coverage decisions to ensure that patients are able to obtain the treatments they need based on existing data. While the use of CED may help provide coverage in these circumstances through the use of registries and other data collection initiatives, CED should not become a reason for failing to promulgate a NCD where existing non-CED data adequately supports a coverage decision. As it moves forward with the CED initiative, CMS should take advantage of this opportunity to improve its existing processes so that all coverage decisions, CED or otherwise, are issued in a timely fashion based on existing data, in order to provide patients access to the safest and most effective therapies at the earliest possible time.

V. CMS Should Be Sensitive to the Burdens Data Collection Requirements Will Impose on Entities Participating in CED

Physicians at Alliance member institutions face difficult decisions every day about whether sufficient data exists to offer emerging drugs and technologies to desperately ill patients, so we have a deep appreciation for the difficult decisions CMS faces in making coverage decisions for these services. Keeping informed and up-to-date on the latest information about drug-disease combinations is an enormously challenging task, even for institutions like ours whose resources are focused exclusively on oncology. Designing trials and collecting data to measure outcomes, toxicities and efficacy are activities that require dedicated resources and state-of-the-art expertise. The resources required for structured data collection are expensive. While we appreciate that CMS is proposing to pay for services that would otherwise not be covered, the cost of CED, especially at institutions like ours that are more likely to provide those services affected by this initiative, will be significant.

Notwithstanding CMS's statement that it expects to use CED rarely, we anticipate that oncology may be a frequent subject for CED, given the growing number of new and expensive cancer drugs and imaging techniques. We also are concerned that CMS does not fully appreciate the effort and resources it will require to make CED meaningful. Perhaps our biggest concern is that the Draft Guidance provided very little information about how this proposal will be operationalized.

Data collection efforts may be particularly challenging when expanded beyond clinical trials. As you are aware, clinical trails are carefully designed to answer specific questions and measure well-defined endpoints. Quality control and validation of data is a standard practice in trials. Institutions conducting clinical trials have existing processes

and procedures in place to address these issues. By comparison, registries are less-structured and therefore collect data of more limited use. However, depending on their design, participating in a registry could impose an administrative burden that is disproportionate to the data collected. While, as discussed above, we appreciate the expansion of coverage that registries may offer, enrollment should not unduly burden physicians or institutions and their use should complement the data collection efforts of clinical trials and studies. Further, because of the existing quality control and data validation procedures in clinical trials, we recommend that CMS not impose additional data collection burdens on institutions participating in CED trials.

We strongly urge CMS to be mindful of these concerns in implementing this initiative.

VI. The CED Initiative Should Not Limit Local Contractor Discretion to Extend Coverage to New Therapies

As noted in our comments on the recent NCD for colorectal cancer chemotherapy, the Alliance supports maintaining local contractor discretion to make individual coverage determinations to extend coverage to new therapies. Consequently, we were pleased that CMS stated unequivocally in the Draft Guidance that it does not intend to limit contractors' ability to make such determinations. See Draft Guidance, at 6. We encourage the agency to reiterate this statement in the final guidance so that contractors do not withhold coverage while the results of CED-approved trials and other studies are pending. The Alliance remains concerned that the mere existence of guidance such as this Draft Guidance and the NCD for colorectal cancer could have a chilling effect on local contractors and make them very reluctant to extend coverage to therapies under study unless specifically required by the Medicare regulations. As noted in the Draft Guidance, limiting drug approvals for the several years needed to complete clinical trials will mean denying the drug to many patients who could benefit from them. Consequently, we ask CMS to reiterate that contractors should not withhold coverage pending the outcomes of CED-approved trials if there is sufficient clinical evidence demonstrating the appropriateness of Medicare coverage.

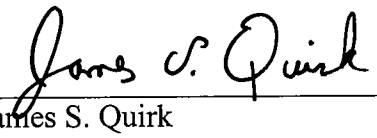
We also urge CMS to implement the CED process aggressively to expand coverage in situations where local decisions are inconsistent across coverage regions. The Alliance appreciates the flexibility and speed that the local coverage decision process provides, but we have also experienced problems in that different contractors may view the same clinical evidence differently, often to the detriment of patient care. In particular, some Alliance members have experienced difficulty obtaining coverage for off-label uses of anti-cancer therapies, notwithstanding the existence of compelling evidence in non-compendia publications that such uses are appropriate. We urge CMS to use the CED process to improve the uniformity of coverage decisions among contractors so that patients are able to obtain access to new therapies that have clinical support regardless of where they live.

VII. CONCLUSION

Thank you for your willingness to consider our views. We are hopeful that CMS will incorporate the recommendations described above in the Draft Guidance. If you

have any questions or require additional information, please contact Dr. James B. Dougherty of the Arcus Group, LLC, at (212) 785-2236.

Sincerely yours,



James S. Quirk
Senior Vice President
Memorial Sloan-Kettering Cancer Center

Organization: American Academy of Molecular Imaging

(Comment on next page.)

ACADEMY OF MOLECULAR IMAGING
www.ami-imaging.org ami@mednet.ucla.edu

BY HAND DELIVERY

June 6, 2005

Administrator Mark McClellan, M.D. Ph.D.
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building
Room 445-G
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: Draft Guidance for Coverage with Evidence Development

Dear Administrator McClellan:

The Academy of Molecular Imaging (AMI) appreciates this opportunity to comment on the draft guidance issued by the Centers for Medicare and Medicaid Services (CMS) on April 7, 2005 for making a determination of Medicare coverage with evidence development (CED). We submit this comment letter in support of the use of coverage with evidence development for certain innovative technologies with acknowledged efficacy that may have obstacles for data collection for certain indications or patient types. We support the use of CED to expand Medicare coverage but not to restrict access or limit utilization.

AMI has worked closely with the Centers for Medicare and Medicaid Services (CMS) over the past several years on expansion of Medicare coverage of Positron Emission Tomography (PET scans) for oncology, as well as neurological and cardiovascular diseases. As the draft guidance describes, PET scans were among the first technologies that CMS chose to cover through a CED approach. Since October 2004 AMI has been working closely with CMS to design and implement a "PET data registry." In January 2005 CMS announced the final National Coverage Decision expanding coverage for PET scans for cancer through a CED process, as well as to provide a PET Biomarker for FDA approved cancer drug trails. Over the past several months AMI has worked closely with CMS, the American College of Radiology Imaging Network (ACRIN), and other professional societies to finalize the PET data registry. We strongly urge CMS to implement the PET data registry as soon as possible so patients can have access to PET for all cancer indications and to help demonstrate the value of the CED process in improving the delivery of healthcare.

Background on PET

PET is a noninvasive molecular imaging procedure through which the molecular errors that cause disease can be accurately identified and understood in terms of the biological nature of disease. This separates PET from conventional anatomic imaging modalities such as x-ray films, CT and MRI. PET assists physicians in improving the diagnosis and management of patients with cancer, cardiac diseases and neurological disorders. PET studies assists physicians in eliminating unnecessary surgeries, reducing the number of diagnostic procedures and improving the selection of the most effective treatments to improve patient outcomes.

By monitoring alterations in cellular glucose metabolism throughout the body, PET provides very sensitive and specific information regarding biological transitions from health to disease. CT meanwhile provides detailed information about the location, size, and shape of various lesions but cannot detect malignant tumors, differentiate malignant lesions from benign ones or the healing processes following treatment with the accuracy as PET.

History of Medicare Coverage of PET Scans

When PET scans were initially reviewed by the Health Care Financing Administration (HCFA) for Medicare coverage, HCFA decided to review PET, not for all of oncology, but rather for individual tumor types. Under this new framework HCFA, and subsequently CMS, looked for published peer review evidence that supported changes in health outcomes in patient management. This was a significant decision that impacted the way PET was utilized and available to Medicare beneficiaries (state what you mean more specifically by this). Additionally, many private payers followed decisions made by Medicare.

Beginning January 1, 1998, FDG PET was covered when used for the initial staging of suspected metastatic non-small cell lung cancer (NSCLC) and for the characterization of suspected solitary pulmonary nodule (SPN). On July 1, 1999, FDG PET coverage was expanded to include 3 additional oncology indications. These were: 1) location of recurrent colorectal tumors when rising CEA suggests recurrence; 2) staging and restaging of lymphoma only when used as an alternative to gallium scan; and 3) evaluating recurrence of melanoma prior to surgery only when used as an alternative to gallium scan.

In December 2000, Medicare expanded PET scans for the most prevalent cancers, including non-small cell lung cancer, melanoma, esophageal, and head and neck cancer. Medicare specifically stated that all other indications were not covered by Medicare. As a result of this decision in December 2000, the Academy of Molecular Imaging (AMI) worked with academic centers and patient organizations to present individual applications for additional types of cancer to CMS for Medicare coverage. This has been a very long time intensive process.

Separate applications from numerous academic medical centers were submitted, including testicular, brain, cervical, prostrate, myeloma and ovarian cancer. Over the next two years AMI worked and met with CMS on several occasions to advance the coverage of these cancers. CMS consistently stated that there was not sufficient published literature for these cancer types similar to the data for the already covered tumor types. Scientists and clinical experts presented scientific and clinical evidence to CMS that the combination of the evidence from covered indications, cancer biology evidence regarding alterations in glucose metabolism and existing, although limited, literature on non-covered types of cancer, could be extrapolated and applied to non covered cancers. The group also made arguments that there was less available evidence for the noncovered types of cancer because of their lower individual incidence and that it would be difficult to obtain data without Medicare coverage. Another approach was needed.

Implementation of PET Data Registry

In the Fall of 2004, AMI met with CMS to discuss covering all presently non-covered cancers as part of a "PET Data Registry." PET scans would be covered if the physician completed a form and submitted data to CMS regarding changes in management due to the PET scan. The "PET Data Registry" would cover all PET scans not presently covered, as well as provide PET imaging of glucose metabolism as a biomarker for FDA approved drug trials in cancer.

In November, 2004 CMS released a proposed decision on expanding coverage of PET scans and CMS released a final coverage decision in January, 2005. The announcement of the PET data registry has generated tremendous positive attention and support within the oncology provider and patient community. AMI has received hundreds of inquiries from patients and physicians regarding the expanded coverage and when the registry will be implemented.

AMI, ACR, ASCO and other societies have worked diligently with CMS on implementing the expanded cancer coverage through the PET data registry. This has been an example of a collaborative effort among CMS, academics, physicians, and industry to invent a novel dynamic method for expanding coverage while collecting and analyzing the data to progressively make decisions based on the outcomes. This approach is helping to bring CMS, other agencies, academics, physicians and patients together in healthcare decisions. AMI believes that when implemented the PET Registry can be the first working model for CED proposal and new evidence based medicine framework. AMI, the other involved societies and practicing physicians are committed to CMS in making the CED be a successful demonstration project.

At present we understand that HHS and CMS are working on numerous legal and policy issues relating to the coverage with evidence development. AMI is very concerned that any further delay in finalizing the PET data registry could jeopardize the successful implementation of the CMS demonstration project of the CED and would continue to deny Medicare beneficiaries access to the benefits PET scans provide in the noncovered cancers. We would like to work with your office to finalize the registry as soon as possible. We believe that ACRIN would be able to implement the registry within 60 days of CMS finalizing any efforts. We would like to set a common goal to have the PET CED fully operational by September 1, 2005. We will do our part as you require. Does this seem reasonable to you?

We applaud this innovative method of gathering evidence to be used for making coverage determinations. We look forward to working with you to complete the PET Data registry and make it a model for others CEDs.

Very truly yours,

Ed Coleman, M.D.

Organization: American Association for Clinical Chemistry

The American Association for Clinical Chemistry (AACC) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS's) draft guidance, "Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED)," which further elaborates on how the agency will make national coverage decisions. AACC has long advocated that CMS and the Food and Drug Administration (FDA) streamline the regulatory review process for new technologies. We believe this effort is a good first step towards rationalizing the clearance and payment processes.

AACC supports a number of concepts outlined by CMS in the document, such as:

- The CED process should be employed rarely;
- Requests for additional information should be very specific, both in what data is requested and how that data will be used;
- The local coverage decision-making process should be preserved; and
- CMS and FDA should increase their level of cooperation to reduce regulatory hurdles for manufacturers.

Although AACC agrees with CMS's evidence-based approach, we urge caution in linking coverage decisions solely with improved patient outcomes. For some health care services, such as laboratory testing, it is not always be possible to isolate the test from other intervening factors when assessing patient outcome.

By way of background, AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and its application to health care.

Organization: American Cancer Society

The American Cancer Society, as a leading national voluntary organization dedicated to the elimination of cancer, appreciates the opportunity to comment on the CMS draft guidance, *Factors CMS Considers in Making a Determination of Coverage with Evidence Development*. We strongly support current CMS policy of providing comprehensive coverage of off-label drugs to cancer patients.

We applaud the efforts of CMS to reduce the devastating burden of cancer on Medicare beneficiaries, and stand behind those efforts to reduce pain and suffering and deaths caused by cancer. However, with respect to the draft guidance, the Society is particularly concerned that this coverage with evidence development (CED) initiative could negatively affect the favorable coverage and payment of off-label drugs.

It is critical that there is no change in this policy, as more than 60% of cancer patients rely on off-label drugs for their treatment—these drugs are the reasonable and necessary treatment for the majority of cancer patients. The ability to maintain this type of treatment is vital to effectively reducing the tremendous pain, suffering, and mortality caused by cancer. Moreover, we know that early diagnosis followed by timely and appropriate treatment are critical to a patient's survival.

The draft guidance in its current form will be cause for concern and potentially confusing for many people. For example, providers will question if they may be asked to collect data without mechanisms for appropriate reimbursement. The main concern for cancer patients themselves is whether their current strong coverage protections for life-saving drugs will be reduced by the new CED policy.

We strongly urge you to clarify this new policy, to ensure that the favorable coverage for off-label cancer drugs does not change. Too many cancer patients depend on these drugs for life-saving treatments for coverage to be reduced.

Organization: American Clinical Laboratory Association

The American Clinical Laboratory Association ("ACLA") is pleased to have this opportunity to submit comments to the Centers for Medicare and Medicaid Services ("CMS") in response to its recent Draft Guidance on Coverage With Evidence Development (April 7, 2005) ("Draft Guidance.") ACLA is an association representing independent clinical laboratories throughout the country, including local, regional and national laboratories.

ACLA has two primary interests in the matters raised by the Draft Guidance. First, ACLA members are involved in the development of new and innovative clinical laboratory tests. Some of the tests that are currently in the pipeline could be candidates for National Coverage Decisions ("NCD") at some point in the future. ACLA is concerned that the use of CED procedures could result in delays in these new tests reaching the market or could inhibit their availability to patients who need them. Second, the tests that laboratories perform will often serve as the basis for the evidence development that is required for other medical interventions. ACLA members are concerned that the requirements related to testing for the CED process may raise specific issues for laboratories. For example, how will this testing be billed? Who will be responsible for payment? What types of regulatory requirements will apply to this testing? These issues are discussed in greater detail below.

For convenience, we have generally attempted to organize our comments along the line of the general headings that were included in the Draft Guidance.

I. Background

ACLA is supportive of an expanded and expedited coverage process, and we recognize the importance of ensuring that medical decisions are made on the basis of the best available evidence. However, a number of concerns are raised by the Draft Guidance. First, the agency's legal authority to impose the types of requirements that are at issue here is far from clear. The position of the Draft Guidance is basically that Medicare will cover certain products or services, through the NCD process, if there is in place a procedure for obtaining additional evidence about the clinical utility of the product or service. While this approach may be beneficial with respect to items or services for which coverage would otherwise be denied due to insufficient evidence of clinical utility, application of CED to such items or services seems inconsistent with the Medicare statute's basic requirement that the Program will only cover products or services that are reasonable and necessary. Where there is a sufficient basis for determining that a product or service meets that standard without further evidence development, then CMS should cover it and not limit that coverage based simply on its salutary desire to obtain additional information about how the product or service performs.

This is not simply a legal distinction. CMS is not a research agency; thus, there are significant questions as to whether this is an appropriate role for CMS. Other agencies within the federal government, such as the Agency for Healthcare Research and Quality or the National Institutes of Health, may be better positioned to perform these functions and should be the ones carrying them out. Therefore, we think it is appropriate for CMS to carefully consider whether or not it is the appropriate agency to oversee the

types of evidence development that are contemplated by the Draft Guidance. If, however, CMS decides to proceed with CED, its focus should be on new technologies and services, not on the entire spectrum of technologies and services that are currently available.

Furthermore, if this Draft Guidance is implemented in some way, then it should be clear that the use of evidence development is an option that is only available as part of the NCD process. Given the likely costs and the enormous complexity of the process, as well as the expertise that will be required to oversee and implement it, it would not be appropriate for local carriers or intermediaries to attempt to utilize a similar process when making local coverage decisions. As a result, the Draft Guidance should make clear that this process is only to be used as part of the NCD process, after significant deliberation by CMS. It should not be used as part of the local coverage process.

II. Factors Considered As Part of the Coverage Development Process

While ACLA welcomes the additional direction offered by the Draft Guidance concerning CMS's views, it is still unclear when and how CED will be used. For example, is it CMS's intention that all new NCDs will now include a CED component or will the decision be made on a case by case basis? Further, CMS states that the data collection required "should be aligned with any clinical study requirements associated with FDA review." Is this language suggesting that FDA clearance or approval may not be a prerequisite for CED coverage? This would be unusual, because Medicare does not usually cover a product or service subject to FDA clearance or approval that is not yet cleared or approved by the FDA. Further, in the Draft Guidance, CMS notes that the clearest benefit of CED is likely to be realized in situations where patients have a chronic condition (Draft Guidance at 5). It is unclear, therefore, how this guidance would apply to clinical laboratory tests, which are diagnostic in nature, rather than therapeutic.

The use of the CED process has implications beyond Medicare. For example, we are concerned that some private insurers may take the position that the decision to impose CED requirements means that the underlying service is still experimental, unproven or not medically necessary. In that way, a CED may inhibit, rather than promote, the rapid spread of new technology because private payors may take the position that they need not cover new technologies subject to CED. Thus, we think CMS should be very clear concerning the meaning and impact of CED requirements.

One of the most important questions with regard to CED development is who will be responsible for paying the additional costs of the CED process. Clearly, clinical trials and the establishment and monitoring of a data base will involve significant additional costs. Because laboratories will often be part of the data collection process, another important question is likely to revolve around whether Medicare will pay for any follow-up testing that is required as part of the CED, or whether the entity overseeing the data collection will be responsible for bearing these costs. The answer to this question should be clearly spelled out so that laboratories are not left wondering whether they must look to a private entity operating the data collection effort for payment or whether they should look to Medicare for that payment.

Another key concern in this area is that the CED process should not stifle innovation by requiring burdensome or insurmountable requirements. There are a number of ways this could occur for clinical laboratories, in particular. First, if a new test

is developed that is predictive for a particular condition or for the effectiveness of a particular therapy, then it may be unreasonable to expect that there will be randomized clinical trials as part of the CED follow-up because most patients will want to take action in response to the test results. Thus, patients may be less willing to enroll in the control arm of such a study. As a result, the types of evidence development utilized must be flexible or the spread of new technologies could be affected.

CED could also impose certain unique problems for laboratories because they do not usually see or have interaction with the patient. This may make CED difficult where a laboratory test is the subject of the coverage decision. If Medicare decides to subject a new laboratory test to CED, it is the laboratory that will be paid for the test. However, the laboratory has little interaction with the patient; thus, it will be unable to ensure that the patient participates in the follow up process. It will usually be up to the physician to ensure that the patient participates in any subsequent evidence development; however, Medicare will have little leverage over the physician in this case, because it is not paying the physician for the testing. Thus, CED for clinical laboratory tests may present unique challenges.

Finally, ACLA is concerned about recent proposals that would require laboratories to report test results or related clinical data to Medicare with claims. This proposal has been made recently as part of pay-for-performance initiatives designed to promote the spread of health information technology. While ACLA is supportive of appropriate efforts to promote health information technology, currently, neither the technology nor the shared computer language exists to permit such widespread, integrated data reporting. Thus, ACLA would be concerned if, as part of CED, clinical laboratories were required to report test results or related clinical data within, or as an attachment to, Medicare claims data. Where necessary with respect to new clinical laboratory tests covered under CED, ACLA would not object to submitting such information separately from the claims process.

III. Study Design Implementation

As suggested above, following up on patients that are included in the specific evidence development process will often be the most important and most problematic issue presented by this process. Researchers often note that the most difficult part of any clinical study is the follow-up of patients after the initial enrollment of participants. A number of questions related to issues of follow-up are raised by the Draft Guidance. For example, how will the agency ensure that patients continue to participate in a study? What action would be taken if there is not sufficient follow-up? What action will Medicare take with regard to its NCD if patients do not continue to participate in subsequent evidence development efforts? As suggested above, this type of follow-up will be particularly difficult in the instance of clinical laboratories.

Furthermore, ACLA believes there must be clear time limits on the evidence development process. We do not believe it is sufficient simply to suggest that evidence development should continue until all of the relevant questions have been answered. As time passes, the relevance of particular questions may change, and the level of participation may diminish. Therefore, it seems far more reasonable and fair to set a specific time period for the requirements, i.e., specific dates for the commencement and termination of the data collection. Once the end date is reached, the requirements should be re-evaluated or eliminated if no longer necessary.

Finally, the Draft Guidance raises a number of questions about how to balance the cost of evidence development with its possible benefits. ACLA believes that the benefits should be weighed in terms of objective end points, such as reduced mortality, shortened hospital stays, or other reduced costs. The value of these benefits may, however, be difficult to measure. On the other hand, the costs associated with the new product or service may be more apparent and easier to calculate. Therefore, ACLA believes that it is important in any data collection effort to weigh carefully the costs and benefits involved, so that this process does not unfairly discourage the development of new products and services.

ACLA is pleased to have the opportunity to submit these comments. We look forward to working with the agency as it continues to develop its position in this area. If you have any further questions or comments, do not hesitate to contact us.

Organization: American College of Cardiology

The American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions (SCAI) appreciate the opportunity to comment on proposed revisions to the CMS National Coverage Determination (NCD) process. The ACC is a 31,000 member non-profit professional medical society and teaching institution whose mission is to advocate for quality cardiovascular care through education, research promotion, development and application of standards and guidelines, and to influence health care policy. The SCAI is a professional association representing 3,300 invasive cardiologists. SCAI promotes excellence in cardiac catheterization and interventions through physician education and representation, clinical guidelines and quality assurance to enhance patient care.

We commend CMS for its continued efforts to improve the national coverage determination process. As we stated in previous comments to the agency, we believe a more transparent and predictable process is necessary to ensure that Medicare beneficiaries have access to breakthrough medical technologies.

This draft guidance document addresses significant issues of scientific oversight, hypotheses, data collection methods, and sample size. The ACC and SCAI offer the following comments for consideration.

Evidence Based Medicine

Our organizations strongly support an evidence-based approach to medical practice to facilitate the provision of safe and cost effective care to patients. Many professional medical societies have developed evidence-based clinical guidelines and expert consensus documents and continuously revise these documents to include new technologies. To assist in decision-making on national coverage determinations, we encourage CMS to consult with professional medical societies at least yearly, but more frequently as necessary, to gather updated information from clinical guidelines and expert consensus documents. We propose that CMS consider an initial meeting with professional medical societies to establish priorities for discussion, and then relevant societies should identify expert representatives to participate in working groups to discuss specific clinical areas and evaluate existing evidence-based practice guidelines, or the need for new guidelines and study, including study design, population, sample size, study sponsors, endpoints and funding.

Data Collection, Interpretation and Oversight

The ACC and SCAI encourage CMS to call for post coverage data collection in only a limited number of circumstances where there is a well defined need for new information on outcomes and quality care. Importantly, the scientific questions should be carefully defined early in the process, with all stakeholders having the opportunity for input. Care should also be taken to ensure that data collection is not burdensome and costly to providers, both financially and in additional work (clerical and other resources). We

encourage CMS not to rely on administrative claims data but instead, utilize focused and prospectively collected clinical data from a registry setting.

We believe that nationally recognized clinical trial/study design experts and database researchers should work with CMS to determine the appropriate study duration, statistical requirements, population and data collection methods (registry collection). As mentioned above, professional medical societies should be afforded the opportunity to identify experts to work with CMS in this process. Such experts should also be called upon to consult with CMS to adjudicate conflicts in the execution and interpretation of data. Experts in the relevant fields should oversee each proposed database or registry to (a) assure validity of the data elements (both definition and utilization); (b) set appropriate guidelines to govern access to the database for research and analysis purposes; and (c) determine appropriate sample sizes for any conclusions drawn from the databases/registries and confirm the statistical significance and validity of any conclusions generated by analysis of the contents therein.

We also ask CMS to clarify the terms for analysis of databases and registries and particularly the term "studies." These terms appear to be mixed and interchangeable throughout the document.

Withdrawal of Coverage

The ACC and SCAI urge CMS not to undertake a large-scale reconsideration of coverage decisions based on the provisions set forth in this guidance document. We are concerned that there is a major risk that an insufficient sample size will be used to deny services or procedures to the Medicare population. We also ask CMS to clarify the standards (ratio of absolute or relative benefit to cost of the service) that would be imposed to establish withdrawal of coverage.

Organization: American College of Radiology

(Comment on next page.)

June 6, 2005

Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail stop: C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

RE: Coverage with Evidence Development (CED) Draft Guidance Document

Dear Members of the Coverage and Analysis Group:

The American College of Radiology (ACR), representing over 32,000 members in radiology, radiation oncology, interventional radiology and nuclear medicine would like to thank the Centers for Medicare and Medicaid Services (CMS) for this opportunity to provide comments on the draft guidance document relating to the concept of coverage with evidence development (CED). The ACR would like to extend its appreciation to CMS for their efforts in engaging stakeholders in a public dialogue to assist the agency in developing a guidance document on Medicare coverage decisions that are linked to prospective data collection requirements.

The ACR reviewed the draft guidance document titled "Factors CMS Considers in Making a Determination of Coverage with Evidence Development" and feels that overall it is straightforward and consistent with other CMS educational efforts (e.g., physician open door forum conference calls). However, the ACR believes there remain many uncertainties regarding how any data collection or similar evidence development efforts will be managed and how they might ultimately impact patient access to new technology. We, therefore, encourage the agency to proceed cautiously and limit the use of CED until it is possible to acquire more experience with the concept. In addition, to the extent that ongoing and future CED initiatives relate to services provided by radiologists, the ACR urges CMS to be mindful of the unique aspects of technology assessments for such services[1], as the measurements of diagnostic accuracy/evidence may differ from typical health care interventions in ultimately identifying the net health outcomes.

While the ACR recognizes the potential promise of the new CED process, CMS should continue to consider the overarching impact of the respective national coverage requirement for practicing physicians as well as quality patient care. Practicing radiologists rely on other physicians for the respective referrals. The ACR is concerned that if a study requires coordination with physicians whose reimbursement is not linked to performing the examination (e.g., ordering or referring physicians), they will have little

[1] Sunshine JH, Applegate KE. Technology Assessment for Radiologists. Radiology 2004; 230:309-314.

incentive to provide the follow up data associated with a registry or clinical study. Therefore, we ask that CMS take proactive measures and develop solutions to help alleviate this potential problem between referring and practicing physicians (e.g., radiologists) whenever an item or service subjected to CED involves a number of different physicians, each playing a specific role in determining the need for and/or providing such item or service.

Within the draft CED guidance document, CMS states that "the primary purpose of obtaining additional evidence through CED is for the agency's use in making payment determinations, i.e., that a treatment is reasonable and necessary". It further states that a future guidance document will provide greater detail of the interpretation of "reasonable and necessary". The ACR asks that CMS take careful consideration in defining/interpreting "reasonable and necessary" and utilize the established and available resources.

The Carrier Advisory Committee (CAC) process and local physician input on local level consolidation and development of local coverage determinations (LCDs) is an invaluable system for health policy and gleaning medical need. The ACR has nationwide networks of Radiology and Radiation Oncology CAC representatives who review draft LCDs in detail and provide comments to their local Carrier Medical Directors (CMDs). Local CAC and LCD development processes are vitally important to the functioning of physician practices, the education of providers and the exchange of information between providers and Medicare contractors. In addition, these established processes provide medical necessity/reasonable and necessary information. ACR believes quite strongly that any CED initiative must provide for a similar level of consultation with relevant physician specialists and their respective associations.

III. Factors Considered in Applying CED, page 10

The ACR reviewed the questions posed in the CED draft guidance document under Section III referenced above and recommend that an agreed understanding of the scope and endpoint of a study should be determined prior to a CED. End points should be provided by those physicians having to abide by the CED rules (e.g., radiologists when CED relates to a service they provide) and, as such, the method should not require radiologists having to rely and obtain data from referring physicians who may not be required to participate. The ACR would urge CMS to provide solutions to this potential issue. In addition, the ACR encourages CMS to utilize the diagnostic measurements referenced in the enclosed article titled "Technology Assessments for Radiologists."[2]

IV. Process for Deciding When and How to Apply CED, page 11

In response to bullet 2, under Section IV referenced above, the ACR recommends that CMS publish a separate rule in advance of the proposed rule for the Medicare Physician Fee Schedule, if new codes requiring CED are implemented.

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[2] Ibid.

In response to bullet 3, under Section IV referenced above, the ACR feels that there are existing mechanisms and processes that would serve as a useful model for obtaining public input to identify and prioritize topics for CED. Rulemaking or comparable requests for public input (e.g., notices in the *Federal Register*), stakeholder conference calls, CMS high priority work with medical specialty societies to approve a data collection model prior to implementation of a new code (i.e., a six month or less development process) are all available mechanisms.

Answers to questions in Section V will vary with each study and should be answered on a case by case basis. Also, CMS should continue to rely on peer review medical literature and only do one of the CED projects if the data seem insufficient for determining coverage.

The ACR appreciates CMS' consideration of the comments above and welcomes any questions. If you should need clarification on the items addressed in this comment letter or would like to discuss further, please contact Anita Pennington at (800) 227-5463, ext. 4923 or via email at anitap@acr.org.

Respectfully Submitted,

Harvey L. Neiman, M.D., FACR
Executive Director
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cc: Herb Kuhn, Director, CMS Center for Medicare Management
John A. Patti, M.D., Chair, ACR Commission on Economics

Enclosure

Radiology

Jonathan H. Sunshine, PhD
Kimberly E. Applegate, MD, MS

Index terms:
Cancer screening
Efficacy study
Radiology and radiologists, outcomes studies
Technology assessment

Published online
10.1148/radiol.2302031277
Radiology 2004; 230:309–314

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Technology Assessment for Radiologists[1]

Health technology assessment is the systematic and quantitative evaluation of the safety, efficacy, and cost of health care interventions. This article outlines aspects of technology assessment of diagnostic imaging. First, it presents a conceptual framework of a hierarchy of levels of efficacy that should guide thinking about imaging test evaluation. In particular, the framework shows how the question answered by most evaluations of imaging tests, "How well does this test distinguish disease from the nondiseased state?" relates to the fundamental questions for all health technology assessment, "How much does this intervention improve the health of people?" and "What is the cost of that improvement?" Second, it describes decision analysis and cost-effectiveness analysis, which are quantitative modeling techniques usually used to answer the two core questions for imaging. Third, it outlines design and operational considerations that are vital if researchers who are conducting an experimental study are to make a quality contribution to technology assessment, either directly through their findings or as an input into decision analyses. Finally, it includes a separate discussion of screening—that is, the application of diagnostic tests to nonsymptomatic populations—because the requirements for good screening tests are different from those for diagnostic tests of symptomatic patients and because the appropriate evaluation methods also differ.

Technologic innovation and diffusion of technology into daily practice in radiology have been nothing short of remarkable in the past several decades. Health technology assessment is the careful evaluation of a medical technology for evidence of its safety, efficacy, cost, cost-effectiveness, and ethical and legal implications (1). Interest and research in health technology assessment are growing in response to the wider application of new technology and the increasing costs of health care today (2).

The goal of this article is to describe some of the rationale and the methods of technology assessment as applied to radiology. For any health care intervention, including diagnostic imaging tests, the ultimate questions are, "How much does this do to improve the health of people?" and "How much does it cost for that gain in health?" We need such an understanding of the radiology services we provide to advocate for our patients and to use our resources efficiently and effectively.

OUTCOMES

Measures of diagnostic accuracy, which are the metrics most commonly used for evaluation of diagnostic tests, answer the question, "How well does this test distinguish disease from the nondiseased state?" The answer to that question often does not provide an answer to the questions about improvement of health and the cost of that improvement, which are the core outcome questions about health care interventions (3,4).

The most productive way to think about this gap between diagnostic accuracy on the one hand and outcomes on the other hand and to think about the inclusion of relevant outcomes in the evaluation of diagnostic tests is to use the conceptual scheme of a six-level "hierarchy of efficacy" developed by Fryback and Thornbury (5,6) (Table). They point out that efficacy at any level in their hierarchy is necessary for efficacy at the level with the next highest number but is not sufficient. In their scheme, diagnostic accuracy is at level 2, and patient and societal outcomes are at levels 5 and 6, respectively. Thus, there may be "many a slip between cup and lip"—that is, between diagnostic accuracy of an imaging test on the one hand and improved health and adequate cost-effectiveness on the other.

Let us trace partway through the schema, starting at the lowest level, to understand the principle that efficacy at one level is necessary but not sufficient for efficacy at the next level. Technical efficacy (level 1), such as a certain minimum spatial resolution, is necessary for diagnostic accuracy (level 2), but it does not guarantee it. Similarly, diagnostic accuracy is necessary if a test is to affect the clinician's diagnosis (level 3), but it is not sufficient. Rather, other sources of information, such as patient history, may dominate, so that even a highly accurate test may have little or no effect on the diagnosis. In such an instance, fairly obviously, the test does not contribute to the level 5 goal of improving patient health.

As the Table shows, there are multiple measures that can be used to quantify the efficacy of a diagnostic imaging test at any of the six levels. Hence, evaluations of imaging tests can involve a variety of measures. Thinking in terms of the hierarchy is also helpful for identification of the level(s) at which information should be obtained in an evaluation of a diagnostic imaging test. Experience, as well as reflection, has taught some lessons. The most important of these include:

1. Because higher-level efficacy is possible only if lower-level efficacy exists, it is often useful to measure efficacy at relatively low-numbered levels.

2. In particular, in the development of a test, it is helpful to measure aspects of technical efficacy (level 1), such as sharpness, noise level, and ability to visualize the anatomic structures of interest. An important aspect of test development consists of finding the technical parameters (voltage, section thickness, etc) that give the best diagnostic accuracy; these measures of technical efficacy are often key results in that process.

3. Diagnostic accuracy (level 2) is the highest level of efficacy that is characteristic of the test alone. For example, the sensitivity and specificity of a test are not dependent on what other diagnostic information is available, unlike level 3 (diagnosis). Also, the methodology and statistics used in measurement of diagnostic accuracy are relatively fully developed. Therefore, measurement of diagnostic accuracy is usually worthwhile.

4. Above diagnostic accuracy, effect on treatment (level 4), an "intermediate outcome," is relatively attractive to measure. It can be measured fairly easily and reliably in a prospective study, and it is closer in the hierarchy to the ultimate criteria, effect on patient health (level 5) and cost-effectiveness (level 6).

Hierarchy of Efficacy for Diagnostic Tests

Level	Typical Measures
1, Technical efficacy	Resolution of line pairs Pixels per millimeter Section thickness Noise level
2, Diagnostic accuracy	Sensitivity Specificity Area under the receiver operating characteristic curve
3, Diagnosis	Percentage of cases in which image is judged helpful in making the diagnosis Percentage of cases in which diagnosis made without the test is altered—or altered substantially—when information from the test is received
4, Treatment	Percentage of cases in which image is judged helpful in planning patient treatment Percentage of cases in which treatment planned without the test is changed after information from the test is received
5, Patient health outcomes	Percentage of patients improved with test conducted compared with that improved without test conducted Percentage difference in specific morbidities with test compared with those without Mean increase in quality-adjusted life years with test compared with that without
6, Societal value	Cost-effectiveness from a societal perspective Cost per life saved, calculated from a societal perspective

Source.—Adapted and reprinted, with permission, from reference 6.

5. Effect on patient health (level 5) is usually observable only after a substantial delay, especially for chronic illnesses, such as cardiovascular disease and cancer, which are currently the predominant causes of mortality in the United States. Also, it is the end result of a multistep process of health care. Because diagnostic tests occur near the beginning of the process, and some random variation enters into the results at every step, the effect of a diagnostic test on final outcomes is usually difficult to observe without an inordinate number of patients. For example, the current principal randomized controlled trial of computed tomographic (CT) screening for lung cancer requires some 50,000 patients and is expected to take 8 years and cost $200 million (7). Thus, effects on patient health (level 5) and cost-effectiveness (level 6) are uncommon as end points in experimental studies on the evaluation of diagnostic tests.

CLINICAL DECISION ANALYSIS AND COST-EFFECTIVENESS ANALYSIS

Instead, assessments of imaging technologies at levels 5 and 6 of the efficacy hierarchy are generally conducted by using decision analysis rather than direct experimental studies. Decision analysis (8–11) is an objective and systematic technique for combining the results of experimental studies that cover different health care steps to estimate effects of care processes more extensive than those directly studied in any single experimental research project. Cost-effectiveness analysis is a form of decision analysis that involves evaluation of the costs of health care, as well as the outcomes (12,13). What follows is a brief explanation of clinical decision analysis and cost-effectiveness analysis and the role they may play in technology assessment in radiology. Although we concentrate on cost-effectiveness analysis, the same methods and applications apply to decision analysis.

Cost-effectiveness analysis recognizes that the results of care are rarely 0% and 100% outcomes but rather are probabilistic (14). It involves the creation of algorithms, usually displayed as decision trees, as shown in Figure 1, which incorporate probabilities of events and, often, the valuations (usually called "utilities") of possible outcomes of these events. Individual or population-based preferences for certain outcomes and treatments are factored into these utilities.

Cost-effectiveness analysis can be divided into three basic steps: defining the problem, building the decision model, and analyzing the model.

Defining the Problem

For any cost-effectiveness analysis, one of the most difficult tasks is defining the appropriate research question. The issues to address in defining the problem are the

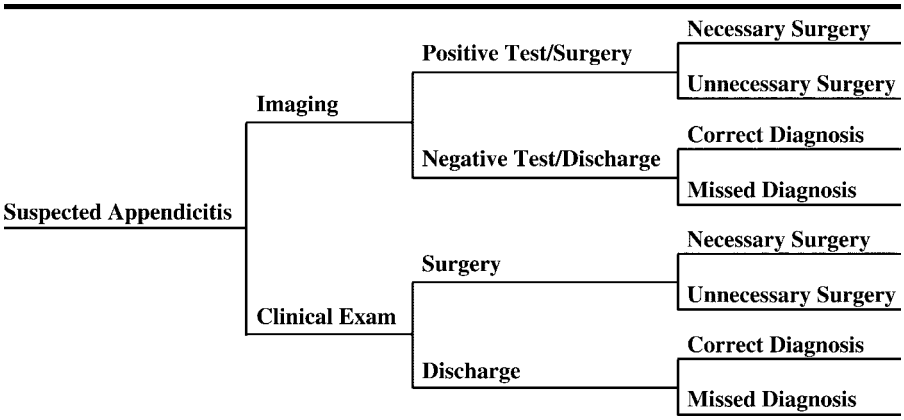

Figure 1. Example of a typical imaging decision analysis tree. In this example, an imaging test is compared with clinical examination for the correct diagnosis of acute appendicitis.

population reference case, strategies, time horizon, perspective, and efficacy (outcome) measures. The reference case is a description of the patient population the cost-effectiveness analysis is intended to cover. For example, the reference case for the cost-effectiveness analysis in Figure 1 consists of persons with acute abdominal pain seen in the emergency department.

The issue of strategies is, what are the care strategies that we should compare? Too many strategies may be confusing to compare. Too few may make an analysis suspect of missing possibly superior strategies. The decision tree in Figure 1 compares costs and outcomes of a clinical examination versus an imaging test for the diagnosis of acute appendicitis; in a fuller model, ultrasonography (US) and CT might be considered separate imaging strategies. In general, cost-effectiveness analysis and decision analysis address whether a new diagnostic test or treatment strategy should replace the current standard of care, in which case the current standard and the proposed new approach are the strategies to include. Alternatively, often the issue is which of a series of tests or treatments is best, and these then become the strategies to include.

The time horizon for which the cost-effectiveness analysis model is used to evaluate costs, benefits, and risks of each strategy must be stated and explained. Sometimes, the time horizon may be limited because of incomplete data, but this creates a bias against strategies with long-term benefits.

Finally, cost-effectiveness analysis allows costs to be counted from different perspectives. The perspective might be that of a third-party payer, in which case only insurance payments count as costs, or that of society, in which case all monetary costs, including those paid by the patient, count, and so—at least in some analyses—do nonmonetary costs, such as travel and waiting time involved in obtaining care.

Building the Cost-Effectiveness Analysis Model

Cost-effectiveness analysis is usually based on a decision tree, a visual representation of the research question (Fig 1). These decision trees are created and analyzed with readily available computer software, such as DATA (TreeAge Software, Williamstown, Mass). The tree incorporates the choices, probabilities of events occurring, outcomes, and utilities for each strategy being considered. Each branch of the tree must have a probability assigned to it, and each path in the tree must have a cost and outcome assigned. Data typically come from direct studies of varying quality, from expert opinion (which is usually unavoidable because some needed data values can not be obtained in any other way), and from some less directly relevant literature. For example, in Figure 1, the probability of a positive test result may be selected from published literature and added to the decision tree under the branch labeled "Positive Test/Surgery." Costs are frequently not ascertained directly, but rather are estimated by using proxies such as Medicare reimbursement rates or the charge and/or cost data of a hospital. Building the decision tree requires experience and judgment.

The complexity of cost-effectiveness analysis sometimes makes it difficult to understand and therefore undervalued (14,15). One way to improve understanding and allow readers to judge for themselves the value of a cost-effectiveness analysis model is to be explicit about the assumptions of the model. Many assumptions are needed simply because of limited data available to answer the research question.

Analyzing the Cost-Effectiveness Analysis Model

Once the model has been created, analysis should then include baseline analysis of cost and effectiveness and sensitivity analysis. The average cost and effectiveness for each strategy, considering all the outcomes to which it might lead, are computed simultaneously. We calculate averages by weighting the end probabilities of each branch and by summing for each strategy by moving from right to left in the tree. In cost-effectiveness analysis decision trees such as that in Figure 1, the costs and utilities for each outcome would be placed in the decision tree at the right end of each branch.

Possible results when comparing two strategies include the following: One strategy is less expensive and more effective than another, one strategy is more expensive and less effective, one strategy is less expensive but less effective, and one strategy is more expensive but more effective. The choice in the first two situations is clear, and the better strategy is called "dominant." The final two situations involve trade-offs in cost versus effectiveness, however. In these situations, one compares strategies by using the incremental cost-effectiveness ratio, which allows evaluation of the ratio of increase in cost to increase in effectiveness. What maximal incremental cost-effectiveness ratio is acceptable is open to debate, but for the United States, $50,000–$100,000 per year of life in perfect health (usually called a "quality-adjusted life-year") is commonly recommended as a maximum.

Almost all payers in the United States state that they consider only effectiveness, not cost. Implicitly, then, they accept an indefinitely high incremental cost-effectiveness ratio—it does not matter how much more expensive a strategy is, as long as it is the least bit more effective or the public demands it intensely.

The final task in cost-effectiveness analysis is sensitivity analysis. Sensitivity analysis consists of changing "parameter values" (numerical values, such as probabilities, costs, and valuation of outcomes) in the model to find out what effect they have on the conclusions. A model should be tested in this way for "robustness," or strength of its conclusions with regard to changes in its assumptions and uncertainty in the parameters taken from the literature or expert opinion. If a small change in the value of

a parameter leads to a change in the preferred strategy of the model, then the conclusion is said to be sensitive to that parameter, and the conclusion is weak. Sensitivity analysis may persuade doubtful readers of the soundness of the conclusions of the model by showing that the researchers were thorough and unbiased and the conclusions are not sensitive to the assumptions or parameters the readers question. Often, however, sensitivity analysis will show that conclusions are not robust. Alternatively, another cost-effectiveness analysis, conducted by different researchers by using different assumptions and parameters (which is really a form of sensitivity analysis), will reach different conclusions. While discouraging, a similar situation is not uncommon with experimental studies (such as clinical research), with one study having findings different from another. Also, identification of the parameters and assumptions to which the results are sensitive can be very helpful, because it tells researchers what needs to be investigated further through experimental studies to reach reliable conclusions.

CHARACTERISTICS OF HIGH-QUALITY EXPERIMENTAL STUDIES

Whether an experimental study is intended to provide direct findings (principally, as we have seen, at efficacy levels 1 through 4) or to provide findings to be used as input into decision analysis and/or cost-effectiveness analysis (which are then used to assess level 5 and 6 efficacy), several design and operational considerations are important for the study to be of high quality and substantial value (2,16–19). Regrettably, the quality of studies on the evaluation of diagnostic imaging is very often poor (20–23). Therefore, radiologists should be aware of these considerations so that they may read the literature critically and also improve the quality of the technology assessment studies they conduct.

The most important considerations follow. We focus on studies of diagnostic accuracy, since these are most common and constitute the principal focus of radiologists, but most of what is said applies to experimental studies of other levels of the hierarchy of efficacy.

Patient Characteristics

Patients in a study should be like those in whom a test will be applied in practice. Often, in initial studies, a test is applied predominantly to very sick patients or completely healthy individuals. This "spectrum bias" exaggerates the real-world ability of the test to distinguish disease from health because intermediate cases that are less than totally clear cut are eliminated. As a result, initial reports on a new test are often overly optimistic. On the other hand, such spectrum bias can be useful in initial studies to ascertain if a test has any possible promise and to help establish the operating parameters at which the test works best.

Number of Cases

The number of cases included in studies should be adequate. Almost always, the smaller the number of cases, the larger the minimum difference that can reliably be observed. Before a study is begun, a statistician should be asked to perform a power calculation to ascertain the number of cases required to detect, with desired reliability, the minimum difference regarded as clinically important. Often, the number of cases included in actual studies is inadequate (22). Such studies are referred to as "underpowered" and can lead to errors.

Design Considerations

Prospective studies are almost always preferable to retrospective studies. "Well begun is half done" carries a corollary that "poorly begun is hard to salvage." In a retrospective study, one has to work from someone else's design and data collection, and these are typically far from optimal from the standpoint of your purposes.

The temptation to include in the research everything that might be studied should be resisted, lest the study collapse from its own complexity.

Often, the purpose of a study is to compare two diagnostic tests—for example, to compare a proposed new test with an established one. In this situation, unless data on patient health outcomes and cost must be directly obtained, an optimal design consists of applying both tests to all study patients, with interpretation of each test performed while blinded to the results of the other. In contrast, the common practice of using "historical controls" to represent the performance of the established test is usually a poor choice. The patient population in the historical control may be different, and the execution of the historical series may not meet standards of current best practice.

Reference Standard

The reference standard (sometimes less formally called the "gold standard") needs to be chosen carefully. While a perfect reference standard—one with 100% accuracy—often cannot be attained, it is important to do as well as possible. Methodologists routinely warn (4,22,24) that a reference standard that is dependent, even in part, on the test(s) being evaluated involves circular reasoning, and they say it is therefore seriously deficient, but they note that such standards are nonetheless not infrequently used.

Timing

Timing is important because diagnostic imaging is a field that is changing relatively rapidly. There is little point in undertaking a large-scale study when a new technique is in the initial developmental stage and is changing particularly rapidly; results will be obsolete before they are published. On the other hand, it is not wise to wait until a technique is fully mature because, by then, it will often be widely disseminated, making the study too late for its results to readily influence general clinical practice. Use of techniques that lead to rapid completion of a study, such as gathering data from multiple sites, is highly desirable because imaging evolves relatively rapidly.

Efficacy and Effectiveness

Most evaluations of diagnostic tests—and of any other medical care—are studies of efficacy, which is defined as results obtained under ideal conditions, such as those of a careful research project. Initially, efficacy is important to ascertain, but ultimately, one would want to know effectiveness, which is defined as results obtained in ordinary practice. Effectiveness is usually poorer than efficacy. For example, studies in individual academic institutions—that is, efficacy studies—showed that abdominal CT for patients suspected of having appendicitis significantly reduced the perforation rate and unnecessary surgery rate (25,26), but a study of essentially all hospital discharges in Washington state—that is, an effectiveness study—showed no improvement in either rate between 1987 and 1998, a period when laparoscopy and cross-sectional imaging techniques, including CT, became widely available (27). The systematization necessary for an organized study tends to preclude observation of effectiveness—the study protocol ensures uniform application of the test with its parameters set at optimal levels, and people are generally more careful and consistent and do better

Project Selection and Definition Phase
- Evaluate measures of diagnostic accuracy that are highly clinically relevant
- Use an experienced statistician, involving him or her from the beginning
- Involve the treating physicians from the beginning

Study Design and Start-Up Phase
- Specify the protocol carefully and in detail
- Use a sophisticated statistical analysis, including multivariate techniques
- Hold face-to-face meetings of the full range of study participants at critical points
- Conduct extensive pretesting

Project Operation Phase
- Use existing experienced data management and statistical analysis centers
- Include multiple sites, preferably involving some nonacademic participants
- Hold periodic telephone conference calls
- Have "fill-ins" available in case initial participants drop out and in case—as almost always happens—participants obtain fewer patients per month than they anticipate
- Require participants to have a data manager on site
- Send participants periodic reminders about overdue forms

Figure 2. Additional procedures for enhancement of study quality and rapidity, with particular reference to a study of substantial scale.

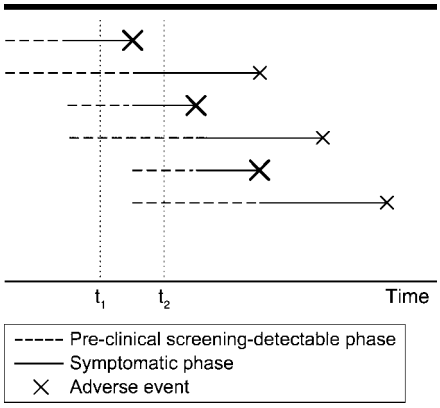

Figure 3. Example of length bias. Half of the cases are the more indolent form (longer preclinical phase, longer symptomatic phase, and less severe adverse events, as shown by a smaller x). At any point in time (*t1* and *t2* are randomly chosen points in time), however, two-thirds of the cases detectable only with screening are indolent.

when they know their activity is being observed (this is called the Hawthorne effect).

Figure 2 lists some additional important considerations for high-quality studies. Sunshine and McNeil (16) discuss the above considerations and those in Figure 2 in more detail.

SCREENING

Screening (28,29) is the performance of a diagnostic test in an asymptomatic population with the aim of reducing morbidity and/or mortality from disease. The requirements of efficacious screening are somewhat different from those of "conventional" diagnostic testing—that is, testing applied to symptomatic patients. These differences apply to the diagnostic test, available treatment, and evaluation of the test.

The Test

Because the prevalence of disease in a screening population is very low—for example, approximately one-half percent in screening mammography—a screening test must be highly specific. Otherwise, false-positive findings will greatly outnumber true-positive findings (even at the relatively high 90%–95% specificity rate for mammography—ie, 5%–10% recall rate—false-positive findings outnumber true-positive findings by 10–20 to 1), and the cost and morbidity of working up patients with false-positive findings will outweigh the gains from early detection in those with true-positive findings. Similarly, the cost and morbidity of the screening test itself (which apply to every patient screened) must be relatively low; otherwise, they will outweigh the gains of screening, which can occur only for the very small percentage of patients with true-positive findings.

In contrast, sensitivity can be modest. For example, screening mammography has an approximate 75% sensitivity, yet it allows us to identify three of every four possible breast cancers that could be detected if the test were perfectly (100%) sensitive. These requirements for a screening test can be somewhat eased if a high-risk population is identified, because the proportion of true-positive findings will increase. Note that while a screening test optimally has high specificity and may only need modest sensitivity, an optimal diagnostic test for symptomatic patients should have a high sensitivity, but the specificity may be modest.

Treatment

Oddly, the available treatment must be intermediate in efficacy. If treatment is fully efficacious—more specifically, if treatment of symptomatic patients is as efficacious and no more costly than the presymptomatic treatment made possible by screening—then nothing is to be gained by identifying disease before it becomes symptomatic. Conversely, if treatment is completely inefficacious—that is, there is no useful treatment for even presymptomatic disease—there is also no possible gain from screening. Screening can only be beneficial if treatment of presymptomatic disease is more efficacious than treatment of symptomatic disease (29–31). (However, some hold that screening for untreatable genetic diseases and other untreatable diseases can be reasonable because parents can alter reproductive behavior and patients can gain more time to prepare for the consequences of disease.) Given these requirements regarding treatment effectiveness for screening to be sensible, new developments in treatment—for example, the introduction of pharmaceuticals such as donepezil hydrochloride (Aricept; Eisai America, New York, NY) that slows the previously unalterable rate of progression of Alzheimer disease—can completely alter the relevance of screening.

Evaluation of Screening

In general, the efficacy of treatment of presymptomatic disease relative to that of symptomatic disease is not known, although this is a critical issue for screening, as indicated in the previous paragraph. The reason for the lack of knowledge is as follows: if screening has not been done previously, relative efficacy simply is not known because presymptomatic cases have not been identified and treated. On the other hand, if the issue is introduction of a more sensitive screening test, one does not know the efficacy of treating the additional, presumably less advanced cases the new test detects. Partly for this reason, evaluation of screening generally has to consist of a randomized controlled trial in which *(a)* the intervention consists of the test and the treatment in combination and *(b)* the end point studied is the death rate, morbidity, or other adverse outcome(s) from the disease being screening for in the intervention population compared with the rates in the control population.

Biases

Three well-known biases (30,32,33) also generally necessitate this randomized controlled trial study design for evaluation of screening tests and generally preclude the use of other end points, such as 5-year survival from time of diagnosis. These three biases should be understood by all radiologists.

"Lead-time bias" refers to the fact that screening will allow detection of disease

earlier in its natural history than will waiting for symptoms, so any measurement from time of diagnosis will be biased in favor of screening, regardless of the effectiveness of treatment. Consider an oversimplified example: For lung cancer, 5-year survival from diagnosis is currently 10%–20%. Assume that CT screening advances diagnosis by 5½ years, but treatment has absolutely no value. Then 5-year survival would nonetheless increase to essentially 100% with screening. In short, survival time in a screened group will incorrectly appear to be better than that in a nonscreened group.

"Overdiagnosis bias" or "pseudodisease" (29,31) refers to the fact that applying a diagnostic test to asymptomatic individuals will identify "positive cases" that will never become clinically manifest in a person's lifetime. Prostate cancer provides a striking example. It is the most common nonskin malignancy in men in the United States, affecting 10% of them, but careful histopathologic examination at autopsy shows microscopic prostate cancers in nearly 50% of men over the age of 75 years (34). If an imaging test as sensitive as histologic examination at autopsy were developed, but early detection had absolutely no effect on outcomes, the percentage of "cases" showing adverse outcomes would nonetheless decrease by four-fifths—but only because four-fifths of the "cases" never would have shown any effects of the disease in the absence of screening and treatment. The general point is that, because of overdiagnosis bias, any study of the outcome of cases identified with a screening test will be biased toward screening, for many of the cases identified with screening would never have had any adverse outcomes, even in the absence of treatment. Incidentally, the morbidity and cost of treating such cases is one of the negative consequences of screening.

"Length bias" can be thought of as an attenuated form of pseudodisease. It arises because cases of a disease vary in aggressiveness, with the faster-progressing cases typically also having a natural history with greater morbidity and mortality. Cases detected with screening are typically disproportionately indolent. This is because slow-progressing cases remain longer in the presymptomatic phase in which they are detectable only with screening and do not manifest symptoms. Thus, a test that helps identify asymptomatic cases disproportionately uncovers indolent cases, as Figure 3 shows. Hence, cases detected with screening disproportionately have a relatively favorable prognosis, regardless of the effectiveness of treatment. Thus, any study of outcomes in cases detected with screening (vs those detected when symptoms occur) will be biased toward screening.

Other Considerations

While change in morbidity or mortality from the disease being screened for is the prime measure of the effect of screening, changes in other morbidity and mortality possibly caused by screening and/or treatment should also be considered. Concerns of this type include surgical complications, chemotherapy toxicity, radiation treatment–induced secondary cancers, radiation dose from screening, patient anxiety, and changes in patient satisfaction.

The percentage reduction in the risk of an adverse effect from the disease being screened for, called "relative risk reduction," is a common measure of the benefit of screening, but this measure needs to be set in context (35). For example, if screening reduces an individual's risk of dying of a particular disease over the next decade from 1.0% to 0.4%, that is a 60% decrease in relative risk, but only 0.6 of a percentage point increase in the probability of surviving the decade.

In conclusion, for any health care intervention, including diagnostic imaging tests, the ultimate questions are, "How much does this do to improve the health of people?" and "How much does it cost for that gain in health?" By using the methods described in this article, we have the ability to answer these questions as we assess the remarkable imaging technologies available today.

References

1. Perry S, Thamer M. Medical innovation and the critical role of health technology assessment. JAMA 1999; 282:1869–1872.
2. Eisenberg J. Ten lessons for evidence-based technology assessment. JAMA 1999; 282: 1865–1869.
3. Clancy CM, Eisenberg JM. Outcomes research: measuring the end results of health care. Science 1998; 282:245–246.
4. Hillman BJ. Outcomes research and cost-effectiveness analysis for diagnostic imaging. Radiology 1994; 193:307–310.
5. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991; 11:88–94.
6. Thornbury JR. Clinical efficacy of diagnostic imaging: love it or leave it. AJR Am J Roentgenol 1994; 162:1–8.
7. American College of Radiology Imaging Network. Contemporary screening for the detection of lung cancer. Available at: *www.acrin-nlst.org/6654factsheet.html*. Accessed August 20, 2003.
8. Weinstein MC, Fineberg HV. Clinical decision analysis. Philadelphia, Pa: Saunders, 1980.
9. Hunink MG, Glasziou PP, Siegel J, et al. Decision making in health and medicine: integrating evidence and values. Cambridge, England: Cambridge University Press, 2001.
10. Chapman GB, Sonnenberg FA. Decision making in health care: theory, psychology, and applications. Cambridge, England: Cambridge University Press, 2000.
11. Janne D'Othee B, Black WC, Pirard S, Zhuang Z, Bettman MA. Decision analysis in radiology. J Radiol 2001; 82:1693–1698.
12. Singer ME, Applegate KE. Cost-effectiveness analysis in radiology. Radiology 2001; 219:611–620.
13. Soto J. Health economic evaluations using decision analytic modeling: principles and practices—utilization of a checklist to their development and appraisal. Int J Technol Assess Health Care 2002; 18:94–111.
14. Kleinmuntz B. Clinical and actuarial judgment. Science 1990; 247:146–147.
15. Tsevat J. SMDM presidential address: hearsay or heresy—are health decision scientists too left-brained? Med Decis Making 2003; 23:83–87.
16. Sunshine JH, McNeil BJ. Rapid method for rigorous assessment of radiologic imaging technologies. Radiology 1997; 202:549–557.
17. Baum RA, Rutter CM, Sunshine JH, et al. Multicenter trial to evaluate vascular magnetic resonance angiography of the lower extremity. JAMA 1995; 274:875–880.
18. Lilford RJ, Pauker SG, Braunholtz DA, Chard J. Decision analysis and the implementation of research findings. BMJ 1998; 317:405–409.
19. Blackmore CC. The challenge of clinical radiology research. AJR Am J Roentgenol 2001; 176:327–331.
20. Kent DL, Haynor DR, Longstreth WT, Larson EB. The clinical efficacy of magnetic resonance imaging in neuroimaging. Ann Intern Med 1994; 120:856–871.
21. Holman BL. The research that radiologists do: perspective based on a survey of the literature. Radiology 1990; 176:329–332.
22. Blackmore CC, Black WC, Jarvik JG, Langlotz CP. A critical synopsis of the diagnostic and screening radiology outcomes literature. Acad Radiol 1999; 6:S8–S18.
23. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD Initiative. Radiology 2003; 226:24–28.
24. Sox H, Stern S, Owens D, Abrams HL. Monograph of the council on health care technology: assessment of diagnostic technology in health care-rationale, methods, problems, and directions. Washington, DC: National Academy Press, 1989.
25. Rao PM, Rhea JT, Novelline RA, Mostafavi AA, Lawrason JN, McCabe CJ. Helical CT combined with contrast material administered only through the colon for imaging of suspected appendicitis. AJR Am J Roentgenol 1997; 169:1275–1280.
26. Sivit CJ, Siegel MJ, Applegate KE, Newman KD. When appendicitis is suspected in children. RadioGraphics 2001; 21:247–262.
27. Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time? a population based analysis. JAMA 2001; 286:1748–1753.
28. Herman CR, Gill HK, Eng J, Fajardo LL. Screening for preclinical disease: test and disease characteristics. AJR Am J Roentgenol 2002; 179:825–831.
29. Black WC, Welch HG. Screening for disease. AJR Am J Roentgenol 1997; 168:3–11.
30. Black WC, Ling A. Is earlier diagnosis really better? the misleading effects of lead time and length biases. AJR Am J Roentgenol 1990; 155:625–630.
31. Morrison AS. Screening in chronic disease. New York, NY: Oxford University Press, 1992; 125–127.
32. Black WC, Welch HG. Advances in diagnostic imaging and overestimation of disease prevalence and the benefits of therapy. N Engl J Med 1993; 328:1237–1243.
33. Morrison AS. The effects of early treatment, lead time and length bias on the mortality experienced by cases detected by screening. Int J Epidemiol 1982; 11:261–267.
34. Brant WE, Helms CA, eds. Fundamentals of diagnostic radiology. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 1999; 825.
35. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988; 318:1728–1733.

Organization: American Gastroenterological Association

(Comment on next page.)

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June 6, 2005

Stephen Phurrough, MD, MPA
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7500 Security Blvd.
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RE: Draft Guidance on Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

The American Gastroenterological Association (AGA) is the nation's oldest not-for-profit medical specialty society, and the largest society of gastroenterologists, representing more than 14,000 physicians and scientists who are involved in research, clinical practice, and education on disorders of the digestive system. The AGA appreciates the opportunity to comment on this guidance document outlining the process for coverage with evidence development.

CMS staff has discussed this guidance document publicly at recent meetings attended by many public stakeholders, including the medical specialty societies. It has been indicated that CMS's intent is to use coverage with evidence development in limited circumstances when there are unanswered questions that would benefit from additional research to assist physicians with clinical decision-making. We request clarification in the final guidance document that it is not CMS's intent to revisit existing current coverage policies and impose data collection requirements as a means of revising or reducing current indications for coverage.

AGA supports CMS's ability to provide coverage with evidence development as an alternative to a noncoverage determination. CMS said that evidence development can be accomplished in a variety of ways, including data registries, post-coverage claims review and evidence-based guidelines. We recommend that CMS work with the affected medical specialties and industry jointly to help design the data collection solution and determine specific well-defined questions to research. CMS should also base evidence requirements

on the specific product or service at issue in the most cost-effective way of collecting the information CMS is seeking.

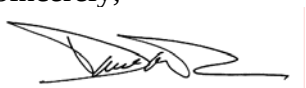
In terms of development of evidence-based guidelines, AGA believes that the physician community should take the lead role but not be the responsible party for funding this development. Industry and/or CMS should bear the costs of the evidence development regardless of the data collection methodology.

AGA requests that during the post-coverage data collection time period that CMS continue to cover Category B clinical trials for both the costs of routine patient care and the medical devices under investigation at contractor discretion. CMS should also permit coverage of Category B clinical trials upon issuance of a national noncoverage decision in order to allow the continued development of evidence and the possibility of a favorable coverage decision in the future.

Lastly, AGA requests that CMS allow a second comment period on this draft guidance document due to the number of concerns and issues for input.

Thank you for consideration of our comments. If we may provide any additional information, please contact Anne Marie Bicha, AGA Director of Regulatory Affairs at 301-654-2055, ext. 664 or abicha@gastro.org.

Sincerely,



David A. Peura, M.D.
AGA President

Organization: American Medical Association

(Comment on next page.)

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Re: Draft Guidance; Factors CMS Considers in Making a Determination of Coverage with Evidence Development (Apr. 7, 2005)

Dear Dr. Phurrough:

The American Medical Association (AMA) appreciates the opportunity to submit our comments to the Centers for Medicare and Medicaid Services (CMS) concerning its draft guidance on *Factors CMS Considers in Making a Determination of Coverage with Evidence Development* (Apr. 7, 2005).

The AMA has long supported the development of data collection systems that maintain high standards of confidentiality, accuracy and fairness. We also support making national coverage decisions based on the best available scientific evidence, as well as systematic, protocol-driven data. The draft guidance, however, raises certain issues that the AMA urges CMS to explore before implementing the requirements under the draft guidance.

Patient Access

It is critical that any Medicare or other government effort to gather data on effectiveness or quality of service appropriately balance the need for the information against the potential to create barriers to patient access. It is possible that linking coverage to data collection could lead to discrepancies in the data and prevent those who most need medical services from having access to them.

If the evidence is sufficient for a service to be covered by Medicare, then all patients who could benefit from that service, device or drug should be able to access it. Patients should

not be denied Medicare coverage for a service for which they qualify in every respect simply because their physician does not or cannot afford to participate in data collection efforts. Medicare should not become an exclusive or two-tiered program, where patients whose physicians participate in data collection are covered and those whose physicians do not or cannot afford to participate will have to pay for the procedure themselves or do without it. This kind of exclusivity could exacerbate existing disparities between majority and minority populations and between urban and rural areas.

Ensure Reliability and Validity of Evidence

The draft guidance proposes that national coverage by Medicare of certain items and services may be linked to a requirement for prospective data collection. While coverage decisions should be based on the best available scientific evidence, there may be obstacles to developing reliable and valid data. CMS should take steps to ensure the utility, reliability and validity of any evidence developed for coverage purposes. For example, if the proportion of patients enrolled in clinical cancer trials who are seniors is lower than the proportion of cancer patients who are seniors, clinical trials may not yield accurate results for seniors with cancer. It is also important that any new clinical trials be appropriately focused to yield information that will be useful to clinicians and policymakers. The AMA cannot support data collection for the sake of data collection. Certain questions must be asked of every clinical trial if it is to be adequately assessed for its value in improving information about the service under study:

1. Are the risks to trial subjects reasonable compared to the anticipated benefits?

   Under the principle of beneficence, any clinical trial should have a favorable benefit to risk ratio. Risks should be minimized such that the risks are reasonable compared to the anticipated benefits.

2. Will the clinical trial improve health and well being and/or increase knowledge?

   A clinical trial should provide social or scientific value by improving health and well being and/or increase our scientific knowledge base.

3. Will the selection of subjects for the clinical trial be fair and equitable?

   Under the principle of distributive justice, there must be fair subject selection based on scientific objectives, not vulnerability or privilege.

4. Does the clinical trial comply with federal regulations relating to the protection of human subjects and, has the trial been reviewed and approved by an Institutional Review Board (IRB)?

Any clinical trial should be in compliance with federal regulations relating to the protection of human subjects. The clinical trial must be independently reviewed for appropriateness and approved by an IRB.

5. Will adequate informed consent be obtained from clinical trial subjects?

   Clinical trial subjects must be sufficiently informed that the study involves research, of the study's purpose, its procedures, of the potential risks and benefits from participation, and of alternative interventions when appropriate. Voluntary written and informed consent must be obtained from each study subject except when consent is waived for research based on emergency, life-saving interventions for unconscious subjects and when family or proxy consent is not immediately available.

6. Does the clinical trial assure that potential and enrolled subjects will be treated with respect?

   Under the principle of individual autonomy, written and informed consent must be provided to assure respect for the rights of study participants. This includes assurance of confidentiality, availability of medical treatment in the event of injury, provision of contact persons who can respond to the subject's research rights and to questions about the research protocol, and an understanding that the subject's participation is voluntary and that no penalty or loss of benefits will incur if the subject withdraws from the clinical trial.

7. Does the clinical trial have a written protocol that shows the study has scientific validity?

   Any clinical trial should have a written protocol that shows the study is methodologically rigorous and, therefore, has scientific validity. The following elements must be addressed (presented in question format for purposes of identifying qualifying criteria):

   a) Is there a clearly stated scientific objective (outcome) for the clinical trial?
   b) Is the clinical trial protocol designed using acceptable scientific principles to answer the research question (e.g., experimental or observational study, appropriate control group, clearly defined inclusion/exclusion criteria for study subjects, and use of measurement tools that will yield reliable and valid data)?
   c) Does the study have sufficient power to definitively test the research question (e.g., adequate sample size and other statistical requirements)?
   d) Does the written protocol provide a plausible data analysis plan?

e) Does the clinical trial protocol include mechanisms to minimize observer, subject, and instrument bias to enhance the study's accuracy?

8. Can the proposed clinical trial be executed properly with respect to investigator expertise, subject recruitment, and logistical and financial resources, and be completed within the proposed time period?

   The facility and personnel conducting the clinical trial must be capable of doing so by virtue of their expertise and/or training. Also, the population of potential clinical trial participants must be sufficient to assure that enough subjects can be enrolled into the trial. Finally, the clinical trial must be adequately funded so it can be successfully completed.

Funding of Clinical Trials and Data Collection Activities

In ensuring that clinical trials and data collection efforts are appropriately focused, CMS needs to ensure proper funding. Often such trials or data collection activities are underfunded and rely on voluntary efforts of physicians and other health care professionals and their staffs, which can lead to inaccuracies in the data as well. CMS should consider making an additional payment to physicians to compensate for the additional costs of participation in a study. Proper funding of clinical trials and data collection efforts will help produce accurate and valid results. In addition, CMS should keep in mind that if funding and other resources are not available to develop data, poor data or little or no data collection will result in little or no advances in medicine.

Administrative Burden

We appreciate that CMS acknowledges in the draft guidance that the "potential value of information generated through coverage linked to evidence development must be carefully considered in the context of the burden associated with the collection of this data." We urge CMS to carefully consider whether the effort and resources required to collect data are justified by the value of the information that will be generated. The physician community cannot absorb additional unfunded mandates, especially on top of expected Medicare payment cuts of 26% over six consecutive years, beginning January 1, 2006, as well as ongoing paperwork burdens, and skyrocketing medical liability premium costs. Physicians are the cornerstone of the Medicare program, and, to maintain the viability and quality of the program, physicians must be able to continue to afford to treat Medicare patients.

Further, CMS states that evidence development requirements should "assure that no unnecessary costs are imposed." The draft guidance also discusses that data collection should involve the "least resource-intensive mechanisms possible" and that "greater adoption and use of health information technology by providers in all settings has the

potential to significantly reduce the burden associated with observational and experiential data collection."

The AMA strongly agrees that evidence development requirements should not impose unnecessary costs. We urge CMS, however, to also consider the potentially necessary cost burden of data collection. If physicians cannot absorb these costs, they will not be able to undertake data collection efforts. This can only hamper progress in extending important new technology and services to Medicare patients. In addition, many physician practices, which operate as small businesses, are not able to invest in health information technology, especially in rural areas. Thus, CMS should ensure that funding for data collection and investment in health information technology is readily available. If physicians cannot afford to develop and collect data, patients could lose access to needed services, as discussed above.

Funding of Newly Covered Medicare Services

There is already a serious problem with funding for newly-covered Medicare services. CMS does not recognize the cost of providing these services in calculations of the sustainable growth rate (SGR) target, which is the formula for updating Medicare payments for physicians' services each year. As discussed above, the Medicare Trustees are forecasting six years of consecutive steep Medicare physician pay cuts, totaling about 26% in payment cuts. Yet, to date, CMS, when calculating the SGR target for allowable Medicare spending on physicians' services, does not reflect in the target the increased physician spending due to national coverage decisions.

CMS has expanded Medicare coverage of implantable cardioverter defibrillators, diagnostic tests and chemotherapy treatment for cancer patients, carotid artery stenting, cochlear implants, pet scans for Alzheimers disease, and photodynamic therapy to treat macular degeneration. While not every coverage decision significantly increases Medicare spending, taken together, even those with marginal impact contribute to increased use of physicians' services.

Some coverage expansions are expected to have a major impact on spending. The recent expansion of coverage for implantable defibrillators is expected to make this device available to some 500,000 people, with CMS anticipating that 25,000 will receive the device in the first year alone. Expansion of the use of photodynamic therapy for treatment of macular degeneration is conservatively estimated by the National Opinion Research Center (NORC) to increase expenditures by more than $300 million a year and could boost spending by more than twice that amount if used by all the eligible Medicare beneficiaries.

While the AMA strongly supports Medicare beneficiary access to these important services, physicians and other practitioners should not have to finance the costs resulting from the attendant increased utilization. Requirements for data collection will further increase

physicians' costs. Some economic resources must be identified to fund the data collection efforts, without exacerbating the SGR problem.

We appreciate the opportunity to provide our views on the draft guidance concerning factors to be considered in making a determination of Medicare coverage with evidence development, and we look forward to working with CMS in addressing the issues raised above.

Sincerely,

Michael D. Maves, MD, MBA

Organization: American Podiatric Medical Association

The American Podiatric Medical Association (APMA) has reviewed the document, Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development.

In general, we support the decision by the Centers for Medicare & Medicaid Services (CMS) to describe factors CMS may consider in a decision to extend national coverage for certain items and services with coverage linked to a requirement for prospective data collection. We recognize that the collection of additional information may be useful in determining that a treatment is reasonable and necessary while also serving to ensure the safety of those receiving the treatment in question. Additionally, we believe that coverage with evidence development may better ensure that Medicare beneficiaries have appropriate access to new medical technologies and services at an earlier stage. Finally, we believe that this approach could result in decreased costs and improved outcomes to the healthcare system.

The draft document refers to the "quality of the evidence available" as the core consideration in determining when an item or service is reasonable and necessary and whether it improves net health outcomes. How the quality of the evidence will be assessed is not defined in the draft and we request that CMS define what it means by "quality."

The APMA is encouraged by the commitment from CMS to seek collaboration from stakeholders because we believe it imperative that interested parties, including podiatric physicians, have the opportunity to be actively involved in the data collection and evaluation of outcomes process.

The draft discusses the need to minimize the financial and other resources required to obtain the data and recommends using the least resource-intensive mechanisms possible. Greater adoption and use of health information technology by providers is seen as reducing the burden associated with the collection of data. We believe that advancements in information technology will certainly support the use and measurement of protocols much better. While we agree that this may be the best way to collect data, we believe there is cause for concern regarding who will be collecting the data and evaluating the connection between services provided and outcomes. We urge CMS to carefully construct the process for data collection and outcomes analysis.

In summary, we believe that the introduction of coverage with evidence determination may be positive for Medicare beneficiaries, as well as for all providers. We look forward to working cooperatively with CMS as it applies this new type of coverage.

Organization: American Society for Therapeutic Radiology and Oncology

(Comment on next page.)

ASTRO
American Society for Therapeutic Radiology and Oncology

June 6, 2005

Steve Phurrough, M.D., M.P.A.
Director, Coverage and Analysis Group
Mail Stop C1-12-28
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

Dear Dr. Phurrough,

The American Society for Therapeutic Radiology and Oncology (ASTRO)[1] appreciates the opportunity to provide comments on the "Factors CMS Considers in Making a Determination of Coverage with Evidence Development" issued on April 7, 2005. In general, we are supportive of the coverage with evidence development (CED) initiative, which is intended to provide Medicare beneficiaries with faster and broader access to an item or service while also providing support for doctors and patients to use the technology effectively in individual cases. However, we have specific concerns that are described below in our comments on the major sections of the draft guidance document. We look forward to working with CMS and other stakeholders in addressing these concerns and in developing a final guidance document that will meet the goals of CMS and help improve the medical care of its beneficiaries.

Background

CMS cites Section 1862(a)(1)(A) of the Social Security Act as the statutory authority for linking coverage decisions to the collection of additional data. This section of the statute states that Medicare may not provide payment for items and services unless they are "reasonable and necessary" for the treatment of illness or injury.

The draft guidance describes and gives examples of two types of circumstances when the CED initiative may be considered:

1) When a particular medical intervention has been demonstrated to improve health outcomes in a broad population of patients, but the assurance that individual patients are receiving medically necessary care would be significantly more likely to occur when specific data is collected; and,
2) When a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit.

CMS believes that in both cases collection of data for evidence development helps ensure that the care provided to individual patients will improve net health outcomes.

[1] ASTRO is the largest radiation oncology society in the world, with more than 8,000 members who specialize in treating patients with radiation therapies. As a leading organization in radiation oncology, biology and physics, the Society is dedicated to the advancement of the practice of radiation oncology by promoting excellence in patient care, providing opportunities for educational and professional development, promoting research and disseminating research results and representing radiation oncology in a rapidly changing socioeconomic healthcare environment.

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We question whether the first circumstance is appropriate for CED since the demonstration of improved health outcomes should be a sufficient basis for concluding that a service is "reasonable and necessary." If there is sufficient evidence to demonstrate improved health outcomes, the cost of collecting additional data under protocol for a particular subpopulation may not be justified. We also question the CMS premise that the act of collecting data on a particular subpopulation might lead the physician "to reevaluate the original conclusions, alter the management plan, and potentially improve health outcomes."

We believe the second general circumstance is appropriate for CED and that it is the one with the greatest potential to provide Medicare beneficiaries with faster and broader access new technologies.

In this section of the guidance document, CMS also states "It is not the intent of this approach to reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program." We believe local coverage is critical to assuring beneficiary access to care. Unfortunately, it has been our experience that many carriers are less willing to grant coverage for a new item or service if CMS has decided to subject the item or service to a national coverage decision (NCD). Under the new CED initiative, CMS must make a firm commitment to instruct the carriers to continue making coverage decisions under the discretion that is provided to them in CMS regulations and manual instructions. If this is not done, it is likely that CED will lead to restrictions in coverage, rather than expansions in coverage as envisioned by CMS.

Factors Considered in Applying CED

CMS provides an initial list of nine circumstances in which coverage with data collection might be valuable and poses a series of questions about this list. Our responses and comments are as follows:

- Safety issues related to drugs and devices are appropriately handled by FDA, not CMS. Before initiating CED because of safety concerns, CMS should demonstrate why FDA post-marketing surveillance is insufficient for collecting safety data.
- CMS includes utilization and costs in its list of outcomes for which CED might be appropriate. We believe it is acceptable to consider utilization and costs when setting priorities for national coverage decisions but that it is unacceptable to consider utilization and in the context of an NCD itself. In other words, we do not believe CED should be applied if a possible outcome is non-coverage of an item or service simply because it is frequently used or it is costly, especially if there is demonstrated evidence of improved health outcomes. In fact, we believe such an outcome would be a violation of the reasonable and necessary provisions of the statute that preclude payment for items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. There is no reference to cost in this section of the statute and we are unaware of any other section of the statute that would permit consideration of only costs in the context of determining whether an item or service is reasonable and necessary.
- Many of the items on the CMS list describe important issues for which further research is needed. For example, CMS identifies the need for comparative effectiveness studies of new items and services compared to existing alternatives or to usual care. We acknowledge the importance of all the identified research issues but question the appropriateness of CED as the means for obtaining needed data since the CMS is a payer, not a research entity. We appreciate CMS' statement that they plan to carefully consider all ongoing publicly and privately funded clinical studies to ensure that there is a need for additional data collection that is linked to coverage. This is an important principle that must be incorporated into the final guidance document.
- The evaluation of interventions for rare conditions such as the use of orphan drugs and humanitarian use devices through CED is unlikely to generate useful data. We believe decisions regarding rare conditions are best handled at the local carrier level with input from the local medical community.

Process for Deciding When and How to Apply CED

In this section, CMS asks a series of questions related to process. As a preface to our responses that follow, we wish to thank CMS for all the steps it has taken to date to make the process for coverage decision-making more open and transparent.

- We support the use of the Internet as a vehicle for obtaining public input. We recommend a link in the Coverage section of the CMS website for CED where the public would be given the opportunity to comment on NCDs that might involve CED. This section should include all existing and proposed NCDs that involve data collection and provide information about the following items that are listed on pages 13 and 14 of the draft guidance document:
    - The individual or organization responsible for providing scientific oversight
    - The hypotheses
    - The data collection methods
    - The sample size
    - Plans for patient safety and monitoring
    - Timeframe
    - Training requirements
    - Patient confidentiality and protection
    - Data security and quality assurance
    - Efficiency and data collection burden
- CMS should consider using the FDA workshop approach to obtain public input because it provides a meaningful opportunity for dialogue with the agency and all stakeholders. Public meetings where CMS simply listens to public comment without interacting with the public are not very useful.
- We believe there will need to be a second draft guidance document based on the public comments CMS receives on this first draft. There are many complex issues that require further public debate before a final guidance document is released. We also encourage CMS to recognize that the guidance document will need to be revised as more experience is gained with its use. We recommend that CMS look to the FDA guidance documents and their development process as a model.

Evidence Development Methods

In this section of the guidance document, CMS states they will avoid stipulating the use of a particular design, recognizing that data collection protocols will vary according to the item or service being provided, the purpose of the data collection, and the group of patients receiving the item or service.

We believe that clinical research and study designs are so complex and so far removed from the day-to-day activities of CMS that CMS should consider the use of an outside body to establish a framework for purposes of informing coverage decisions under CED. In addition, we offer the following comments specific to the field of radiation oncology:

- Many of the patients treated by radiation oncologists have advanced disease and poor prognoses, which makes enrollment in clinical trials problematic. Numerous studies have proven that higher doses of radiation delivered to cancerous tumors are better than lower doses and that higher doses of radiation delivered to normal tissue are more harmful than lower doses. Thus, when technological advances permit higher doses of radiation to tumor and/or lower doses of radiation to normal tissue, it is generally accepted that it would be unethical to do randomized trials comparing older technologies with the newer technologies.
- Any study that involves radiation oncology must take into account the severity of disease of the patients under study to avoid the risk of obtaining misleading or inaccurate findings. Otherwise, the result could be that coverage will be inappropriately restricted to technologies that are not as beneficial or are more harmful to normal tissues than newer technologies.

Process for Study Design and Implementation

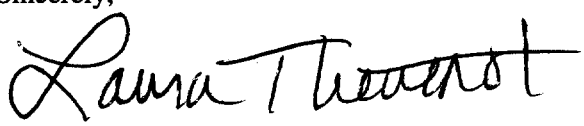
In this section of the draft guidance document, CMS acknowledges that when they require evidence development they must be assured that there is appropriate oversight of data collection enterprises and an efficient operations system. In the questions for the public, numerous critical issues are identified. Our responses and comments are as follows:

- We believe that study oversight and implementation should be handled by qualified investigators without potential conflicts of interest. We believe CMS has a potential conflict of interest that precludes the agency from having primary responsibility for study oversight and implementation.
- An important oversight and operational issue not identified in the draft guidance document relates to the Federal policies for the Protection of Human Research Subjects that are included in Title 45, Part 46 in the Code of Federal Regulations. It is essential that any research conducted under CED comply with these regulations. We are concerned that any NCD that restricted coverage to only those beneficiaries who agreed to participate in a clinical trial or other type of study could be viewed as coercive since coverage would not be available if the beneficiary exercised their rights not to participate in a study.
- The duration of studies and the closure of data collection should be determined prospectively, consistent with the need to answer specific evidence questions.
- There must be a firm commitment by CMS to assure that the results of all studies and data collected under CED are made widely available, preferably through publication in the peer-reviewed medical literature.
- Physicians who participate in clinical research currently bear considerable uncompensated costs, including patient counseling, data collection, and the extra staffing required to comply with trials' requirements. If CMS plans to impose new data collection requirements on physicians, it must offer adequate compensation for these costs. We agree that CED should use the "least resource-intensive mechanisms possible," but we also urge CMS to reimburse physicians for the remaining costs. In addition to compensation for the costs described above, CMS also should assist with the costs of developing the information technology infrastructure needed for data collection.

Conclusion

We appreciate the opportunity to submit comments on the important issue of coverage with evidence development (CED). We trust you will find our comments helpful and we look forward to working with you in the future. If you have any questions, please contact Ms. Trisha Crishock, ASTRO's Director of Health policy and Economics, via telephone at 703-502-1550 or by e-mail at trishac@astro.org, and she will be happy to assist you in any way possible.

Sincerely,



Laura Thevenot
ASTRO, Executive Director

Organization: American Society of Clinical Oncology

(Comment on next page.)

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Re: Comments on the Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

As the leading medical society for physicians involved in cancer treatment and research, the American Society of Clinical Oncology (ASCO) is pleased to offer comments on the Draft Guidance concerning Medicare Coverage with Evidence Development (CED). ASCO is dedicated to evidence-based cancer care and thus supports the Centers for Medicare & Medicaid Services (CMS) in its efforts to combine expanded coverage for new technologies with a data collection process that will enhance the available information for patients and physicians alike.

CMS sets out a number of questions in the Draft Guidance. Many of the answers depend heavily on the clinical question of interest and therefore ASCO would like to work with CMS to answer these questions. ASCO's general comments are set forth below.

Background

The Draft Guidance sets forth circumstances in which CMS might extend national coverage for certain items and services with this coverage linked to a requirement for prospective data collection. One such circumstance, seen recently in the coverage decision for implantable cardioverter defibrillators, might be where there is evidence of improved health outcomes in a broad population but CMS wishes to collect more information on which patients are most likely to benefit from the intervention. A second circumstance where CED might be pursued would be where there is insufficient evidence to make a coverage decision, and CMS would extend coverage to items or services that are being studied in clinical trials or subject to data registries outside the clinical trial context.

Permanency of Coverage

To the extent that CED truly represents an expansion of existing coverage, ASCO endorses it. ASCO also supports the collection of data on safety, efficacy, and clinical benefit, both in quality clinical trials and in reliable data registries. Nevertheless, we are somewhat concerned by the absence of discussion in the guidance about the circumstances in which access to items and services under CED might be withdrawn

based on the data collected through that process. ASCO does not advocate continued payment for items or services that have been definitively established as having no clinical benefit, but the degree of evidence that would be required to terminate access under CED deserves further consideration. ASCO asks that CMS provide more specific information about how the collected data will affect the coverage determination, at what time intervals CMS will review the data, and how that review will affect or modify the existing CED.

Recognition of Statutory Framework

Since 1993, the Medicare statute has recognized the importance of off-label uses of cancer drugs and has thus compelled coverage of such uses if supported by referenced medical compendia; in addition, coverage of cancer drugs cannot be less than the scope of the FDA-approved labeling. Under §1861(t)(2) of the Social Security Act, drugs or biologics in an anticancer chemotherapeutic regimen are covered for "any use which has been approved by the Food and Drug Administration," as well as for other uses not approved by FDA if such off-label uses are cited in certain listed medical compendia.

While we appreciate that CMS has no intention of using the CED process to restrict existing coverage (Draft Guidance, p. 6), we believe the cancer community would be reassured if the Guidance explicitly recognized the special coverage terms that apply to cancer drugs by statute. Given the significance of these provisions for cancer patients and their health care providers, it would seem prudent to state expressly that nothing in the Guidance will interfere with the statutory scope of coverage for cancer drugs.

Local Carrier Discretion

ASCO has concerns that the new CED policy would interfere with the ability of individual Medicare contractors to make positive coverage decisions that are more liberal than the scope of national coverage. The document indicates no intention to change the local coverage determination process, but we would request more detail on how the new CED system will interface with that process. In addition, we believe that CMS should affirmatively tell the Medicare carriers that they are not limited by the CED or registries in determining coverage.

Coverage of Drugs in Clinical Trials

ASCO recommends that CMS cover the drugs in any clinical trials that qualify for coverage of routine patient care under the statute. For example, ASCO previously commented in December 2004 on the CMS national coverage decision with respect to off-label uses of colorectal cancer drugs, expressing serious concern about the terms and scope of the coverage. Specifically, ASCO raised questions about the limited number of clinical trials in which off-label coverage of colorectal cancer drugs would be extended, together with the fact that coverage was available only in trials sponsored by the National Cancer Institute (NCI). We remain concerned that this coverage decision is apparently going forward as originally conceived even though questions remain unanswered as to why and how the nine trials qualifying for coverage were designated. There is reason to believe that, as currently constituted, access to these important colorectal cancer drugs will be constrained and unevenly distributed in the nine designated trials.

ASCO continues to believe that coverage should extend to colorectal cancer drugs included in any clinical trial that would qualify for coverage of routine patient care costs under the 2000 national coverage

decision. In addition, if CMS decides to use the CED process for coverage of drugs in clinical trials, then the covered trials should be those deemed by the 2000 coverage decision.

Administrative Burdens

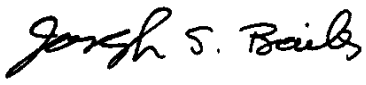
Acceptance of the CED process by the cancer community depends largely on the extent to which CMS can adopt procedures and policies that fairly reimburse providers for their efforts in data collection. Participating in this process will clearly add significant administrative costs including, but not limited to, physician and staff time. The additional administrative costs will strain most cancer care providers in this time of decreasing reimbursement for cancer care. ASCO believes that CMS should consider a reasonable payment that would cover the additional administrative costs of collecting the data.

If CMS proceeds with CEDs for cancer care, it should ensure that all Medicare beneficiaries – including those in Medicare Advantage plans – have their services covered. In addition, CMS should develop transmittal and reporting methodologies that make the information readily accessible to patients and providers. Although a substantial part of the rationale for the CED process is to provide information for consumers, primarily patients but also physicians, it is not clear how the data will be collected and reported to make it user-friendly as well as accurate and timely. ASCO requests that CMS provide more information as to how it will handle data management and dissemination.

Conclusion

If CMS decides to move forward with CED affecting cancer care and delivery, ASCO would like to work with CMS to develop the necessary tools to make the CED program practical, including bringing the appropriate health services and other experts to the table. ASCO appreciates the work of the CMS Coverage and Analysis Group and CMS Administrator Mark McClellan, M.D., in their continued efforts to expand coverage for Medicare beneficiaries while also striving to collect data to support the goal of evidence-based quality cancer care.

Sincerely,



Joseph S. Bailes, MD
Co-chair, Government Relations Council

Organization: Amgen

(Comment on next page.)

Joshua J. Ofman, MD., MSHS
Vice President, Reimbursement
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June 6, 2005

Re: Comments on the "Coverage with Evidence Development" (CED) Draft Guidance.

Dear Drs. McClellan and Phurrough,

Amgen Inc. is pleased to provide comments on the guidance titled *"Factors CMS Considers in Making a Determination of Coverage with Evidence Development [*CED*]"* (the Draft Guidance). Amgen is a leading, global biotechnology company. Our research mission is to discover therapies that treat grievous illnesses and address unmet medical needs. We support the production and promotion of scientific knowledge that enhances health outcomes, patient safety, and quality of medical care. As a science-based organization, we routinely generate evidence demonstrating judicious use of our licensed products across a variety of indications. In addition, we spend hundreds of millions of dollars annually on research and development to find new, innovative therapies that improve patients' lives.

Improvements in patients' lives are also facilitated by carefully developed coverage and evidence generation policies. Care must be taken to ensure that these policies do not

inadvertently produce market access barriers or unduly increase the time and expense required for drug development, which could hinder the discovery and approval of breakthrough therapies. Researchers and manufacturers continually face important trade-offs in drug development including the number of molecular compounds to be promoted for additional investigation, the depth of information to be studied per molecule, and the breadth of indications that should be pursued. Due to the limited amount of R&D investment available, the costs of pursuing these endeavors play an important factor in these "go, no-go" decisions. Increased evidence requirements for successful product commercialization will have a dramatic impact on innovation because this diverts funds from research on pipeline products to supporting commercialization of licensed products. Stringent research requirements for reimbursement lower both the number of therapeutic compounds that we can study as well as the depth of evidence that can be established on any given product. Furthermore, drug development requires long-term capital investments, frequently lasting greater than 10 years. Predictable, reasonable, and transparent coverage policy is needed to promote capital investments, stimulate innovation, and make the appropriate clinical development and trade-off decisions necessary to advance novel therapies to the marketplace to serve patients.

As the CED policy is developed, CMS should consider the macroenvironment of evidence development and fit the policy to address areas where evidence development is unlikely to germinate and where coverage expansion is needed. Evidence development is an integral part of the pharmaceutical and biotechnology industries. Academia, private sector and industry researchers have many incentives to develop evidence on technology interventions. These incentives include establishment of safety and efficacy for regulatory approval, product differentiation from competing agents, proof of a product's value proposition to payors, and attainment of compendia listing and publication in peer-reviewed literature. All of these factors contribute to obtaining adequate coverage and reimbursement from local contractors and private payors.

In addition the reimbursement market is becoming more evidence-based, further stimulating manufacturers to provide as much credible evidence as possible and in a timely manner. Evidence on product effectiveness facilitates reimbursement of physician-administered therapies. For oncology products, physicians have been reluctant to prescribe large amounts of off-label chemotherapy[1] due to concerns about coverage and reimbursement. Historically this was an area of concern,[2] prompting the Congress to create alternative mechanisms for obtaining coverage such as compendia listing and peer-reviewed evidence for off-label uses of anticancer agents. These statutory mechanisms require an evidence-based approach to achieve listing in a compendia or publication in a journal, again stimulating pharmaceutical and biotechnology manufacturers to produce credible and valid evidence for both licensed and pipeline products.

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[1] Please see the Pharmaceutical Research and Manufacturers Association comment letter for specifics about the off-label survey of oncologists by Covance, Inc.

[2] *See* GAO, "Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies" (Sept. 1991) (GAO/PEMD-91-14) (report to the Chairman, Sen. Comm. on Labor and Human Resources) ("GAO Report"), at 4. As a result of the GAO findings, Congress amended the Social Security Act as part of the Omnibus Budget Reconciliation Act of 1993 (OBRA '93) to extend uniform Medicare coverage to off-label uses of anticancer drugs and biologicals.

Moreover, academic scientists and clinical investigators are continually gathering evidence on new uses of approved products across a variety of conditions and subpopulations. This research, which is funded through a variety of private and public sources, leads to innovation and advances in treatment. As evidence about off-label effectiveness becomes established, technology diffusion occurs.

We submit that for most therapeutic areas the U.S. is rapidly moving into a marketplace where evidence precedes off-label use not the other way around. With or without a CED policy in place, this evidence-based local reimbursement environment is unlikely to tolerate unsubstantiated widespread off-label use.

CMS has publicly stated that the CED policy will be used rarely and only for purposes of coverage expansion.[3] [4] We agree with CMS that CED is only appropriate under such circumstances, and add that evidence development policies should predominantly focus on situations where evidence of effectiveness is not present, is unlikely to develop, and is needed for improving patient access. CMS should exercise discretion in applying this policy equally to drugs and biologics as compared to devices or other items and services. CMS should consider the extent of regulatory hurdles for each item and service when considering application of CED.

We recommend revising the Draft Guidance so that the scope is more clearly defined and the Draft Guidance is used in a way that is consistent with CMS statutory authority. We request CMS to reissue new Draft Guidance on this topic after greater in-depth consideration of this issue.

A. Statutory Basis for CED

Amgen appreciates that CMS is attempting to support the development of a more substantial body of evidence supporting technology, but we are concerned that the use of coverage policy for this purpose may not be consistent with statutory intent. CMS should provide assurance that the Draft Guidance will not interfere with the accepted statutory framework of reasonable and necessary for coverage of drugs and biologicals. We believe that some aspects of the Draft Guidance are unclear in this regard.

CMS's authority in this arena stems from the Social Securities Act (SSA § 1862(a)(1)(A)), which prohibits payment under the Medicare program for any expenses incurred for services "which are not 'reasonable and necessary' for the diagnosis or treatment of illness or injury to improve the functioning of a malformed body member." Legal questions could be raised if the agency were to use CED only to develop better evidence regarding items or services, which appears to be one of the rationales included in the Draft Guidance.

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[3] Open Door Forum "Draft Guidance Document on Coverage with Evidence Development (CED)", May 9th, 2005.

[4] CMS Plans Limited Use of "Coverage with Evidence Development" Option, The Pink Sheet, Vol 67, No. 020, page 15, May 16th 2005.

While we support CMS in its endeavor to develop a transparent and predictable coverage policy, we have found nothing to support the idea that Congress intended CMS to use the coverage process for "supporting the development of better scientific knowledge." Moreover, Congress has passed legislation that provides mechanisms *outside* the coverage process to advance scientific knowledge. For example, Section 1013 of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (the MMA) authorizes the Agency for Healthcare Research and Quality (AHRQ) to "conduct and support research to meet the priorities and requests for scientific evidence and information identified by [Medicare and certain other programs]" subject to certain requirements. Among other things, AHRQ must "ensure that there is broad and ongoing consultation with relevant stakeholders in identifying the highest priorities for research," and CMS "may not use data obtained in accordance with [Section 1013] to withhold coverage of a prescription drug." Adopting restrictions on coverage simply to generate evidence would essentially circumvent these statutory requirements.

Indeed, using the coverage process in this manner does not address the medical needs of an individual beneficiary seeking the item or service, but rather may provide evidence years later regarding that item or service. In the long history of CMS issuances in this arena – from the first proposed rule to the various notices that it has issued, while CMS has noted the need for clinical evidence that supports coverage (which is certainly something we support), it has always made the touchstone of coverage whether there was current evidence that supports the use of the product or service to meet the needs of its beneficiaries.[5]

The notion that items and services are more "reasonable and necessary" in data collection settings is not consistent with past regulations, statutory authority, or Congressional intent. We submit that questions about quality of care across settings of care are a separate and independent issue from determination of the "reasonable and necessary" standard, which should be based on whether an item or service is needed for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.[6] We urge CMS to support medical technologies that improve patient safety, allow greater ease of administration, simplify medical processes of care, improve adherence, and facilitate patient satisfaction and convenience of care. Along with other measures, these endeavors will improve the quality of medical care.

We request CMS to revise the Draft Guidance so that it is consistent with its statutory authority. We are concerned about the unintended consequences of a CED policy that is not carefully designed and administered.

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[5] *E.g.* 65 Fed. Reg. 31124, 31126 (May 16, 2000) (a national coverage decision is a policy that applies to some beneficiaries and describes the clinical circumstances under which it will be available); 54 Fed. Reg. at 4384 (use evidence to assess whether a service is accepted in the medical community for the condition for which it is used).

[6] 142 U.S.C. § 1395y(a)(1)(A).

B. Unintended Consequences of Current Draft Guidance

The frequent application of internally generated national coverage determinations (NCDs) with CED for drugs and biologicals could result in 1) diverting resources away from important basic science and clinical research by reshaping the national research agenda, 2) increasing cost of drug development with resulting reductions in innovation and increases in drug prices, 3) restricting patient access, 4) limiting physicians' ability to practice medicine and reducing quality of medical care, and 5) generating biased or less clinically relevant evidence.

1. National Research Agenda

CMS must realize that the CED policy reshapes and reprioritizes the national research agenda. By issuing or sponsoring research studies within an NCD, as in the collaboration with the National Cancer Institutes trials for the colorectal cancer drugs, CMS has influenced the allocation of eligible trial participants, the types of studies that will be performed and the quantity and quality of future research in a particular therapeutic area. Such activities must be carefully deliberated and analyzed, as the consequences of such reallocation affects the type of information that is generated. CMS should coordinate with other agencies such as the Agency for Healthcare Research and Quality and the National Institutes of Health with regard to the impact of CED sponsorship on other initiatives.

CED initiatives sponsoring comparative drug analysis, while important, can be costly as well as time consuming. Should the majority of research dollars fall predominantly on such expensive studies the availability of resources for other studies could be insufficient. Initiatives promoting comparative effectiveness research should carefully consider the quality and scientific rigor of these endeavors as well as the stability of the payor-relevant research questions. Since drug comparative trials are time consuming, advances in clinical management could render the results of these trials, which cannot change protocol and technologies easily, irrelevant to payors by the time of publication. Because CED will necessitate reallocation of research funds, a conscientious and explicit deliberation should be undertaken so that stakeholders will know what questions will go unanswered due to reprioritization of evidence collection efforts.

2. Drug Development Costs

The cost of drug development affects manufacturers' innovative capacity, investment decisions and research trade-offs, as well as pricing decisions.[7] Due to the intensive, risky and slow process of drug development, experts estimate that the average cost per successful product launch is $800 million dollars or higher.[8] Higher development costs lead to higher drug prices as manufacturers attempt to recoup drug development expenses. The Department of Health and

[7] F.M. Scherer, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," *Health Affairs*, vol. 20, no.5 (September – October 2001).

[8] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003; 22:151-85.

Human Services (HHS) and the FDA have been concerned about these costs and have sought means to decrease the cost of development through their "Critical Path" initiative.[9]

CED policies could run counter to these initiatives if additional research demands are placed on drug manufacturers. Prior to issuing CED, CMS must recognize that newly approved drugs will always have uncertainty surrounding their precise contribution to health and safety, especially for uses in diseases or subpopulations that were not originally studied. Nevertheless, society has adopted these technologies because they are FDA-approved and the clinical risk/benefit assessment suggests significant potential for net benefit despite the aforementioned uncertainty. Should technology use become restricted until conclusive evidence is established many patients will have gone untreated and effective patent life of products would dramatically decrease, making the business model for drug development untenable.

Previous experience in Europe demonstrates the deleterious effects of market access barriers and price control policies on R&D and subsequent innovation.[10] Today, approximately 67% of phase III and preclinical testing is conducted in the U.S. compared with only 18% in Europe.[11] Furthermore the quantity of innovative products produced by European industry has decreased since price controls have been implemented.

From the manufacturer's perspective, the potential consequences of an overly stringent CED policy are:

- **Higher development costs due to more stringent evidence required for coverage.**
- **Inhibition of research and development in therapeutic areas with restrictive coverage environments or difficult evidence hurdles,** with implications for the types of products that will be brought to market and corresponding impairment of innovation.
- **Reductions in a product's effective patent-protection period** due to limitations in technology use and market access barriers among certain populations.

As mentioned before, CED directly impacts innovation because it would require drug manufacturers to spend more on coverage approval, which diverts funds from investigating promising pipeline candidates or label expansions. CMS has stated in the Draft Guidance process that evidence collection should not be burdensome[12], but has not outlined how they will evaluate

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[9] US Department of Health and Human Services – Food & Drug Administration. *Innovation Stagnation – Challenge and Opportunity on the Critical Path to New Medical Product,* March 2004.

[10] U.S. Department of Commerce, International Trade Association, *Pharmaceutical Price Controls in OECD Countries: Implications for U.S. Consumers, Pricing, Research and Development, and Innovation,* Washington D.C., December 2004.

[11] Charles River Associates, *Innovation in the Pharmaceutical Sector: A Study Undertaken for the European Commission* (London: Charles River Associates, 8 November 2004), http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/nov/EU%20Pharma%20Innovation_25-11-04.pdf (accessed 31 May 2005).

[12] Draft Guidance, page 14.

burden to researchers and manufacturers and the opportunity costs of CED. We request CMS to explicitly consider these issues in the next Draft Guidance.

3. Patient Access

Medicare beneficiaries are older, have a higher disease burden, are more likely to be disabled or on dialysis, and are poorer than patients who are insured through the private sector. These factors place Medicare beneficiaries at particularly high risk of poor health consequences if restrictive coverage policies limit access to needed treatments. Empirical data demonstrate that lack of adequate coverage or excessive cost sharing is associated with poor health outcomes and increased health services utilization.[13] [14] [15] Coverage limitations across several chronic conditions have been associated with increases in ambulatory and emergency room visits, as well as increased direct medical costs.[16]

CED policy can only increase access to technology if existing local coverage policies did not cover the item or service or failed to do so within a reasonable timeframe. Most local contractors cover FDA-approved drugs and biologicals in a timely fashion. Indeed, CMS should carefully consider the impact of NCD with or without CED on patient access relative to the standard local coverage processes that the manufacturer would have gone through.

For those beneficiaries involved in the CED-sponsored studies, burdensome evidence collection requirements such as filling out baseline and follow-up registry forms may discourage use of the therapy. If the process of enrolling and qualifying for coverage became cumbersome, many patients and their physicians could be deterred from using the item or service that would have otherwise been prescribed. It is unclear whether the CED policy will allow for additional reimbursement for physicians and investigators involved in data collection. Failure to reimburse for this additional time and service may impact participation in research.

CMS should also consider whether CED would disproportionately affect beneficiaries with lower income and those from other vulnerable populations who are historically underrepresented in clinical trials. Special care must be taken to ensure that coverage policies do not aggravate existing gender and ethnic health disparities in clinical trial enrollment or health outcomes. CMS should assess how its policies affect access for those living in rural areas.

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[13] Lurie N, Ward NB, Shapiro MF, Gallego C, Vaghaiwalla R, Brook RH. Termination of Medi-Cal benefits. A follow-up study one year later. *N Engl J Med*. 1986;314(19):1266-1268.

[14] Lurie N, Ward NB, Shapiro MF, Brook RH. Termination from Medi-Cal—does it affect health? *N Engl J Med.* 1984; 311(7):480-484.

[15] Rice T, Matsuoka KY. The Impact of Cost Sharing on Appropriate Utilization and Health Status: A Review of the Literature on Seniors. Kaiser Foundation. 2004. http://www.kff.org/medicare/med120104oth.cfm. Last accessed 04/28/05

[16] Soumerai SB, McLaughlin TJ, Ross-Degnan D, Casteris CS, Bollini P. Effects of a limit on Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. *N Engl J Med.* 1994; 331(10):650-655.

4. *Physician's Ability to Practice Medicine and Impact on Quality of Medical Care*

CED policies may also impact providers' ability to deliver appropriate care. Limiting coverage to certain medical centers or physicians will reduce quality of care for patients and providers who are excluded and therefore cannot gain access to important technology. If the item or service affected by such a CED policy were an innovative new drug or biological, physicians may not be able to practice medicine according to new standards of care. Physicians who care for patients outside of these trial sites will have fewer therapeutic options, which could jeopardize patient health and reduce quality of medical care.

5. *Quality of Clinically Relevant Evidence*

As currently written, the Draft Guidance fails to provide direction to researchers and manufacturers involved in CED. Specific details that are required but not included in the guidance are identification of the problem statement, methodology specifics such as sample and power calculations, articulation of the specific research questions, understanding of the clinical relevance of potential findings, policy implications of the results, and prioritization of such endeavors relevant to alternative questions that need to be answered.

For example, uncontrolled registry or observational studies are not designed to answer questions about comparative drug effectiveness. Should these studies be employed to answer such questions, there is high likelihood of arriving at either inconclusive or biased results. The Draft Guidance does not provide sufficient detail to inform stakeholders on when registries are required, what problems it is trying to address, and what information it will yield. Retrospective data may also provide biased or inconclusive results, as identification of key variables or cofactors may not be available or the quality of the data may be poor. CMS must realize that good quality research starts with asking the correct research question. Clear articulation of the research question informs all other aspects of research including study design, enrollment criteria, sampling methods, power calculations, ethical considerations, and analytical plan. The consequences of a poorly articulated research question are development of faulty or biased data, or engagement in data dredging exercises and its inherent risk of making spurious inferences.

C. Recommendations

Due to aforementioned concerns, the new coverage guidelines need to be carefully constructed to improve the transparency, predictability, and scientific rigor of the Medicare coverage process while not denying patients access to necessary therapy. As a science-based and patient-centered company, we are pleased to provide constructive comments and specific recommendations about the 1) scope of CED, 2) criteria for applying CED, 3) means to improve transparency of the NCD and CED processes, and 4) safeguards for protecting beneficiaries' access and producing required evidence.

1. *Reissue new Draft Guidance and clearly articulate scope of CED*

CMS should reissue a new Draft Guidance document that is more consistent with statements made in the Open Door Forum and other documents on this topic. For example, in the notice for the CED Open Door Forum, CMS stated:

> CED is intended to be limited to only those items and services that would normally be covered under the NCD process. For example, the NCD process does not generally apply to self-administered drugs or outpatient prescription drugs payable under Part D.
>
> CED will only be used in those instances where an NCD has been opened and the evidence is less convincing and would have resulted in non-coverage.

These statements indicate limited use of CED. However, in the Draft Guidance, CMS issues a broad list of circumstances that would encompass practically every possible item or service. In the Open Door Forum, CMS stated it would use CED in limited and narrow circumstances but the Draft Guidance states CMS "intends to apply CED to issues with the greatest potential benefit for Medicare beneficiaries and the Medicare program," which signifies broad and frequent use of the CED policy.

In addition, CMS has offered conflicting primary reasons on why it needs to apply CED. Page one of the Draft Guidance states that CED will be used for setting payment determinations. However, in the open door forum, CMS has stated that it will be used primarily to inform patients and physicians. CMS should provide stakeholders with greater clarity about the scope and use of CED.

Consistent with the Open Door Forum discussion, CMS should clearly state in the next draft that:

- CED will not be applied if access is already provided or will likely be provided by local contractors
- CED can only be issued in the context of an NCD
- CED will not be applied to Part D drugs

We believe that further drafts of this guidance should specifically address detailed circumstances that require CED, the levels of evidence that are sufficient to grant conditional vs. unconditional coverage, termination of CED policy, specifically when data collection efforts would stop and the subject would be reevaluated for expanded coverage. After reissuing a new draft, CMS should provide adequate time, at least 90 days, for comment so that stakeholders can fully understand and respond to this complex issue.

2. *Revise the criteria for initiating CED*

In the Draft Guidance document, CMS asks for specific comment on when it would be appropriate to use CED. We have considerable concerns about the use of CED, particularly

given its description in the draft document. The criteria listed in the Draft Guidance[17] are vague, lack specificity, and make the process of CED unpredictable. CED should be limited to coverage expansion and modeled on the coverage expansion that the agency provided in 1995 through the investigational device exemption ("IDE") regulations consistent with its prior interpretations of the key statutory language.

Prior to 1995, the agency took the position that medical devices that were not approved by the Food and Drug Administration ("FDA") were experimental and thus were not "reasonable and necessary" under section 1862(a)(1)(A) of the Social Security Act ("SSA"). In a final rule issued on September 19, 1995, the agency decided to expand Medicare coverage for medical devices by authorizing coverage for investigational devices used in accordance with an FDA-approved protocol and "for which the FDA has determined that the device type can be safe and effective. For example, we will consider for possible coverage those investigational devices that are of the same type as a device for which a manufacturer has received FDA clearance or approval for marketing." [18] The IDE policy truly was an expansion of Medicare coverage and has provided Medicare beneficiaries with greater access to new medical device technologies.

We believe that any use of CED should follow the model of the IDE policy and should only be used to increase Medicare coverage of certain items and services. To that end, the agency's use of CED should be limited to instances in which:

- there is inadequate evidence for CMS to determine it would make a positive national coverage decision and there has been a prior national non-coverage decision on the use of the item or service; and
- the agency wants to supplement the local coverage process (which would remain available under existing agency policy) with a mandated expanded coverage under certain conditions that provide for beneficiary protections and access to the item or service.

CMS should not issue CED for a drug or biological that:

- is used in accordance with its FDA labeled indication(s); or
- is used for an unlabeled indication listed in a major drug compendium or supported by peer-reviewed literature; or
- is believed to be medically acceptable by local contractors as safe and effective for an unlabeled use; or
- is used for an unlabeled indication that has been found generally by contractors to be the accepted standard of medical practice; or
- is new to the market and the scientific community has not had time to study it in different settings.

[17] Draft Guidance, pages 9-10

[18] 60 Fed. Reg. 48417, 48418-19.

Applying CED under these circumstances would be consistent with agency practice in many respects. It is consistent with statutory authority for off-label coverage[19] and practices established in the Medicare manual.[20] As already explained, it would be consistent with another interpretation of the "reasonable and necessary" statutory language in the IDE context. Further, it is consistent with the approach taken in the PET scan NCD, which provides for expanded coverage for indications that remain nationally uncovered. Finally, we believe that this approach is consistent with the agency's view of its coverage mandate as ensuring that Medicare funds are "expended only for medical services that are appropriate to meet an individual's medical needs." [21] We believe that the use of CED we have articulated above is more faithful to the statute and the regulatory history of Medicare coverage than those described in the Draft Guidance or for using CED simply to obtain additional clinical evidence for future use.

3. Implement a "screening phase" to improve the transparency, predictability, and scientific rigor of the NCD with CED process

In response to the "*Factors CMS Considers when Opening an NCD*" Draft Guidance, many stakeholders urged CMS to issue a "queue", a waiting list, or screening phase in the NCD process. This phase would alert stakeholders to items and services CMS is evaluating for an NCD. Prior to an NCD being officially issued, time spent in discussions during the screening phase would not count toward the statutory timeframes for completing an NCD. During this phase, CMS should engage in dialogue with directly affected stakeholders, examine evidence available on the item or service in question, and reach agreement that criteria for opening a national coverage assessment has been achieved. Discussions of the need for an external technology assessment or an MCAC review can also take place during this phase.

CMS and stakeholders should jointly analyze the need for CED within this phase. CMS officials have publicly stated that CED would only apply within the NCD process. We urge CMS not to engage in internal assessments of evidence and CED without engaging with directly affected stakeholders first. CED discussions should only occur for those items and services publicly listed on the waiting list or queue. CMS should also clarify, apriori, what levels of evidence are sufficient for CMS to issue an unconditional or unrestricted coverage decision. CMS should clearly state when CED ends and what would occur if CED results are inconclusive.

Throughout this process, CMS should work with affected stakeholders to determine the best way to achieve a positive coverage determination.

CMS should also consider having an independent third party, such as the MCAC, determine if the CED is required to meet the "reasonable and necessary" standard if disagreement persists between the Agency and directly affected stakeholders.

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[19] 42 U.S.C. § 1395x(t)(2)(B). This definition was added to the Medicare statute by a provision in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) entitled "Uniform Coverage of 'Off-Label' Anticancer Drugs."

[20] Medicare Benefit Policy Manual, Chap. 15 § 50.4.5.

[21] 54 Fed. Reg. 4302, 4303 (Jan. 30, 1989).

4. Ensure safeguards of evidence development in all CMS policies to prevent the aforementioned unintended consequences

To avoid the previously mentioned unintended consequences, certain evidence related safeguards are required to improve the transparency of the NCD and CED process:

a) **Evidence should be conducted in a manner that maximizes internal validity and determines whether an item or service is "reasonable and necessary"–** Coverage is determined by finding that the item or service is "reasonable and necessary". Therefore, CED should be conducted to maximize the probability of finding internally valid or non-biased information on this topic. This requires a protocol driven process that includes 1) determination of the problem statement, 2) finalization of specific research questions, 3) listing of primary and secondary endpoints, 4) identification of sample population, 5) statistical and analytic plan, 6) quality control and assurance, and 7) transparent evaluation and communication of results with relevant stakeholders. The choice of study design is contingent on the specific research questions and the types of evidence that will be needed for determining "reasonable and necessary."

   CMS should hold itself to the same standards that it applies when critically appraising data during a national coverage determination's evidence-based reviews. CMS-sponsored research should be of high quality. It would be problematic if CMS-sponsored research were not accepted by the very peer-reviewed journals that CMS informs its local contractors to use for determining off-label coverage decisions.

   CMS should consult with directly affected stakeholders of the technology to determine this protocol. Given the large opportunity costs and the limited supply of research dollars, the costs of evidence collection must carefully considered. Evidence should not be collected simply to provide interesting information or generate hypotheses.

b) **Allow for four types of coverage decisions** – In the Draft Guidance, CMS has stated that it no longer anticipates issuing unrestricted coverage decisions. We believe this statement is inconsistent with the "reasonable and necessary" language. To stay consistent with the statutory requirements for coverage and existing CMS policy, four types of coverage decisions should be available: 1) no coverage, 2) conditional coverage, 3) unconditional coverage, and 4) no national policy, decisions deferred to local contractors. The last type of decision was recently issued by CMS for radioimmunotherapy agents[22] as well as the drugs in the anticancer NCD.[23]

c) **Evidence collection protocols must meet well-established ethical standards –** The scientific community abides by certain ethical standards established over the years by

[22] Proposed Decision Memo for Radioimmunotherapy for Non-Hodgkin's Lymphoma (CAG – 00163N)

[23] NCD for Anti-Cancer Chemotherapy for Colorectal Cancer (110.17)

landmark doctrines such as the Belmont report[24] and the World Medical Association Declaration of Helsinki.[25] Evidence development policies should also conform to these standards. Furthermore, institutional review boards should examine protocols to determine the impact on patient access and health disparities for minority patients and women, as well as to ensure that certain fundamental principles of human subjects research[26] are upheld. For example, the principle of justice in the Belmont report requires "fairness of distribution". As per the report, "an injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly." CMS should carefully examine if its policies abide by these principles.

d) **Evidence development should be targeted, feasible and mindful of the research opportunity costs and total study costs.** Coverage with evidence development should not be burdensome on participants or their physicians. The evidence development project should not deter patients and physicians from selecting needed therapy. Evidence development should not create a market access barrier. Evidence development has opportunity costs, which represent research opportunities foregone. CED will necessitate reallocation of research funds, and a conscious deliberation should be undertaken so that stakeholders will know what questions will go unanswered due to reprioritization of evidence collection efforts. For these reasons, the costs of running the CED research studies should be minimized.

e) **Evidence development should not duplicate ongoing or planned clinical trials -** Frequently manufacturers have clinical trials ongoing or planned to investigate salient questions. Government-sponsored trials should not create additional resource appropriations for research that duplicates trials that are already in progress or are planned by the private sector.

f) **The results of evidence collection should be carefully examined before inferences of causality are presumed -** Causality is typically established when 1) there is a reasonable temporal association between cause and effect, 2) the effect is unlikely to be attributable to concurrent disease or other medicines, 3) a clinically reasonable response follows withdrawal, and 4) the information is reproducible. Evidence development plans should not be presumed to demonstrate causality until these criteria are fulfilled.

g) **The level of evidence required to inform policy must be decided early in the process –** The results from the evidence collection effort should be shared amongst

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[24] *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Department of Health, Education and Welfare, April 18th 1979.

[25] *World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

[26] As per the Belmont report, the fundamental principles of human subject research are 1) respect for persons, 2) beneficence, and 3) justice.

all directly affected stakeholders and the process for arriving at conclusions agreed upon by all parties. Should there be significant ambiguity about the conclusions due to the limitations of the data, these limitations and conclusions must be clearly articulated to patients and physicians so that they can weigh the evidence for its worth. The process by which this is performed must be open, transparent, and predictable.

5. *Describe the format of the CED policy*

The format for the study protocol should be described in the Draft Guidance. CMS, in consultation with the affected stakeholders(s) should clarify for each decision:

- the rationale for issuing the CED decision,
- why the CED decision is consistent with agreed-upon criteria in the consensus guidance documents,
- the results of the value of information analysis,
- how the data will establish that the item or service is "reasonable and necessary,"
- the problem statement that CMS is attempting to address,
- the specific research question that needs to be addressed to determine if the item or service is "reasonable and necessary,"
- the study design and criteria for patient selection,
- the sample size,
- the quality assurance mechanisms to ensure appropriate data collection,
- the data analysis plan,
- the informed consent form, and
- the budget for the study as well as the sources of study funding.

6. *Reinforce local coverage during the NCD and CED processes.*

In the Draft Guidance (page 6), CMS states that it does not "anticipate circumstances under which CED would represent a net reduction in coverage available under local coverage policies." CMS should ensure that local contractors continue with existing coverage policies while an NCD or CED evaluation is underway. Any ongoing local coverage should not be disrupted, as many patients may not be eligible for participating in the CED studies. Medicare beneficiaries are older and may have difficulty participating in research studies. CMS should clearly state that local contractors have the discretion to provide access outside of the CED requirements.

D. Conclusion

Amgen supports development of a transparent, predictable, and rigorous Medicare coverage policy. This requires ensuring that the CED policy is well-grounded in its strong statutory basis and prevents unintended consequences that adversely impact patient access, physicians' ability to offer important therapies, quality of medical care, drug development costs, and the quantity, quality and types of research performed. For these reasons, CMS should consult with directly affected stakeholders throughout the NCD and CED processes. CMS should discuss the need for

CED prior to initiating the NCD so as to give researchers and manufacturers adequate time to prepare.

We believe CMS should not finalize the draft until it gets in-depth feedback from patients, physicians, researchers, and manufacturers. The reissued document should inform researchers and manufacturers of the scope of the CED policy, to what items and service it would apply, what levels of evidence are sufficient, when it ends, and how to obtain a positive or unrestrictive coverage decision.

Amgen looks forward to collaborating with CMS on these and other Draft Guidance documents on coverage policy. If you have any questions, please contact myself or Parthiv Mahadevia, MD, MPH, at (202) 585-9637.

Thank you,

Joshua Ofman, MD, MSHS

cc: Dr. Barry Straube, Acting Chief Medical Officer, Acting Director of the Office of Clinical Standards and Quality, CMS
Dr. Steve Phurrough, Director, Coverage and Analysis Group, CMS

Organization: Association of Community Cancer Centers

(Comment on next page.)

The premier education and advocacy organization for the oncology team

Association of Community Cancer Centers

June 3, 2005

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Re: Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

On behalf of the Association of Community Cancer Centers (ACCC), I appreciate this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) "Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development" (Draft Guidance). ACCC is a membership organization whose members include hospitals, physicians, nurses, social workers, and oncology team members who care for millions of patients and families fighting cancer. ACCC's more than 700 member institutions and organizations treat 45% of all U.S. cancer patients. Combined with our physician membership, ACCC represents the facilities and providers responsible for treating over 60% of all U.S. cancer patients.

ACCC is committed to ensuring that cancer patients have access to the entire continuum of quality cancer care, including access to the most appropriate cancer therapies. We share CMS' interest in developing better evidence for use by patients, physicians and policymakers. All of our members depend on valid clinical data to provide the best quality care to their patients, and many of our members are involved in the clinical research that produces these data. We believe that continued clinical research is essential to improving patient care and must be a priority for all stakeholders involved in cancer care, including CMS. We also recognize that many patients, particularly the elderly, are not eligible to participate in clinical trials and must be assured access to appropriate therapies even if they do not participate in evidence development.

CMS proposes to use coverage with evidence development (CED) to allow Medicare beneficiaries access to items and services while collecting clinical data about those treatments. Although we support these goals in principle, we are concerned that CED, as described in the Draft Guidance, will not achieve these objectives. The Draft Guidance is confusing and conflicts with both the agency's oral descriptions of CED and its recent application of it in national coverage determinations (NCD). Until these contradictions are resolved, we cannot be confident that CED will be used in a predictable, transparent, and open manner or that it will successfully encourage research and expand beneficiary access to care. We urge CMS to incorporate its clarifying statements and comments from ACCC and other stakeholders into a new draft of the guidance document with an additional comment period. We strongly recommend that CMS include the following points in its next draft of the guidance document.

1. CED will be used very rarely and never will be used for on-label uses of drugs[1] or off-label, compendia listed uses of drugs used in an anti-cancer chemotherapeutic regimen;

2. CED only will be used to expand access to care and will not be used to curtail access to therapies currently covered through the local coverage process;

3. CED will not be used to force patients or providers to enroll in clinical trials;

4. CMS will apply CED in a manner that minimizes increased costs for beneficiaries and providers;

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[1] Throughout these comments we use the term "drugs" to refer to both drugs and biologicals.

5. When CMS uses CED, it must use data collection methods that fully acknowledge the heterogeneity of the Medicare population; and

6. The decision to use CED will be made after consultation with stakeholders, including providers, and will be made only at the request of trial sponsors who believe Medicare coverage could help a trial move forward.

We discuss these recommendations in more detail, as follows.

I. CMS' authority to apply CED is unclear.

Before discussing our detailed suggestions for the Draft Guidance, we note our uncertainty about CMS' authority to apply CED. CMS says its authority to use CED is derived from Section 1862(a)(1)(A) of the Social Security Act, authorizing Medicare payment only for items and services that are "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Historically, CMS and its contractors have exercised this authority to determine whether an item or service is "reasonable and necessary" for a particular patient, based on the evidence available. In contrast, the Draft Guidance describes CMS as using this authority, not to make payment decisions now, but to promote research for use in future coverage decisions. Furthermore, during the Open Door Forum, CMS staff acknowledged that the data collected under the use of CED for implantable cardioverter defibrillators might not rise to the level needed for use in coverage decisions, but could be useful for patients and physicians. This suggests that CMS is using CED to encourage research for purposes unrelated to its authority as a payer for health care services. We believe that CMS must continue to use the coverage process as it always has – to ensure Medicare beneficiaries' access to appropriate treatment options, based on available evidence today – and should not transform the process to create a new research role for CMS. We look forward to the forthcoming draft guidance document on the agency's interpretation of "reasonable and necessary" in the context of coverage determinations.

II. CED must be used rarely and never for items and services expressly covered by statute.

ACCC thanks CMS for meeting with us to discuss CED during the comment period. Agency staff made several important clarifications of the scope of CED during our meeting with the agency and May 9, 2005 Open Door Forum on the Draft Guidance. These statements include:

1. CED will be used rarely and in narrow circumstances;

2. CED will not be used for on-label uses of drugs;

3. CED will not be used where there are statutory coverage requirements, such as for off-label uses of drugs that are used in an anticancer chemotherapeutic regimen and for which the use is listed in a compendia or is supported by peer-reviewed literature; and

4. CED will be used only when requested by a trial sponsor who approaches CMS and asks for help with Medicare payment to enable a trial to move forward.

We greatly appreciate these clarifications, and we believe they must be included in the next draft of the guidance document on CED to clarify when, and for what therapies, CMS will and will not consider using CED. Although the Draft Guidance claims that CMS "does not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirement,"[2] CMS' recent use of CED in several NCDs, including the internally-generated NCD on anticancer chemotherapy for colorectal cancer, has raised concerns about the agency's plans. The clarifications listed above would help to ensure that CED is used in a transparent and predictable manner. We urge CMS to reiterate these statements in the next draft of the guidance document. Once these clarifications have been made, we will be happy to provide more detailed comments on other questions CMS raised in the Draft Guidance and the appropriate use of CED.

To provide greater clarity about the use of CED, we also request that CMS clarify its statement that it "does not anticipate issuing additional decisions" without conditions.[3] This statement has caused concern among stakeholders. We urge CMS to clarify that "coverage with conditions" does not mean that CED will be used in every NCD. CMS should explain in the next draft that "coverage with conditions" refers to coverage limited to beneficiaries with specified diagnoses, test results, or other characteristics or when performed in certain facilities, as is the case with most recent NCDs.

In addition, we recommend that CMS acknowledge a fourth outcome to the NCD process. The Draft Guidance lists three possible outcomes: non-coverage, coverage with conditions, and coverage without conditions. CMS has reached a fourth outcome, however, when there is insufficient evidence to change its coverage policy for an item or service. In these cases, CMS may continue to allow Medicare

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[2] Draft Guidance, at 2.

[3] Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development, Apr. 7, 2005, at 4.

contractors to decide whether to cover the item or service. CMS recently made such a decision in its NCD for radioimmunotherapy for non-Hodgkin's lymphoma.4 This option permits contractors to protect beneficiary access to care when CMS does not have adequate evidence to support a change in coverage policy and CED is not appropriate. We urge CMS to recognize this option in the next draft by stating that the NCD process may result in four types of coverage decisions: (1) non-coverage; (2) coverage; (3) coverage with evidence development; and (4) no national decision, with coverage left to the discretion of local contractors.

Finally, we recommend that CMS create one draft guidance document for drugs and another for devices. This would allow CMS to discuss its plans for each type of product in further detail and with a greater recognition of the differences in the Food and Drug Administration's data requirements for approval of drugs and devices. Should CMS decide to keep drugs and devices together in one document, the agency should create different sections for each of these types of technologies, allowing more specificity as to how CED could be applied to each.

III. CED must be used only to expand access to care and will not be used to curtail access to therapies currently covered through the local coverage process.

ACCC strongly supports Medicare's local coverage process because it allows beneficiaries access to innovative therapies, based on clinical evidence and in conformity with evolving standards of care. By statute, carriers must cover off-label uses of anticancer drugs when such uses are supported by citations in certain compendia or by clinical evidence in peer-reviewed literature.5 CMS' longstanding instructions to carriers also allow coverage when the use is "determined by the carrier to be medically accepted generally as safe and effective for the particular use."6 This process ensures that Medicare coverage adapts to new discoveries in cancer care and allows carriers the discretion to make appropriate coverage decisions based on an individual patient's needs. We are pleased that the Draft Guidance recognizes the importance of this process to protecting access to care. CMS notes that "it is not the intent of this approach to reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program. We also do not anticipate

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4 Proposed Decision Memo for Radioimmunotherapy for Non-Hodgkin's Lymphoma (CAG-00163N), May 4, 2005, http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=38.

5 Social Security Act § 1861(t)(2).

6 Medicare Benefit Policy Manual (CMS Pub. 100-02), ch. 15, § 50.4.5.

circumstances under which CED would represent a net reduction in coverage available under existing local coverage policies."[7]

We are concerned, however, that Draft Guidance's vague descriptions of CED will not ensure expanded access to critical cancer therapies. As we noted in our comments on the anticancer chemotherapy for colorectal cancer NCD, CMS' approach to CED could be a slight expansion of access by specifically applying CMS' existing clinical trial coverage policy to certain trials, or it could severely restrict beneficiaries' access to care.[8] Although CMS claimed that the NCD was a coverage expansion, we are not able to determine yet whether it has had that effect. We recommend that CMS monitor and report on the care provided after this NCD, and all other NCDs that use CED, to ensure that contractors continue to provide coverage. In future decisions, we urge CMS to ensure that CED is used only to expand access to care by including a statement that the NCD is not meant to interfere in any way with a carrier's discretion to determine whether other uses are medically accepted. It should not be used to curtail access to therapies currently covered through the local coverage process.

IV. Medicare should support clinical research, but must not use CED to force patients to enroll in clinical trials.

As we stated above, ACCC believes that clinical research is essential to improving patient care. Clinical research yields benefits for all patients, either through direct participation in trials or through implementation of improved treatment regimens based on trial results. We believe that Medicare should encourage all beneficiaries to participate the most appropriate clinical trial for their condition and care needs. Beneficiaries' choice of treatment options would be greatly enhanced if providers were encouraged to participate in trials too. We urge CMS to revise its coverage and payment policies for clinical trials to assist more patients and providers to participate in research projects.

First, instead of selecting a few trials for coverage, we urge CMS to expand access to all clinical trials by finalizing the agency's criteria for coverage of clinical trials under the 2000 NCD. This NCD currently covers the costs of routine services in qualifying clinical trials, including trials sponsored by the National Institutes of Health and other federal agencies.[9] Other trials, such as those

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7 Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development, Apr. 7, 2005, at 6.

8 Letter from Patti A. Jameson-Baker, President, ACCC, to Mark McClellan, Administrator, CMS, Dec. 30, 2004.

9 National Coverage Determinations Manual § 310.1.

sponsored by industry or other groups, currently are not eligible for coverage, but could be if CMS finalized its criteria. Finalizing these criteria would expand beneficiaries' choice of trials and would help physicians determine whether a trial is covered, making it easier to advise Medicare beneficiaries about their treatment options.

Second, CMS should evaluate its payment policies to ensure that providers are compensated adequately for the costs of participating in clinical research. The American clinical trial enterprise is vastly underfunded and relies on providers' donations of time and resources. Many of the costs of participating in clinical research, such as data collection, patient consent forms, screening and counseling, regulatory reporting, extra staffing, and drug administration services, are not compensated by trial sponsors. For example, the per patient cost incurred by an ACCC member practice participating in SWOG study for breast cancer is between $7,000 and $11,000 (depending upon whether cost of the drug is included or excluded, respectively), of which the practice will be reimbursed approximately $1,725. The figures do not include the significant costs associated with patient follow-up (including record storage, phone calls, and audits) once treatment is completed which may not be fully compensated by insurers or trial sponsors. Several of our members estimate that only one-quarter to one-third of follow-up costs per patient are ever covered on a clinical trial. Caring for cancer patients is often a life-long endeavor because of the necessity to monitor for long-term sequelae of treatment, the risk of second cancers, and the need for overall surveillance strategies.

As Medicare revises its reimbursement rates for drugs and drug administration services, and as physicians face payment cuts under the Medicare physician fee schedule, many providers are likely to find themselves unable to afford to participate in research. We urge CMS to develop methods to reimburse providers for their uncompensated non-routine costs. For example, CMS could create G-codes with appropriate payment for evaluating a patient's eligibility for clinical trials. Finalizing its criteria for coverage of clinical trials also would help ensure that providers are reimbursed for their routine costs, such as drug administration services that are not paid by trial sponsors, in a larger number of trials. These changes would ease providers' financial burden of participating in clinical trials and would encourage more providers to offer trials as treatment options for their patients.

We also believe that Medicare must acknowledge that trials may not be the best treatment option for all beneficiaries and must ensure access to innovative care for patients who do not participate in trials. Approximately three

percent of adult cancer patients are enrolled in clinical trials,10 and only a small fraction of those patients are over age 70.11 There may be several reasons why so few seniors participate in cancer clinical trials. First, approximately 85 percent of Medicare beneficiaries are ineligible to participate in clinical trials due to comorbidities and complications. If Medicare coverage for innovative therapies requires participation in a clinical trial, these patients unfairly would be denied access to life-saving care. Second, patients might choose not to participate if a trial would require them to experience significant inconvenience, such as traveling long distances for care or having to change physicians. Beneficiaries in rural areas, for example, might not want to receive care far away from their friends and family. Patients often are reluctant to leave the physicians and nurses they know and trust to participate in clinical trials. Medicare beneficiaries must have access to the treatment they need, regardless of whether they participate in a clinical trial. CED must not be used to provide access to care only to those beneficiaries who meet a trial's eligibility criteria and elect to participate.

ACCC believes that mounting a massive education effort may encourage greater patient and physician participation. A public interest campaign, developed by researchers, providers, payors, and patient groups, as well as CMS could help educate patients about clinical trials and the importance of participating in them. Using CMS' existing education resources for Medicare beneficiaries would be an essential element of this campaign. Additionally, payors could use patient counseling about clinical trials and screening for trial eligibility as a quality measure for oncologists. Education also remains a key element in garnering physician participation in clinical research. This could be achieved by better educating providers about clinical trials' eligibility requirements and the Cancer Trials Support Unit (CTSU), which assists physicians with enrolling patients in clinical trials and streamlines data entry and collection.

Although many Medicare beneficiaries are ineligible to participate in clinical trials due to co morbidities, some meet the eligibility criteria. Physicians often assume that all seniors are ineligible, however, and fail to offer trials as treatment options. Better physician education by trial sponsors, NCI, and CMS would help to address physicians' apparent age bias and would ensure that Medicare beneficiaries are offered the opportunity to participate in appropriate clinical trials. CMS should work with NCI to be certain that no clinical trial eligible for CMS payment contains an arbitrary age restriction. We also recommend that CMS work with NCI to make

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10 Centers for Disease Control and Prevention, United States Cancer Statistics: 2001 Incidence and Mortality, http://apps.nccd.cdc.gov/uscs/index.asp?Year=2001.

11 National Cancer Institute, Facts and Figures About Cancer Clinical Trials, http://www.cancer.gov/clinicaltrials/facts-and-figures.

the CTSU less cumbersome in order to better streamline the process of integrating clinical trials into clinical practice.

V. CMS should apply CED in a manner that minimizes increased costs for providers and beneficiaries.

We agree that evidence development requirements should assure that "no unnecessary costs are imposed"12 on providers. Our members can attest to the significant costs of participating in trials and registries. As we noted above, providers who participate in clinical research currently bear considerable uncompensated costs and are less able in the current reimbursement environment to support these efforts. Any new data collection requirements must use the "least resource-intensive mechanisms possible"13 and must be accompanied by reimbursement for the remaining costs. In addition to compensation for the costs described above, CMS also must assist providers with the costs of developing the information technology infrastructure needed for data collection.

We also urge CMS to be sensitive to patients' costs of participating in clinical trials. Currently, trial sponsors, including pharmaceutical companies, provide the drug under investigation and may other drugs and services provided in a trial at no cost to the patient. Thanks to these sponsors' support, patients are not liable for most of the costs of participating in clinical trials. It is not clear how CED will affect this system of trial support. If manufacturers are dissuaded from donating their drugs, patients' costs of participating in trials could increase substantially. We are particularly concerned that patients would be liable for Medicare's 20% co-payment in a CED trial but would be able to get the drug at no cost in another trial. We strongly recommend that CMS ensure that its coverage proposals do not discourage industry support for clinical trials or increase beneficiaries' costs of care. The agency must clarify in its revised guidance that CED will be applied in a manner that weighs and minimizes any increased costs for beneficiaries.

VI. When CMS uses CED, it must use data collection methods that fully acknowledge the heterogeneity of the Medicare population.

In the Draft Guidance, CMS indicates a preference for "simple, inexpensive clinical studies," such as databases and large trials.14 We are

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12 Draft Guidance, at 5.

13 Draft Guidance, at 5.

14 Draft Guidance, at 11-12.

concerned that these methods will not produce the evidence patients, providers, or CMS need to make a coverage decision, and would not be an effective use of CMS' resources. To produce useful data, these studies must be applied to a uniform population. In practice, however, cancer patients are highly varied and so too would the data be that CMS proposes to collect. Even among patients with the same stage of disease, there is significant heterogeneity in terms of patient and tumor characteristics. A one-size-fits-all approach to research, such as the use of databases or simple trial designs, would fail to capture the vital distinctions among patients' conditions and their responses to treatment. Registries, for example, may be impractical or ineffective for studying treatments that are used in a small patient population or in combination with several other therapies.

We urge CMS to consult with knowledgeable stakeholders to identify the data collection methods that are most likely to answer important clinical questions. The current trend in cancer clinical trial design is to construct laboratory-driven protocols to determine the best treatment approach for a particular patient. This approach has the potential to produce significant advances in cancer care. It can increase our understanding of the biology of tumors and may lead to more accurate predictions of treatment efficacy and prognosis for any individual patient. By identifying the specific drug, or combination or sequence of drugs, that is best suited for a tumor, we will be able to use the growing number of targeted therapies more successfully (for example, EGFR inhibitors and anti-VEGF compounds), with less risk of toxicities. We already have seen the benefits of this approach in the use of Herceptin for breast cancer and Gleevec for gastrointestinal stromal tumors. These new paradigms of clinical trial design, integrating concepts of tumor biology and pharmacogenomics, offers our best hope to determine the best use of cancer therapy.

This approach is more likely than some of CMS' proposed data collection methods to produce useful data for cancer care, but also is costlier and much more complex than CMS' methods. To perform this type of research, we must acquire tumor tissue. Although we have developed highly organized tissue banks, such as those created by the United States Cooperative Groups, expanding these collections to support expanded research would difficult and costly. Tissue collection requires extensive patient and physician education and is highly regulated. We doubt that effective research can be conducted through simple or inexpensive means, and we urge CMS to acknowledge the significant investment necessary to expand meaningful research.

VII. <u>The decision to use CED must be made after consultation with stakeholders.</u>

We agree that CMS should work "consultatively and iteratively with external experts and stakeholders in developing the criteria and process for

determining when to apply CED."15 Because CED will impose significant burdens on providers of the applicable treatment, CMS must decide to use CED only after discussing its usefulness and effects on patient access to care with all relevant stakeholders, including providers. We appreciate that CMS has included patient groups, medical professional associations, practicing physicians, physician group practices, and hospitals among the stakeholders whose input will be considered when establishing priorities for the use of CED16 and expect to see that statement included in the final guidance document.

It is equally important, however, that the agency consult with providers and other key stakeholders about the initial decision to move forward with a NCD and the decision to use CED for specific items or services. Our input can help CMS ensure that CED is used only when there is a real need for additional evidence about an item or service, and not just a concern about the therapy's cost. If additional data are needed about an item or service, knowledgeable stakeholders, such as our members, can help define the research questions to be asked and identify the most effective study design to answer those questions. We agree that the "potential value of information generated through coverage linked to evidence development must be carefully considered in the context of the burden associated with the collection of the data."17 Our members' expertise in trial design and implementation would help CMS evaluate the costs and benefits of applying CED to a particular therapy. This evaluation is especially important for cancer research because the heterogeneity of the disease and its patient population makes it difficult to gather relevant data from the "simple, inexpensive clinical studies" that are "essential to optimizing CED."18 To ensure that data collection instruments are "designed to minimize any burden to providers and patients while providing critical information,"19 we urge CMS to consult with stakeholders who understand both the value and costs of researching complex diseases.

Finally, we agree that a "systematic expansion of practical clinical research efforts to address the needs of health professionals and patients"20 would be valuable, but we are deeply concerned that CED is neither an appropriate nor

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15 Draft Guidance, at 9.

16 Draft Guidance, at 11.

17 Draft Guidance, at 5.

18 Draft Guidance, at 11.

19 Draft Guidance, at 14.

20 Draft Guidance, at 4.

effective means to achieve this expansion. CED attempts to satisfy CMS' desire for more data, but does not address the needs of the rest of America's clinical research infrastructure. This system relies on the talent, financial resources, and collaboration of a wide variety of entities, including patients, physicians, researchers, the pharmaceutical and biological industries, and hospitals and other health care providers. Any effort to expand clinical research opportunities must be undertaken with a full understanding of these entities' contributions to the system and the complex relationships among them. Unilateral efforts to change this system could weaken its foundations and discourage continued private sector support for research. We urge CMS to bring all stakeholders together to discuss ways to effectively increase support for and use of our clinical research system.

VIII. Conclusion

ACCC greatly appreciates this opportunity to comment on CMS' draft guidance regarding the use of CED. We greatly appreciate CMS' willingness to meet with us and other stakeholders to discuss the Draft Guidance, and we look forward to working with the agency as it develops future drafts of this document. To help the agency develop a clearer next draft, we recommend that it include the following statements.

1. CED will be used very rarely and never will be used for on-label uses of drugs or off-label, compendia listed uses of drugs used in an anti-cancer chemotherapeutic regimen;

2. CED only will be used to expand access to care and will not be used to curtail access to therapies currently covered through the local coverage process;

3. CED will not be used to force patients or providers to enroll in clinical trials;

4. CMS will apply CED in a manner that minimizes increased costs for beneficiaries and providers;

5. When CMS uses CED, it must use data collection methods that fully acknowledge the heterogeneity of the Medicare population; and

6. The decision to use CED will be made after consultation with stakeholders, including providers, and will be made only at the request of trial sponsors who believe Medicare coverage could help a trial move forward.

We encourage CMS to meet with us and other stakeholders to discuss our comments before it issues the next draft of the guidance document.

We would be pleased to answer any questions about these comments. Please contact our staff person, Deborah Walter, at (301) 984-5067, if we can be of any assistance as you prepare the next draft of this guidance document. Thank you for your attention to this very important matter.

Respectfully submitted,

E. Strode Weaver, FACHE, MBA, MHSA
President
Association of Community Cancer Centers
Executive Director, Oncology Services
University of Colorado Hospital
Anschutz Cancer Pavilion

Organization: Bayer

(Comment on next page.)

Bayer HealthCare
Pharmaceuticals

June 6, 2005

Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mailstop: C1-12-28
Department of Health and Human Services
7500 Security Boulevard
Baltimore, Maryland 21244

Re: Draft Guidance on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development"

Bayer Pharmaceuticals Corporation
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West Haven, CT 06516
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Dear Coverage and Analysis Group:

We are writing in response to the Draft Guidance ("Draft Guidance") issued by the Centers for Medicare and Medicaid Services ("CMS") on April 7, 2005, regarding coverage with evidence development ("CED"). For more that 100 years, Bayer Pharmaceuticals Corporation ("Bayer") has produced high-quality drugs and biologics that have helped patients lead healthier lives. We appreciate your willingness to consult with the Company and the public to ensure that the CED approach achieves its objective of "improving the health of beneficiaries by enhancing access to medical technologies and services that improve health outcomes."

Bayer offers the following comments on the Draft Guidance:

- CMS is correct in stating that the CED approach should not affect or extend to the Part D program;
- the CED approach may exceed CMS' authority under the Social Security Act;
- CED study design and oversight should be rigorous; and
- Data collected through CED studies should be publicly available.

We thank you for the opportunity to comment on the Draft Guidance and address each of these points in detail below.

I. Application of CED to Items and Services Normally Covered by the NCD Process

We are pleased that the Draft Guidance limits CED to those items and services that would normally be covered under the NCD process. In particular, we agree with the decision to exclude self-administered drugs and outpatient prescription drugs payable under Part D from the CED approach. This is a sound decision, and we support the determination that CED should apply only to items and services that are subject to NCDs. In drafting Part D, Congress determined that that the Part D plans, not CMS, should determine what drugs are covered under that benefit. The Draft Guidance is consistent with that intent.

II. Legal Authority for Coverage with Evidence Development

According to the Draft Guidance, the Agency derives the statutory authority to link coverage decisions to the collection of additional data from 42 U.S.C. § 1862(a)(1)(A). Upon review, Bayer is unpersuaded that the CED approach as articulated by CMS complies with the statutory requirement that Medicare limit its payment to items and services that are "reasonable and necessary" for the treatment of illness or injury. According to the Draft Guidance, "CMS will determine that an item or service is only reasonable and necessary when specific data collections accompany the provision of the service."[1] Implicit in this statement is the recognition that without additional information the items or services in question are not "reasonable and necessary." Accordingly, there appears to be significant reason to doubt whether the authority claimed in the Guidance meets the standard for coverage mandated by the Social Security Act.

We are sensitive to the Agency's attempt to ensure that Medicare provides payment for items and services under conditions that help assure significant net benefits of the treatment for Medicare beneficiaries and give rise to additional information. Nevertheless, we remain skeptical of this approach and the Agency's ability to meet the minimum standards for coverage as required by Congress in drafting the Social Security Act.

To the extent that CED is a valid exercise of authority, Bayer agrees with the indication in the Draft Comments that it will be used sparingly. We are pleased that CMS does not anticipate a substantial number of new coverage decisions that apply the data collection requirement. The Agency practice should be to make coverage determinations that appropriately reflect the statutory requirements of 42 U.S.C. § 1862(a)(1)(A).

III. Evidence Development Methods

If the Agency decides to move forward with the CED approach, randomized clinical trials ("RCTs") are the only adequate study design. Because the CED approach is of questionable authority, any flexibility in coverage should be extended only on the promise of the collection of the most compelling evidence using RCTs.

[1] *Factors CMS Considers in Making a Determination of Coverage with Evidence Development*, April 7, 2005 at 6.

Without question, the most statistically significant type of study design is RCTs. Bayer appreciates the usefulness of databases, longitudinal or cohort studies, and prospective comparative studies, proffered by the Draft Guidance as potential alternatives in many contexts. However, these designs fail to provide the same high level of compelling evidence as RCTs. In addition, it is important to stress the limitations associated with the use of retrospective data, which we find equally unacceptable in this context. If items or services are to be the beneficiaries of a flexible coverage standard, they must be willing and able to collect the most convincing data to support that coverage.

The Draft Guidance suggests that randomized studies may be required to provide more definitive evidence on effectiveness or comparative effectiveness in particular types of patients. Bayer agrees. We stress the importance of randomization to ensure confidence that items and services provided through CED do in fact lead to better outcomes for beneficiaries.

IV. Process for Study Design and Implementation

Since requestors for CED coverage will be seeking the benefit of a more flexible coverage standard, Bayer believes that access to the data collected as part of CED studies is critical to the success of this approach and a reasonable condition for granting that benefit. Public access to the data collected will help to preserve integrity and accountability of the CED approach. Where CMS adopts a flexible coverage approach, a transparent approach is needed to ensure there is, in fact, a net benefit of the treatment for beneficiaries.

V. Conclusion

We thank CMS in advance for considering our comments regarding the Agency's authority, its lack of application in a Part D context, the need for rigorous study design and oversight, and the importance of public dissemination of data collected through CED studies.

Respectfully submitted,

Kathleen Gondek, Ph.D.
Head, Global Health Economics and Reimbursement

cc: Herb Kuhn
Steve Phurrough, M.D.
Barry M. Straube, M.D.

Organization: Biogen Idec

Biogen Idec is a global leader in biotechnology headquartered in Cambridge, Massachusetts with Centers of Excellence in San Diego and Cambridge. Our focus on scientific excellence drives product and development programs that address key medical needs in oncology and immunology. The biological therapies developed by Biogen Idec and other manufacturers have increasingly offered Medicare beneficiaries new hope for cure or remission from life-threatening illnesses such as cancer, and for improved health outcomes and greater quality of life from chronic debilitating illnesses such as Multiple Sclerosis. Biogen Idec supports CMS in its efforts toward a more transparent and predictable coverage process through publication of guidance documents. The brief comments that follow outline our concern that the guidance document explaining Medicare's new coverage with evidence development (CED) process do not clearly illuminate the operational impact of such a decision on Medicare beneficiary access, and may open the door to future application of this novel approach beyond the limited scope envisioned by the current administration.

- National coverage decisions generally preclude local contractors from independently evaluating the evidence to support the medical necessity of a particular drug or biological for a specific indication or on a case-by-case basis. CED could impede beneficiary access to beneficial drugs and biologicals unless the final guidance document specifically states that a CED NCD for a drug or biological precludes contractor claim denials for CED uses, yet does not restrict contractor discretion otherwise applicable to off-label use of drugs and biologicals.

- It is not clear how beneficiaries would exercise their appeal rights if claim denials were based upon a CED NCD. For example, the primary "medical necessity" basis for any CED decision is CMS' statement that "systematic, protocol-driven data has the potential to increase the likelihood of improved health outcomes. Care provided under these protocols generally involves greater attention to appropriate patient evaluation and selection, as well as the appropriate application of the technology." Appeals of CED NCDs would be complicated by Department Appeals Board and/or judicial consideration of the evidentiary basis of this

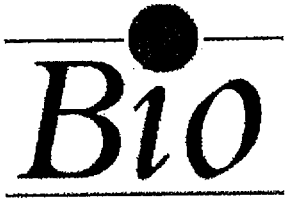
underlying rationale, as well as the evidence supporting use of the specific technology.

- CMS clearly stated in its draft guidance document and the recent Open Door Forum that CED would be utilized rarely, and in very limited situations. The absence of a guidance document delineating CMS' coverage criteria, together with recent agency statements indicating an interest in utilizing the Medicare databases to gather outcomes data generalizable to the private sector, raise the potential that future CMS leadership may apply CED broadly in lieu of coverage criteria development.

Again, Biogen Idec supports CMS in developing guidance documents that clarify Medicare coverage processes and criteria. The CED guidance document may present more controversy than is warranted given the rarity with which it is intended to be applied, and may also create precedents in the Medicare coverage decision process that have an unintended detrimental effect on future Medicare beneficiary access to therapeutic innovations. We urge CMS to evaluate these policy considerations, as well as the comments outlined above, before finalizing this guidance document.

Organization: Biotechnology Industry Organization (BIO)

(Comment on next page.)



BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

June 6, 2005

BY ELECTRONIC DELIVERY

Steve Phurrough, M.D., M.P.A
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Re: Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Centers for Medicare & Medicaid Services' (CMS) draft guidance document (Draft Guidance) regarding factors CMS considers in making a determination of coverage with evidence development (CED).1 BIO is the largest trade organization to serve and represent the

1 Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development, Apr. 7, 2003. (hereinafter "Draft Guidance").

biotechnology industry in the United States and around the world. BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products.

The Draft Guidance on CED continues CMS' ongoing efforts to promote the expanded collection of evidence to help patients, physicians, and payers determine when a medical technology is appropriate for a specific patient. BIO strongly supports evidence-based medicine, and we are committed to increasing the body of evidence available regarding diseases and their treatments. Our members spend millions of dollars each year on clinical studies, both before and after Food and Drug Administration (FDA) approval of their products, to produce high-quality clinical evidence to support medical decision-making. We also support the dissemination of this evidence to further clinical knowledge and enhance and improve the clinical decision-making process.

Our commitment to developing evidence extends far beyond studies of a particular therapy. We support a rigorous evidence development process that encompasses all aspects of a disease from examining how it affects the body to studying the costs and benefits of therapies. Our research initiatives advance the understanding of disease pathology and therapeutic mechanisms of action, clinical effectiveness in naturalistic settings, health-related quality of life, and health economic impacts of therapies in addition to clinical safety and efficacy. The development and evaluation of therapies are parts of this broader process and must be considered in context.

Our members' existing evidence development process, combined with Medicare's current coverage policies, allows Medicare beneficiaries timely access to new therapies and encourages innovation. The Medicare statute and manuals give local carriers the flexibility and freedom to make timely, evidence-based coverage decisions, ensuring Medicare beneficiaries' access to drugs and biologicals for medically accepted uses. These policies also encourage innovation and continued research by giving patients a choice of new therapies as well as new uses of existing therapies. Moreover, these policies create a relatively stable and predicable reimbursement environment, which is critical for many of our smaller members who are dependent on private sector investment.

Unfortunately, the Draft Guidance is vague and confusing and conflicts with many of CMS' statements made during the Open Door Forum[2] and the agency's recent uses of CED. In addition to the questions posed by CMS in the Draft Guidance, our reading of the document raises many questions and concerns. Our comments address these concerns, as well as respond to CMS' questions. Although we recognize that CED could apply to other items and services, we limit our comments to the use of CED for drugs and biologicals only, not devices or procedures. We believe that distinguishing drugs and biologicals from devices and procedures in the Draft Guidance would allow CMS to describe its plans and data requirements with greater specificity, particularly given the different amounts and types of data required for their FDA approvals.

BIO is concerned that CED, as described in the Draft Guidance, could reduce access to innovative drugs and biologicals, harming patient care both now and in the future. CED, if not applied narrowly, could slow technology diffusion and innovation by limiting physicians' choice of therapies and freedom to use cutting-edge regimens. CED could deny many beneficiaries who do not meet clinical trials' criteria access to critical therapies. It also could create uncertainty about reimbursement for medical technologies and could interfere with private market research priorities, slowing the development of new life-saving therapies.

Accordingly, if CMS proceeds with CED, we urge the agency to:

- Add a "scope" section to the next draft that clearly states when CMS might apply CED and the effect of CED on local carriers' authority to make coverage decisions. We support the narrow scope that the agency has articulated publicly, whereby the application of CED must meet all of the criteria outlined below:

  - CED will be used only when it serves as an expansion of coverage;
  - CED will not be used for on-label use of drugs or biologicals;
  - CED will not be used where there are statutory provisions establishing the Congressionally-mandated evidence standard, e.g., for off-label uses of drugs or biologicals used in anti-cancer chemotherapeutic regimens that are listed in the compendia,

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2 Open Door Forum held May 9, 2005.

supported by peer-reviewed literature, or otherwise determined by a local contractor to be medically accepted;

- CED will not supplant carrier discretion, and carriers will continue to apply local coverage as they do today; and
- CED will be used only when requested by a trial sponsor to facilitate enrollment.

- Distinguish drugs and biologicals from devices approved through the 510(k) process, as CMS has done in the past, in recognition of the different amounts of data required for FDA approval.3 This also will allow the agency to be more specific in its descriptions in the CED guidance document.

- Ensure that both its efforts to define CED and to apply CED to specific technologies are open, transparent, and predictable by resolving inconsistencies between statements in the Draft Guidance and in other forums and involving all stakeholders in these key decision processes.

We urge CMS to issue a second draft of the guidance document, with an additional comment period, to address these concerns and allow stakeholders to provide comments on CMS' response, using the consultative and iterative process described by the agency in the Draft Guidance.4 In addition, we urge CMS to treat its recent application of CED to anti-cancer chemotherapy for colorectal cancer as a pilot project and to learn from it before applying a similar CED policy to other drugs and biologicals in the future. Only after a careful analysis verifying that coverage was indeed expanded and assurance that long-term patient access was maintained should CMS evaluate whether and how to apply CED again.

I. CMS' authority to implement CED is questionable.

At the outset, we are deeply concerned because CED is a major policy change, and we question whether it is a proper exercise of CMS' authority. We note that CMS is a payer for health services, not a public research institution. Using its authority as a payer, CMS may examine whether an item or service

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3 Health Care Financing Administration (HCFA), Medicare Program; Criteria and Procedures for Making Medical Services Coverage Decisions that Relate to Health Care Technology Proposed Rule, 54 Fed. Reg. 4302, 4306-07 (Jan. 30, 1989).

4 Draft Guidance, at 9.

meets the criteria for coverage, but it cannot interfere with physicians' practice of medicine.5 Setting the nation's research agenda also is not within CMS' purview.

We are disturbed that CMS inappropriately may be assuming the roles responsibilities of other agencies, such as the FDA, the Agency for Healthcare Research and Quality (AHRQ), and the National Institutes of Health (NIH). Specifically, CMS appears to be interfering with the FDA's authority to mandate post-marketing studies of drugs and biologicals, the AHRQ's mission to sponsor and conduct research to develop evidence-based data on health care services, and the NIH's clinical research mission. For example, Congress approved Section 1013 of the Medicare Modernization Act (MMA), which authorized AHRQ to evaluate the "outcomes, comparative clinical effectiveness, and appropriateness of health care items and services" provided to Medicare beneficiaries. Recognizing the impact that HHS driven research may have, Congress expressly prohibited CMS from using data gathered through Section 1013 to withhold coverage of a prescription drug.6 CMS should not be permitted to circumvent this provision by undertaking activities specifically delegated by law to AHRQ through the application of CED.

We remind CMS that Medicare beneficiaries do not have the same ability to switch health plans as their private sector counterparts who can change plans if desired. If Medicare beneficiaries disagree with CMS' restrictions on the care they receive, they usually have no other option for health coverage and often have no alternate means to pay for the care they need. For these reasons, we urge CMS to ensure that coverage decisions do not restrict Medicare beneficiaries and physicians' ability to choose their most appropriate course of treatment.

As CMS notes in the Draft Guidance, the Medicare statute authorizes the agency to determine whether an item or service is "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."7 Throughout CMS' history, these determinations have been based upon the evidence available at the time of the coverage decision. The Draft Guidance does not explain adequately how this authority extends to CMS' efforts to develop more evidence about an item or service. Moreover, we are unaware of any legislative history supporting the use of the

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5 SSA § 1801.
6 MMA § 1013(d).
7 SSA § 1862(a)(1)(A).

Medicare coverage process to promote evidence development. We will discuss these concerns in more detail in our comments on the forthcoming guidance document addressing the "reasonable and necessary" statutory language.

II. CMS must clearly describe the scope of CED.

In recent weeks, during its Open Door Forum and in meetings with stakeholders, CMS has attempted to clarify the scope of CED. CMS' descriptions of the items and services to which CED may apply and its effect on local carriers' coverage authority have provided some reassurance that CED may not harm beneficiary access to drugs and biologicals, but these details are not included in the Draft Guidance. Instead, the Draft Guidance fails to provide clear examples of when CED will be considered or used. For example, in the Draft Guidance, CMS states that it "does not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirement,"8. Similarly, during the May 9 Open Door Forum, CMS said that it would use CED infrequently and in narrow circumstances.

The Draft Guidance, however, lists broad circumstances in which CED will be considered and could encompass many uses of innovative therapies.9 Moreover, the agency's claims of narrow use of CED are belied by CMS' recent national coverage determination (NCD) on anti-cancer chemotherapy for colorectal cancer. CMS also says that it "intends to apply CED to issues with the greatest potential benefit for Medicare beneficiaries and the Medicare program."10 These conflicting and vague statements and actions provide very little guidance as to exactly when CMS plans to use CED. We ask CMS to provide a more detailed description in the next draft of the circumstances in which CED will be used.

Consistent with its public statements, and as previously stated, CMS should clarify in the next draft of this guidance document that all of the following criteria must be met to apply CED:

1. CED will be used very rarely in narrow circumstances;
2. CED only will be used to expand coverage;
3. CED will not be used for on-label use of drugs or biologicals;

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8 Draft Guidance, at 2.
9 Draft Guidance, at 9-10.
10 Draft Guidance, at 11.

4. CED will not be used where there are statutory provisions setting out the Congressionally-mandated evidence standard, e.g., for off-label uses of drugs or biologicals used in anti-cancer chemotherapeutic regimens that are listed in the compendia, supported by peer-reviewed literature, or otherwise determined to be medically appropriate;
5. CED will not supplant carrier discretion, and carriers will continue to apply local coverage as they do today; and
6. CED will be used only when requested by a trial sponsor to facilitate enrollment.

Limiting the use of CED to these circumstances would ensure that its application is predictable and consistent and used for the benefit of Medicare beneficiaries. For example, in the recent NCD on anti-cancer chemotherapy for colorectal cancer, CMS determined that it did not have sufficient evidence on certain off-label, non-compendia listed uses of four anti-cancer drugs and biologicals. The NCD mandated coverage for these uses in specific clinical trials, but also protected carriers' discretion to cover these uses outside the trials if determined to be medically necessary.[11] We urge CMS to state in the next draft of the guidance document that CED will be used only when all of these criteria are met. CMS also provides little insight into the extent to which it intends to consider cost and utilization in deciding whether to apply CED. While cost and utilizations may be appropriate parameters for CMS to take into account when it is deciding whether to undertake a national coverage decision or entertain the need for a CED, cost and utilization should not, in our view, be considerations when a particular CED is being designed. CMS should clarify the role of cost and utilization in the next draft of the guidance document.

To clarify statements in the Draft Guidance about the use of CED to assist CMS and its contractors in making coverage decisions,[12] the agency should state explicitly that CED is to be applied as a national policy only and is not to be initiated by local contractors. In addition, CMS should clarify that CED will not apply to drugs and biologicals covered under Medicare Part D. BIO is very concerned that Part D plans will view or try to make the claim that drugs subject to a CED are experimental, and, therefore, not eligible for coverage under Part D. Such a consequence would be unfair and potentially

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11 Medicare National Coverage Decision Manual (CMS Pub. 100-3), § 110.17.

12 See Draft Guidance, at 5, 9 ("In general, CMS will consider requiring data collection as a condition of coverage when additional information is needed for *CMS and its contractors* to determine if an item or service is reasonable and necessary.") (emphasis added).

financially devastating to a beneficiary. CMS must be clear about the relationship of CED to Part D and vigilantly monitor treatment denials by MA-PDPs and PDPs, which appear to be related to the inclusion of a drug in a CED trial.

Moreover, the agency should indicate that the agency will contact manufacturers prior to the opening of a NCD and the potential application of CED and involve them in an open and transparent dialogue as the issue is considered. 13 Adding these statements to the next draft would greatly clarify the scope of CED.

BIO is very concerned about the provision in the Draft Guidance that considers the use of CED in circumstances of treatments for rare diseases where CMS alleges that comprehensive evidence of effectiveness is "not always available or feasible to develop in a pre-marketing setting." BIO believes that this provision should be deleted from the final guidance document.

In the development of medicines for rare diseases, the patient population must be less than 200,000 and therefore there are a limited number of patients from which to draw to conduct clinical studies. The clinical studies required for approval usually have very specific inclusion and exclusion criteria and thus an even smaller number of patients are available for enrollment into clinical studies. Many rare diseases are slowly progressive and heterogeneous, and large studies of long duration are not feasible. Nevertheless, the standard for approval of orphan drugs and biologicals is the same as that applicable to drugs and biologicals intended for use in larger populations—substantial evidence of safety and effectiveness for the intended use. Given the challenges of collecting data in such small patient populations, it is important that CMS not try to require additional or different clinical studies to those already underway or committed to by the drug sponsor.

The FDA, and in many cases, experts through FDA Advisory Committees have already given extensive thought and consideration into what clinical data should be collected on an orphan product, its patient population

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13 This issue is discussed in depth in our comments to the agency's first three draft guidances on NCDs. Letter from Jim Greenwood, President & CEO, BIO, to Coverage and Analysis Group, CMS, regarding comments on draft guidance entitled "(1) Factors CMS Considers in Opening a National Coverage Determination; (2) Factors CMS Considers in Referring Topics to the Medicare Coverage Advisory Committee; and (3) Factors CMS Considers in Commissioning an External Technology Assessment," May 6, 2005.

and its use when approval is granted. In fact, any post-marketing study commitments have already been agreed upon by the FDA and drug sponsor at the time FDA approval is given. It would be inappropriate for these post-marketing commitment studies to be delayed in any way to accommodate additional data collection requests by CMS because sponsor are held to very strict timelines by the FDA for completing their commitments. For CMS to conduct its own completely separate analysis and develop a different set of requirements could delay patient access to these needed drugs for rare diseases. Additional requirements would also be expensive and duplicative for the small, biotechnology companies that frequently engage in research in rare diseases. Lastly, additional CMS requirements would be contrary to existing law and Congressional intent to incentivize drug sponsors to develop therapies for rare diseases with small market potential.

III. CED only must be used to expand access to care and must not interfere with the local coverage process.

We are concerned that CED will curtail access to drugs and biologicals currently available through the local coverage process. The local coverage process allows Medicare beneficiaries to have appropriate access to drugs and biologicals through an efficient, timely, and evidence-based decision-making process. As intended by Congress, this process allows beneficiaries to receive anti-cancer chemotherapy drugs and biologicals for off-label indications when the use is supported in certain compendia or peer-reviewed literature, or when the contractor determines that the use is medically appropriate.[14] If these therapies are available only through clinical trials or other evidence gathering methods, many patients could be denied access to critical treatments.

As CMS must be aware, many Medicare beneficiaries are ineligible for clinical trials due to age, co-morbidities, or complications. Others beneficiaries may choose not to participate in a trial if it requires them to travel, change physicians, or experience other substantial inconvenience. This may be particularly true for patients in rural areas, minorities, and women, who traditionally have been under-represented in clinical trials. The local coverage process must remain intact to allow patients who do not qualify for clinical trials or who elect not to participate to receive appropriate therapies.

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14 SSA § 1861(t)(2); Medicare Benefit Policy Manual (CMS Pub. 100-02), ch. 15, § 50.4.5.

In the Draft Guidance, CMS says it does not "anticipate circumstances under which CED would represent a net reduction in coverage available under local coverage policies."15 To ensure that CED does not harm access to care, we ask CMS to commit to specifying precisely which beneficiaries are having difficulty accessing the drug or biological to which CED is applied and how the application of CED is expected to increase patient access. We also urge CMS to provide clearer instructions to carriers that a NCD with CED does not affect their discretion to cover uses of these therapies outside the CED requirements. CMS then should monitor and report on access to care after a CED decision is implemented both to verify that access is expanded as expected and that patients continue to receive the care prescribed by their treating physician, regardless of their participation in the evidence development exercise. This analysis also should be performed for the applications of CED that the agency currently is implementing.

The patient access analysis should be part of a larger formal, comprehensive value of information analysis that CMS should be required to conduct whenever it proposes to apply CED. This analysis should be included in the draft decision memorandum to allow all interested stakeholders the opportunity to respond to it. Such treatment is consistent with the Regulatory Impact Analyses and Regulatory Flexibility Analyses prepared for major rules and rules impacting small entities. CMS would be required to clearly explain the potential costs, burdens, and expected benefits of CED before implementation. These requirements should be incorporated and described explicitly in the next draft of the Guidance Document.

IV. CMS should distinguish drugs and biologicals from devices and procedures in its guidance document on CED.

CMS should distinguish drugs and biologicals from devices and procedures in its next draft of the guidance document. In recognition of the FDA's rigorous drug approval process, CMS historically has treated coverage of drugs and biologicals differently than other items and services, particularly devices approved under Section 510(k) of the Federal Food, Drug, and Cosmetic Act. Indeed, in 1989, the agency said that its national policy is that drugs or biologicals approved for marketing by the FDA are safe and effective for on-label indications, but that FDA approval for marketing of a medical device does not necessarily lead to a favorable coverage recommendation,

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15 Draft Guidance, at 6.

especially when the FDA approval is under Section 510(k).[16] CMS should continue to acknowledge the different amounts and types of data required to approve these technologies by providing separate descriptions of its plans to use CED for drugs and biologicals versus devices. The agency also should separately describe the application of CED to procedures that do not require FDA approval.

V. CMS must clearly state its reasons for using CED.

CMS must clarify its reasons for using CED to allow us to comment more meaningfully on whether and how CED can be used to achieve these purposes. CMS' written statements in the Draft Guidance and its oral communications concerning the guidance (e.g., during the May 9, 2005 Open Door Forum) have caused confusion about why the agency plans to use CED. In the Draft Guidance, CMS states that the purpose of obtaining evidence is to give the agency data to use in making payment determinations[17] and to provide useful information to doctors and patients for clinical decision-making.[18] CMS also says it will consider using CED when "additional information is needed for CMS and its contractors to determine if an item or service is reasonable and necessary."[19] During the May 9, 2005 Open Door Forum, however, agency staff said that the main purpose was to assist patients and physicians and acknowledged that the data gathered through CED might not be adequate for use in coverage decisions. CMS' examples of the two general circumstances in which CED may be used give more reasons for using CED: to ensure patient safety and to provide physicians with more information about a patient's course of treatment. As noted above, Congress explicitly directed that these objectives be met by AHRQ.

The various reasons for using CED have left us confused about exactly what type of policy CMS is proposing. The conflicting written and oral statements make it difficult to understand what policy the agency is advancing and thus to which points we should address our comments. We urge CMS to issue another draft that reconciles the Draft Guidance, the agency's recent use of CED, and the agency's verbal statements about CED.

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16 54 Fed. Reg. 4302, 4306-07 (Jan. 30, 1989). See also, 52 Fed. Reg. 15560, 15561 (Apr. 29, 1987) ("Medicare coverage of drugs and biologicals is treated differently" than other item and services).

17 Draft Guidance, at 1.

18 Draft Guidance, at 5.

19 Draft Guidance, at 9.

VI. CMS must clarify the amount of evidence it needs before applying CED to an item or service.

Additionally, the Draft Guidance is not clear about the amount of evidence CMS needs about an item or service before deciding to use CED. During the Open Door Forum, you stated that CMS would use CED when the evidence is not complete to support full coverage and additional data would help CMS be confident about providing full coverage. The description provided during the Open Door Forum also does not correspond perfectly to the Draft Guidance's descriptions of the evidence required to reach any of the three possible coverage decisions.[20] It therefore is not clear when CMS would determine that enough evidence exists to apply CED instead of issuing a non-coverage determination or no national coverage determination. CMS should specify its evidence requirements in the next draft of the guidance document.

VII. CMS must work with stakeholders to ensure that a proposed evidence collection method will achieve its goals with minimal burdens on patients, providers, and manufacturers.

If CMS applies CED to an item or service, it must take care to ensure that its chosen research methods can achieve intended goals with minimal burdens on patients, providers, and manufacturers. We agree with CMS that:

- the value of the information gathered must be carefully balanced against the burden of collecting it;
- any CED requirements must be aligned with the FDA's clinical study requirements and with other research priorities to ensure that our research resources are used efficiently; and
- data collection only should continue as long as important questions remain and the effort and resources required to collect this data are justified by the potential value of the information to be collected.[21]

The Draft Guidance does not describe CMS' process for ensuring that these criteria are met. In particular, we are especially concerned about how CMS will determine what hypothesis will be examined, when sufficient evidence has been gathered, and when CED will be brought to a close. Unless

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20 Draft Guidance, at 3.
21 Draft Guidance, at 5, 14.

the research question is clearly defined from the outset, we cannot be confident that the study will produce data to satisfy CMS' needs or that coverage decisions will be made in an efficient and timely manner. Robust clinical research starts by asking the correct research question. Clear articulation of the research question informs all other aspects of research, including study design, enrollment criteria, sampling methods, power calculations, ethical considerations, and analytical plan. The consequences of a poorly articulated research question are development of faulty or biased data, or engagement in data dredging exercises and its inherent risks of making spurious inferences.

To ensure that an application of CED achieves its goals(s) while minimally inconveniencing providers, patients and manufacturers, we urge CMS to consult stakeholders at each stage of the CED development process. For example, before beginning any evidence development process, CMS must work with stakeholders to assess the need for more evidence about a drug or biological, the value of the information to be collected, and the burdens on stakeholders of collecting it. With input from stakeholders, CMS must clearly articulate the specific research questions, goals, and limitations of the intended research design. As the evidence is gathered, CMS should consult with stakeholders about the data and its analysis. We support CMS' plan, described during the Open Door Forum, to release aggregate data to the public for additional analysis, but we emphasize that this is not a substitute for initial consensus about the trial's design and purpose.

In the Draft Guidance, CMS asks, "[H]ow should the costs of study design, data collection, analysis and other activities associated with these programs be fairly allocated to various stakeholders?"22 In addition to minimizing these costs as much as possible, we urge CMS to pay particular attention to the costs imposed on beneficiaries and providers. Beneficiaries' cost of care under CED should not be greater than under coverage without evidence development. If beneficiaries are forced to incur greater costs for receiving care in Medicare-covered clinical trials or other evidence development programs, they likely will choose other, potentially less appropriate, care options.

In addition to minimizing patient costs associated with CED, CMS also must minimize physicians' costs of CED. Physicians who participate in clinical trials often donate considerable amounts of time and resources to evaluate

22 Draft Guidance, at 15.

patients' eligibility for trials, data collection, and drug administration services that frequently are not reimbursed by trial sponsors. With Medicare's recent changes to reimbursement for drugs and drug administration and its pending reimbursement cuts for all physician services, many physicians are less able to afford to participate in clinical research. We recommend that CMS develop reimbursement codes and rates for non-routine services to make participation in research more financially feasible. We also recommend that CMS provide reimbursement for the routine costs of care, such as drug administration, in more clinical trials.

BIO also recommends that CMS encourage Medicare beneficiaries to participate in a wide range of clinical trials, rather than a select few identified by the agency. To increase beneficiaries' care options, BIO urges CMS to finalize its criteria for coverage of clinical trials under the 2000 NCD. Since September 2000, Medicare has covered the costs of routine services in qualifying clinical trials, including trials sponsored by the NIH and other federal agencies.[23] CMS, however, has not yet finalized its criteria for covering other trials, such as those sponsored by industry or other groups. We recommend that CMS fully implement the 2000 NCD by finalizing these criteria so that Medicare beneficiaries will be able to participate in the clinical trials that are most appropriate for their conditions.

VIII. CMS must clarify the draft guidance document's description of the NCD process.

The Draft Guidance has caused confusion about the possible outcomes of the NCD process. First, we ask CMS to clarify that its statement that it "does not anticipate issuing additional decisions" without conditions does not mean that it plans to apply CED to every NCD.[24] If the agency intends that every future coverage decision will be coupled with conditions such as patient diagnoses, positive test results, or other factors, CMS should explain this clearly in the revised guidance.

Second, in the Draft Guidance, CMS says the NCD process results in three broad types of coverage decisions: non-coverage, coverage with conditions, and coverage without conditions.[25] The Draft Guidance omits a

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23 National Coverage Determinations Manual § 310.1.
24 Draft Guidance, at 4.
25 Draft Guidance, at 3.

possible outcome to the NCD process, one that has been used recently in the draft Radioimmunotherapy for Non-Hodgkin's Lymphoma NCD.26 In cases for which there is inadequate evidence at this time for a change to coverage, CMS may leave the decision to cover the item or service to the carriers, using current manual instructions. CMS must state in the next draft that the NCD process results in four, not three, types of coverage decisions: (1) non-coverage; (2) coverage; (3) coverage with evidence development; and (4) no national coverage decision, with coverage left to statutory mandate as well as the discretion of Medicare contractors. When the evidence is not adequate to justify a change in coverage policy and CED is not appropriate, the Draft Guidance should clarify that the result should be no national decision, not non-coverage.

IX. CMS must bring all stakeholders to the table to discuss CED and expanding support for clinical research.

BIO shares CMS' belief that the agency must work "consultatively and iteratively with external experts and stakeholders in developing the criteria and process for determining when to apply CED."27 These discussions should bring all stakeholders together to discuss not only the use of CED for specific items and services, but also CED's effects on patients' access to innovative therapies, the broader clinical research system, and the drug and biological industries. CMS appears to view CED as a step toward a "systematic expansion of practical clinical research efforts to address the needs of health professionals and patients."28

The clinical research structure is far more complex than CMS may imagine, and it cannot be expanded successfully without the participation of all of its stakeholders, including patients, providers, researchers, manufacturers, and other government agencies. We believe that CMS' efforts to encourage more research must be pursued only through transparent processes and open dialogue with all interested parties. Furthermore, this dialogue must involve all stakeholders, so that CMS can benefit from a full discussion of individual concerns for all parties involved. We urge CMS to continue to consult with stakeholders on the development of its policies regarding CED and the

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26 Proposed Decision Memo for Radioimmunotherapy for Non-Hodgkin's Lymphoma (CAG-00163N), May 4, 2005, http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=38.

27 Draft Guidance, at 9.

28 Draft Guidance, at 4.

expansion of clinical research. We also request that the agency make special efforts to provide opportunities, such as Open Door Forums, that allow all stakeholders to participate in the conversation at the same time.

X. CMS must make certain that all human subject research conducted under CED meets all federal legal, ethical, and Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements.

On page 3, the Draft Guidance states the following: "The service is delivered in the context of specific data being collected. Coverage may be limited to providers who participate in and beneficiaries who are enrolled into a defined prospective data collection activity, when this data collection activity constitutes part of the evidence required to ensure the item or service provided to that patient is reasonable and necessary." The Draft Guidance should clarify that the prospective collection of outcomes evidence for coverage use, even by CMS, constitutes research with human subjects under the law and the Department's own regulations.[29] Accordingly, the basic principles of informed consent, including patient authorization for use and disclosure of health information, and institutional review board (IRB) review cannot be ignored. Medicare beneficiaries should not be compelled to participate in research as a condition of coverage without the protection that the regulations provide. Finally, CMS indicates that studies under CED often would involve de-identified data. It is not clear how this would be feasible because the de-identification standard under the HIPAA privacy rule is very stringent. We respectfully ask CMS to clarify these issues before moving forward with application of CED.

XI. Conclusion

BIO appreciates this opportunity to comment on the Draft Guidance document regarding the use of CED. We hope our recommendations help CMS to apply CED in a predictable manner that ensures beneficiary access to innovative drugs and biologicals. Specifically, we urge CMS to:

- clearly define the scope of CED;
- work with the Department, AHRQ and public stakeholders to ensure that CED is implemented consistent with Section 1013 of the MMA;

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29 E.g., Federal Food, Drug, and Cosmetic Act §§ 505(i), 520(g), 21 U.S.C. §§ 355, 360j; 42 U.S.C. §§ 289, 289a-1; 21 C.F.R. Parts 50 and 56; 45 C.F.R. Part 46.

- use CED only to expand access to care and not interfere with the local coverage process that exists today;
- distinguish drugs and biologicals from devices and procedures in its guidance document on CED;
- clarify that CED never will be used for on-label uses or off-label uses of drugs or biologicals used in anti-cancer chemotherapeutic regimens that are listed in a compendia, supported by peer-reviewed literature, or otherwise determined by a local contractor to be medically accepted indications;
- clearly state its reasons for using CED to allow us to comment meaningfully on the policy;
- clarify the amount of evidence it needs before applying CED to an item or service;
- work with stakeholders to ensure that a proposed evidence collection method will achieve its goals with minimal burdens on patients, providers, and manufacturers;
- clarify the draft guidance document's description of the NCD process;
- bring all stakeholders to the table to discuss CED and expanding support for clinical research; and
- ensure that all human subject research conducted under CED meets all federal legal, ethical, and HIPAA requirements.

We look forward to working with CMS to protect Medicare beneficiaries' access to innovative drugs and biologicals. If you have any questions regarding our comments, please contact Jayson Slotnik at 202-312-9273. Thank you for your attention to this very important matter.

Sincerely,

/s/

Jim Greenwood
President and CEO
Biotechnology Industry Organization

Organization: Blue Cross Blue Shield of Kansas

Subject: effect / effective New England Journal of Medicine 352; 14: 1411 - 1412 " The Cutter Incident" The ruling in Gottsdanker v. Cutter Laboratories meant that juries could find companies financially liable without finding that the company was negligent in either the production or the design of the product. The law views the company as the entity best able to distribute the unavoidable cost to all persons who benefit from the product if an individual is harmed.

American Journal of Public Health 84; 9: 1515 - 1520 ... What is Medically Necessary" and New England Journal of Medicine 342; 15: 1069 - 1076... Stem cell Transplant for Breast Cancer" In December of 1993 a jury in Riverside California awarded the estate of a patient (name is available in the article) $77 million dollars in a judgment against the insurer. The insurer had determined there was insufficient evidence that stem cell transplantation was beneficial in the case of metastatic breast cancer. Seven years later when the collection of information was complete and the studies published further research into this therapy stopped. Why did it stop? Because there was severe toxicity associated with the treatment and no discernible difference in outcome. Yet before 1993 and between 1993 and 2000 this treatment was recommended because of encouraging pilot studies, which may have been misleading due to selection bias.

These examples are selected to illustrate two points. First there are compelling reasons for all engaged in the health industry to seek products which are fundamentally safe. Safety is not guaranteed. The decision on whether or not a product is safe may not be correct. Nor may the decision be timely but the determination is made by institutions and programs other than Medicare. Second to discover effectiveness and sometimes safety a consistent plan or protocol of study must be followed and this requires time. Information technology does not obviate the value of a consistent and reasoned plan to determined effectiveness. In fact the volume of extraneous information can be increased through information technology.

First, money should be spend before the process is implemented to define the information Medicare will purchase through coverage or reimbursement. I will offer one article: Briggs AH, O'Brien BJ, Blackhouse G, Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies Annu. Rev. Public Health 2002: 23; 377 - 401. Money invested for consultation with experienced mathematicians for the expressed purpose of determining minimal pieces of information that should be collected in every CED and is necessary to make reasoned predictions of effectiveness would be well invested. Second I will offer the name of an individual current practicing medicine, an author, teacher, and a person very capable helping to advise CMS on what is necessary to make the collection of information worthwhile. The person is: Marc Whitacre MD, Heart of America Eye Center, 8901 W 74th, Suite 285, Shawnee Mission KS 66204. A phone number where Dr. Whitacre may be reached is 913 - 362 - 3120. I hope these people could be actively recruited to advise CMS on this project.

Now I will offer some data related suggestions. In the case of diagnostic tests the likelihood ratio is perhaps the most important measure. The likelihood ratio represents the magnitude of change from a physician's initial suspicion of disease, pretest probability to the likelihood of disease after the test result, posttest probability. A ratio of one means the test is of little value. A ratio between 0.01 - 1.0 decreases the test usefulness and a ratio between 1.0 - 10.0 increases the usefulness. A service can be rendered to all providers of care who might order or purchase a test or a diagnostic tool if CMS consistently provided this information within the CED process instead of the more common and far less important reference to sensitivity and specificity. I also hold that the negative predictive value of a diagnostic test is essential to decide its usefulness. This is the probability that if a diagnostic test is negative the patient disease is absent. It is not good to miss disease.

The number needed to treat and the number needed to harm are terms the public can incorporate into an understanding of the consequences of taking a test or undergoing a treatment. These too should be part of the evidence CMS collects and pays for in order to help Medicare patients and providers. These numbers can apply to both diagnostic tests and therapeutic interventions.

Finally the CED process should collect at least enough information on a therapy procedure to derive an absolute risk reduction (ARR) . Here more than in the case of diagnostic tests the article by Briggs is important. When comparing strategies with small differences in outcome, errors of omission, not treating a potentially treatable disease should not be held equal to errors of commission, inducing morbidity in patients who do not require or will not benefit from treatment. This is my argument. A thoughtful plan resolutely implemented can provide information with value not extraneous numbers. Then whether or not the Medicare program subscribes to the argument above can be determined dispassionately and each test procedure and disease may be assessed in equal manner. Information above is an attempt to address the questions listed:

- Can these factors and criteria be put in order of importance? How could CMS or other best determine their relative importance?

- Are there situations listed above that would be unlikely to be constructively addressed through evidence collection linked to coverage decisions?

- How can formal ‘value of information analyses’ be applied to help decide when to require data collection following a coverage decision?

- Are there other ways the data may serve to improve available evidence of safety and benefit of an item or service or improve the decision making process?

- Are there existing approaches to priority setting for clinical studies that could serve as a model for identifying priorities for CED?

Organization: California Healthcare Institute

(Comment on next page.)

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June 6, 2005

VIA E-MAIL; COPY TO FOLLOW BY FEDERAL EXPRESS

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mail Stop: C1-12-28
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Baltimore, MD 21244

Re: Comments on Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

The California Healthcare Institute (CHI) welcomes this opportunity to comment on the Centers for Medicare & Medicaid Services' (CMS) draft guidance document entitled "Factors CMS Considers in Making a Determination of Coverage with Evidence Development" (Draft Guidance). CHI represents the biomedical sector of the California economy and unites more than 250 of California's leading life sciences firms, universities, and private research institutes in support of biomedical science, biotechnology, and pharmaceutical and medical device innovation. California is the global leader in biomedical research and development, with more than one-third of all U.S. biotechnology and medical device firms, turning scientific discoveries into medical products at an unprecedented rate. California firms alone produce more than 20 percent of all medical instruments in the United States and lead the nation in bringing to market frontline treatments and therapies for diseases such as AIDS, breast cancer, stroke, and diabetes.

As the representative of an industry committed to research and innovation, we share CMS' belief that clinical evidence is essential for patients, providers, and policy-makers' health care decisions. In 2003, California's biomedical industry invested $15.5 billion in researching and developing innovative therapies and

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devices.[1] The average company invested 48 percent of its revenues back into research and development.[2] Our members' clinical research helps patients and physicians understand how medical technology can be used most effectively. Because our members comprise the major components of the clinical research system – the manufacturers that develop new therapies and sponsor research and the universities and research institutions that perform it – we understand the challenges inherent in expanding research opportunities and participation. We hope the Draft Guidance will serve as a potential starting point for broader discussions among CMS, other government agencies, patient groups, physicians, researchers, and industry about the best ways to support further research and evidence-based medicine. Successful efforts to increase clinical research will require the agreement and cooperation of all of these stakeholders.

We appreciate CMS' efforts to encourage the development of more clinical evidence, but we are concerned that coverage with evidence development (CED), as described in the Draft Guidance, could restrict beneficiary access to care; impose significant costs on patients, providers and manufacturers; and fail to adequately address the information needs of patients, providers, or CMS. Our concerns are exacerbated because the Draft Guidance is vague and confusing and conflicts with public statements you and other CMS staff have made about CED. The Draft Guidance also raises many more questions than it answers. First, in the Draft Guidance, CMS poses several questions to the public regarding the details of how and when CED should be used. Before we can attempt to answer many of these questions, we need clarification about their meaning and about CMS' goals for CED in general. For example, in the Draft Guidance and the May 9, 2005 Open Door Forum, CMS gave various reasons for using CED, ranging from assisting the agency with coverage decisions to ensuring patient safety. It is difficult for us to respond to CMS' detailed questions about evidence development unless we know the exact purpose of CED data and CMS' broader goals associated with data collection.

Second, in addition to the questions posed by CMS to the public in the Draft Guidance, we have identified several concerns about CED that must be addressed before CMS moves forward with its plans. These concerns include:

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[1] CHI, California's Biomedical Industry, 2004 Report, at 3, available at http://chi.org/brandomatic/othermedia/chi/biomed.pdf.

[2] Id.

- CMS must clearly explain the legal authority supporting its use of CED;

- CMS must use CED rarely, narrowly, and only to protect beneficiary access to care;

- CMS must ensure CED will not impose substantial costs or administrative burdens on patients, providers, and manufacturers; and

- CMS must ensure that CED produces robust, relevant, and useful clinical data.

We propose responses to these concerns in our comments. We also urge CMS to hold public meetings before issuing the next draft of the guidance document in which we and other stakeholders could have a constructive dialogue with the agency to discuss questions and concerns more broadly. We believe the complex nature of the questions involved in this multi-faceted initiative would be addressed more appropriately face-to-face rather than in written comments with formal agency response. Once we better understand CMS' goals and concerns for CED, we can respond more meaningfully to the specific questions the agency has raised in the Draft Guidance.

We fully appreciate and support CMS' plan to work "consultatively and iteratively with external experts and stakeholders."[3] Toward this end, we urge CMS to incorporate the written comments it receives on the Draft Guidance, the oral comments it receives at the stakeholder meetings described above, and the agency's own clarifying statements, such as those made during the Open Door Forum, into a second draft of the guidance. An additional comment period and further opportunities for discussions with large groups of stakeholders should follow before the revised Draft Guidance is finalized. This process will help ensure that this important initiative is implemented in a manner that gives CMS and providers the evidence they need while ensuring beneficiary access to new therapies both now and in the future.

I. CMS must clearly explain the legal authority supporting its use of CED.

[3] Draft Guidance, at 9.

Although we understand that CMS plans to issue a separate guidance document that will discuss the agency's interpretation of "reasonable and necessary"[4] in the context of coverage determinations, we are concerned about the Draft Guidance's description of CMS' authority to use CED. By statute, CMS must not pay for items and services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[5] Medicare's coverage process historically has interpreted whether a therapy is "reasonable and necessary" in light of an individual patient's condition and the evidence available at the time of the decision. In a significant departure from this practice, the Draft Guidance proposes to use the coverage process, not to evaluate the use of a therapy for a specific patient, but to direct evidence development for possible use in future coverage decisions. In fact, many of the data collection methods described in the Draft Guidance will not produce data for years and therefore offer no additional benefit to the patient who receives the item or service under CED. Furthermore, there is no clear causal link between collecting data on a particular patient and improvements in that patient's care. CMS should focus its coverage decisions on ensuring that Medicare beneficiaries, who often are entirely dependent on the Medicare program to pay for their health care, receive the most appropriate therapies available.

We are concerned that CMS might be exceeding its authority as a payer for health services and may be inappropriately assuming the responsibilities of other agencies, such as the Food and Drug Administration (FDA), the Agency for Healthcare Research and Quality (AHRQ), or the National Institutes of Health (NIH). CMS is not a public health research agency; it is a payer for health services. By implementing CED, CMS appears to take on responsibility for mandating post-marketing studies of drugs, biologicals, and devices. To the extent that any federal agency is authorized to require these studies, that agency is the FDA, not CMS. CMS also appears to be duplicating AHRQ's function of sponsoring and conducting research to develop evidence-based data on health care services and the NIH's clinical research mission. We urge CMS to use its resources wisely and not attempt to duplicate the work of its sister agencies.

I. CED must be used rarely and only to expand coverage.

We are greatly concerned that CED could harm beneficiary access to innovative drugs, biologicals, and devices, both in the short term and over time.

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[4] Social Security Act § 1862(a)(1)(A).

[5] Social Security Act § 1862(a)(1)(A).

First, immediate access to advanced therapies could be curtailed severely if beneficiaries are required to enroll in clinical trials or data collection projects in order to receive them. As CMS knows, very few Medicare beneficiaries currently participate in clinical trials. Although we believe that beneficiaries should be encouraged to participate in trials, we recognize that Medicare beneficiaries' age, comorbidities, or complications often exclude them from trials' enrollment criteria. Beneficiaries who are eligible to participate in trials may choose not to enroll if the trial would require them to endure substantial inconvenience, such as traveling long distances or changing physicians. Moreover, as we discuss in Section III below, clinical research imposes substantial costs and burdens on providers, potentially discouraging them from offering therapies subject to CED. The recent positron emission tomography (PET) scan national coverage determination (NCD), for example, requires physicians to complete a lengthy and detailed form. Rather than dedicating uncompensated time for this paperwork, physicians may choose not to offer the service to patients.

Second, CED could restrict beneficiary access to care if it disturbs local contractors' discretion to cover medically necessary therapies. Beneficiaries currently gain access to most therapies through the local coverage process that permits contractors to make timely and evidence-based determinations on whether a treatment is reasonable and necessary for a particular patient. CMS states that it does not "anticipate circumstances under which CED would represent a net reduction in coverage under local coverage policies,"[6] but the Draft Guidance does not explicitly protect local contractors' discretion to cover items and services subject to CED outside the evidence collection process.

Third, over the long term, CED could discourage innovation by inhibiting the diffusion of new technology, creating uncertainty about reimbursement, and diverting resources from studying new therapies to fulfilling CMS' evidence collection requirements. These issues are particularly troubling for our smaller member companies who are very dependent on private sector investment. CED also could negate the statutory incentives for manufacturers to develop orphan drugs and humanitarian use devices. Specifically, Congress recognized that the high cost of developing drugs, biologicals, and devices discourages manufacturers from addressing the needs of patients with rare conditions. Therefore, it created orphan drug status and the humanitarian device exemption as a means to increase the treatment options of patients with rare diseases. In many cases, an orphan drug or humanitarian use device is the only treatment keeping a patient with a rare disease alive. Subjecting these drugs and devices to additional research requirements

[6] Draft Guidance, at 6.

would greatly increase their cost and create new obstacles to care for patients with rare diseases.

We believe that CED must be used in limited, well-defined circumstances that ensure its use expands access to care. During the Open Door Forum and in meetings with stakeholders, CMS has said that CED will be used infrequently and in narrow circumstances, yet the Draft Guidance provides several wide-ranging examples of circumstances in which CED could be used. The breadth of these examples, combined with CMS' recent application of CED to anticancer chemotherapy for colorectal cancer, implantable cardioverter defibrillators (ICDs), and PET scans, is difficult to reconcile with CMS' statement that it does not "anticipate a substantial number of new coverage decisions in the near future" that will use CED.[7] CMS' claim that it "does not anticipate issuing additional decisions" granting coverage without conditions[8] also has caused concern among stakeholders. We ask CMS to clarify that "coverage with conditions" does not mean CED. Instead, CMS should explain in the next version of the Draft Guidance that coverage with conditions merely means that, as has been the case with most recent NCDs, coverage is limited to beneficiaries with listed diagnoses or characteristics or when performed in certain facilities. We also ask CMS to clarify whether "coverage with conditions" is entirely separate from CED or whether the two could be applied together.

We recommend that CMS explicitly state in the next draft of the guidance document that CED will be used rarely in narrow circumstances and only to expand coverage. We urge CMS to state that:

1. CED will not be applied to drugs, biologicals, or devices used in accordance with their FDA-labeled indications;

2. CED will not be used where Congress has established an evidence standard by statute, such as the requirement to cover off-label uses of drugs and biologicals used in anticancer chemotherapeutic regimens that are listed in the compendia or supported by peer-reviewed literature;

3. CED will not be used for well-established off-label indications of devices or off-label indications of drugs and biologicals listed in

[7] Draft Guidance, at 2.

[8] Draft Guidance, at 4.

major drug compendia, supported by peer-reviewed literature, or determined by contractors to be the accepted standard of medical practice;

4. CED will not supplant carrier discretion except to affirmatively mandate coverage, and carriers will be instructed to continue to apply local coverage as they do currently;

5. CED will not be used unless a patient access problem has been observed, such as when coverage denials by local contractors are widespread or when a trial sponsor believes it will have difficulty enrolling patients in a trial without CED; and

6. CED only will be used when there are legitimate clinical questions about an item or service and not just when coverage of the item or service will significantly increase costs to the Medicare program. It should be based on a lack of evidence needed to justify a positive coverage decision, not on the FDA approval pathway.

Patients must have access to appropriate therapies, regardless of whether they participate in evidence development projects. We also recommend that CMS learn from its recent applications of CED before applying it to other items and services. The agency should monitor and evaluate beneficiary access to care after the implementation of the NCDs for anticancer chemotherapy for colorectal cancer, ICDs, and PET scans to verify that patients have been able to receive these therapies, regardless of their participation in evidence collection. Only after long-term patient access has been verified should CMS evaluate whether and how to apply CED again. We reiterate that CMS should clarify that patients will continue to have access to therapies through the local coverage process while evidence is being collected and analyzed. For a well-designed CED, this process could take a while.

II. If CMS applies CED to an item or service, it must ensure that relevant, robust data are collected at minimal cost to patients, providers, and manufacturers.

CHI is concerned that the Draft Guidance and CMS' recent experience with CED provide little assurance that CED will be applied in a manner that will produce relevant, robust data at minimal cost to patients, providers, and manufacturers. For example, during the May 9, 2005 Open Door Forum, agency staff acknowledged that data from the ICD registry might not rise to the level needed to reach a coverage decision. It therefore is not clear that the data will be of

use to CMS, raising questions about how the registry fulfills CMS' stated purpose for CED – to obtain data for use in coverage decisions.

Although CMS hopes to "develop[] methods for conducting simple, inexpensive clinical trials,"[9] our members know that thorough research is costly. Rigorous data collection efforts, such as randomized clinical trials, impose significant costs not only on the manufacturers who sponsor them, but also on the patients and physicians who participate. Patients often receive more services in clinical trials than they would outside a trial, potentially resulting in increased costs to beneficiaries if they are required to pay Medicare's coinsurance on those services. Physicians who participate in trials provide many services, such as evaluating patients' eligibility, data collection, and drug administrations, that are not reimbursed by trial sponsors or by Medicare. Medicare's predicted payment cuts for physicians, in addition to the revised reimbursement for drugs and drug administration services, will reduce many physicians' ability to donate time and resources to clinical research. We urge CMS to minimize the costs of evidence development whenever possible and to develop methods of reimbursing providers for the remaining costs of participating in trials, registries, and other data collection mechanisms.

We agree that "data collection instruments should be designed to minimize any burden to providers and patients while providing critical information."[10] A first step toward ensuring that the value of the information collected outweighs the cost of its collection is to consult stakeholders at each step of the CED process. CMS should begin any consideration of CED by meeting with relevant stakeholders, including manufacturers, to determine whether there is a need for additional data, the value of the information, and the burden of collecting it.[11] These stakeholders can provide important information about the costs to research the technology, other studies underway, and the pending availability of new versions of the technology. For example, because the lifecycle of a device often is as short as 18 to 24 months, a

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[9] Draft Guidance, at 11.

[10] Draft Guidance, at 14.

[11] As described in depth our comments on the agency's draft guidance regarding "Factors CMS Considers in Opening a National Coverage Determination," we believe CMS should list all topics it is considering for internally generated requests and seek further information from the public before officially opening a NCD whether CED is to be applied or not. Letter from David Gollaher, President & CEO, CHI, to Steve Phurrough, Director, Coverage and Analysis Group, CMS, regarding comments on draft guidance entitled "Factors CMS Considers in Opening a National Coverage Determination," May 7, 2005, available at http://www.chi.org/brandomatic/othermedia/chi/Opening_an_NCD_comments.pdf.

large study could barely be started before the next generation device enters the market. In this case, the manufacturer could inform CMS that the costs of collecting data may outweigh its usefulness. Likewise, if CMS considered applying CED to an orphan drug or humanitarian device, stakeholders could educate CMS about the impracticality of creating a large evidence base for treatments for rare conditions. Early stakeholder involvement also will help ensure that CED is used when significant clinical questions need to be answered, and not merely to limit utilization of costly therapies.

If CMS and stakeholders agree that more evidence is needed, they must identify the specific research questions that must be answered. With specific questions in mind, they should review the ongoing or planned research efforts that could develop relevant evidence. CMS correctly observes, "[T]here should be no redundancies in the data collection system."[12] We concur with CMS' conclusions that existing data systems should be used when available to avoid expending resources on new systems[13] and that CED requirements must be aligned with the FDA's clinical study requirements.[14]

If no existing or planned studies will produce the necessary evidence to answer CMS' specific research questions, CMS must work with stakeholders to design an appropriate data collection method with defined endpoints to address those questions. CMS correctly recognizes that "data collection protocols will vary according to the use of the item or service being provided, the purpose of the data collection, and the group of patients receiving the item or service."[15] CMS is fortunate to have access to many stakeholders, such as our university members, with vast experience in clinical trial design and operations. For each item or service considered for CED, we urge the agency to commit to consult with knowledgeable stakeholders to identify an appropriate evidence development method that will produce useful data. CMS also must define the project's endpoints clearly to ensure that data collection continues only as long as important questions remain.[16]

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[12] Draft Guidance, at 14.

[13] Draft Guidance, at 14.

[14] Draft Guidance, at 5.

[15] Draft Guidance, at 11-12.

[16] Draft Guidance, at 5.

Input from experienced stakeholders is crucial to helping CMS overcome the challenges of collecting useful data in a cost-effective manner. We urge CMS to learn from previous data collection efforts and work with stakeholders to identify evidence development methods that will address the agency's data needs.

III. Conclusion

CHI appreciates this opportunity to comment on the Draft Guidance regarding CED. We believe this approach to Medicare coverage could have a substantial impact on beneficiary access to care and continued innovation by research institutions and drug, biological, and device manufacturers. Given the complexity of the issues involved, we urge CMS to hold public meetings on this initiative in order to have a more comprehensive dialogue on the agency's goals as well as questions and concerns regarding CED. We hope that CMS will give careful consideration to our comments and incorporate them along with the agency's clarifications into a second draft of the guidance document for another round of discussion and comment.

In summary, to help CMS refine its approach to CED, we offer the following comments for the next draft of the guidance document.

- CMS must clearly explain the legal authority supporting its use of CED.
- CED must be used rarely and only to expand coverage.
- CED will not be applied to drugs, biologicals, or devices used in accordance with their FDA-labeled indications.
- CED will not be used where Congress has established an evidence standard by statute, such as the requirement to cover off-label uses of drugs and biologicals used in anticancer chemotherapeutic regimens that are listed in the compendia or supported by peer-reviewed literature.
- CED will not be used for well-established off-label indications of devices or off-label indications of drugs and biologicals listed in major drug compendia, supported by peer-reviewed literature, or determined by contractors to be the accepted standard of medical practice.

- CED will not supplant carrier discretion except to affirmatively mandate coverage, and carriers will be instructed to continue to apply local coverage as they do today.

- CED will not be used unless an access problem has been observed, such as when coverage denials by local contractors are widespread or when a trial sponsor believes it will have difficulty enrolling patients in a trial without CED.

- CED only will be used when there are legitimate clinical questions about an item or service and not just when coverage of the item or service will significantly increase costs to the Medicare program.

- CMS must consult with stakeholders at each step of the CED process to ensure that it collects robust, relevant data at minimal cost to patients, providers and researchers.

- CMS must meet with stakeholders prior to issuing the next draft of the guidance document to discuss our concerns.

We look forward to working with CMS as it develops this policy, and we would be happy to discuss these comments with you in more detail. If we can be of any assistance, please contact Todd Gillenwater at 858-551-6677. Thank you for your attention to this important matter.

Sincerely,

David L. Gollaher, Ph.D.
President & CEO

Organization: Cancer Leadership Council

The undersigned organizations in the Cancer Leadership Council (CLC) represent cancer patients, providers and research organizations. Both the CLC and our individual organizations have been engaged in advocacy on Medicare coverage issues for a number of years and have welcomed a newly collaborative approach to those issues on the part of the Centers for Medicare & Medicaid Services (CMS). We regard the draft Guidance on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development" as a continuation of several promising trends in CMS policy: first, a willingness to assume a more expansive approach to coverage of new or unproven technologies; and second, a new emphasis on the collection of data as part of a move toward measurement of quality in treatment of cancer and other serious or life-threatening diseases.

The draft Guidance will raise questions for some, including providers who may be called upon to collect data without mechanisms for reimbursement for their efforts, as well as device manufacturers who may doubt that coverage is in fact being expanded. For cancer patients, the primary concern is whether the new coverage with evidence development (CED) policy will interfere in any way with the strong coverage protections for cancer drugs set forth in the current Medicare law.

Under § 1861(t)(2)(B) of the Social Security Act, Medicare coverage for cancer drugs specifically includes "any use which has been approved by the Food and Drug Administration," as well as those additional uses not approved by FDA but cited in certain medical compendia. These assurances of coverage were prompted more than a decade ago by patient and physician outcry over inconsistent coverage decisions by Medicare contractors and are now considered by the entire cancer community to be vital to quality cancer care for Medicare beneficiaries. The failure to recognize that the new CED policy in no way affects this statutorily mandated coverage has generated some understandable anxiety, which we believe would be dispelled by CMS clarification on the point.

The current leadership of CMS has been very progressive with respect to coverage issues, and we support this additional incremental step toward expanded coverage and enhanced evidence development while encouraging clarification of the matters discussed herein.

Thanks to CMS and its coverage staff for their responsiveness to the needs of people with cancer.

Organization: Chiron

Chiron Corporation is pleased to have the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS) draft guidance, "Factors CMS Considers in Making a Determination of Coverage with Evidence Development" issued on April 7, 2005 ("the Guidance). Chiron is a leading biotechnology company with businesses in biopharmaceuticals, vaccines, and blood testing. Chiron develops and manufactures innovative therapies for the treatment of cancer and infectious diseases. Chiron is located in Emeryville, CA with research and manufacturing facilities around the world.

Chiron expects to play a growing role in the treatment of senior citizens and the disabled for a variety of conditions. Several of our products, as well as products in the pipeline are or will be covered by Medicare Part B. Chiron supports the agency's desire to gather evidence to improve the quality of healthcare, but we urge the agency to ensure that its emerging evidence based medicine policies do not damage patient access to drugs and biologicals covered by Medicare. We hope that CMS will not hesitate to contact Chiron if we can provide assistance or expertise in any area.

I. Introduction

As a company devoted to discovering innovative treatments for cancer, pulmonary diseases and other debilitating and potential fatal conditions, Chiron clearly understands the importance of demonstrating the safety and effectiveness of these therapies. As a result, we appreciate the agency's emphasis on evidence-based medicine—which is a concept that underpins not only our company but the entire biotechnology industry. Our appreciation, however, must be balanced with concern that the CMS evidence-based medicine initiative, along with the coverage with evidence development (CED) decisions that represent one component of this initiative, will create new hurdles for patients seeking to access new and innovative therapies.

We are hopeful that the agency will carefully review the comments it receives on the CED guidance and issue another draft of the guidance, with another round of comments, to continue this important dialogue.

II. Chiron's Contributions to Evidence Based Medicine

The research and development of new drugs, biologicals, vaccines and blood tests that forms the heart of Chiron's business is, by definition, evidence-based. Before Chiron can sell a product for any purpose, it must be subjected to rigorous processes to ensure that the product will be safe and effective for its intended uses. Since its founding in 1981, Chiron has developed screening tests to ensure the safety of the nation's blood supply, vaccines to prevent influenza and other illnesses, as well as important treatments for various forms of cancer, cystic fibrosis, multiple sclerosis and other debilitating and potentially fatal illnesses.

In the case of each of these product areas, Chiron has had to secure the approval of the Food and Drug Administration (FDA) and international regulatory agencies to

market these products. Even after FDA approval, we continue to gather evidence about the current uses of our products and potential additional uses. We continually research the underlying causes of various diseases and seek new ways that these illnesses can be treated, and novel ways that information can be gathered about new treatments when they are identified.

Chiron is in the forefront of a movement that is altering the drug development paradigm to create human disease therapeutics with efficacy and safety profiles that are fundamentally more advanced than those for most drugs today. These new treatments rely on a fundamental integration of pre-clinical science and insights into the drug development process—an approach commonly referred to as "Translational Medicine". Under this approach, pre-clinical investigations are greatly enhancing our understanding of the nature and behavior of biological markers associated with disease states. These insights are then translated into the clinical setting, where the biomarker's behavior enables evaluation of a specific drug candidate's effects, while also informing drug design activities to optimize the targeting of future drugs, particularly in the area of oncology. Biomarkers are usually of two types:

(A) Target-effect biomarkers demonstrate that the drug is affecting (often inhibiting) its designated target in human subjects, ideally in the tumor tissue, or perhaps in a more accessible surrogate tissue such as peripheral blood cells. Data from such biomarkers enable appropriate dose selection for the candidate drug.
(B) Patient-selection biomarkers are readily measured indices that show whether a given patient is more or less likely to respond beneficially to a given drug. A good example would be the tests for tumor Her-2 over-expression or gene amplification that are used to determine whether a breast cancer patient is likely to respond to anti-Her-2 monoclonal antibody therapy. Such tests enable targeted clinical trials, which evaluate a drug's performance in a specific sub-population that is more likely to respond beneficially to the candidate therapy. This targeting of specific therapies toward patients with a higher likelihood of beneficial response will greatly increase the efficiency of healthcare spending in the coming years.

Chiron's decision to adopt and advance the Translational Medicine paradigm grew directly from our company's mission to discover and develop innovative products that greatly improve the quality of patients' lives. In a similar vein, we believe that our Translational Medicine approach—one that yields products targeted towards the patients who are most likely to respond beneficially—is not merely aligned with CMS' intentions on evidence based medicine, but in fact holds the potential to demonstrate the powerful therapeutic and economic benefits that evidence based medicine could bring to patients' lives.

III. The Interaction of the Draft Guidance with Current Regulation of Drugs and Biologicals

As you have acknowledged in public statements recently, there are some areas where the application of CED is not appropriate because CMS does not have the

discretion to impose additional coverage rules over and above those that have already enacted. Chiron urges CMS to issue additional guidance to clarify these limitations, specifically as they apply to drugs and biologicals.

Breakthrough medicines are subject to significant research and development costs, with some estimates suggesting that development through FDA approval could be $800 million or more. The significant time and resources that manufacturers of drugs and biologicals invest to prove to the FDA's satisfaction that their products are safe and effective must be taken into account when CMS considers application of CED. While it may be appropriate to apply CED to items or services that are not subject to this rigorous approval process, we find it difficult to believe that additional evidence that a drug or biological is reasonable and necessary for its intended uses will ever be justified if the relevant uses of that product are FDA approved. If postmarket surveillance is needed because of concerns about a product's safety or effectiveness, the FDA can and will condition approval on so-called "Phase IV" studies.

In addition, Congress has provided specific mechanisms for coverage of off-label uses of oncology products used in chemotherapeutic regimens that is designed to result in additional mechanisms for gathering evidence about these uses. By relying on compendia listings and peer reviewed literature, the statutory provisions governing the off-label use of oncology products ensure that the evidence analyzing the use of these products will be subject to expert vetting and that strong evidence that emerges from this vetting process will be made available for patients and doctors seeking information about these therapies. These provisions are effectively administered in most cases by local carriers—and should not be supplanted by CED decisions. In the event that CMS decides that CED is necessary for off-label uses of oncology products, the agency should make clear that local carriers maintain their discretion to cover these products outside of CED, based on compendia listings or evidence in peer-reviewed literature.

IV. Protecting Patient Access

Chiron's primary concern about the CED process is that it may serve to inhibit patient access to new therapies, either by creating new hurdles to coverage for existing products, or that these new hurdles will serve to chill investment in the innovations that will result in additional breakthroughs.

CMS has said that CED will only be applied in instances where it will expand coverage, but Chiron has some concern about the benchmarks against which such expansions will be measured. For instance, in the recent national coverage decision which imposed CED for certain uses of colorectal cancer treatments in NCI-sponsored clinical trials, it is our impression that in most cases patients in those trials were receiving the medicines being tested free of charge as part of the trial process. In that case, the addition of Medicare coverage for these products under the CED process would detract from current coverage, by imposing additional Medicare cost-sharing. In addition, local coverage decisions providing coverage for the uses in question may have also been in place.

Chiron urges CMS to measure whether or not a national coverage decision with CED will expand coverage based on the level of patient access to the relevant item or service under a variety of mechanisms, including existing clinical trials, before imposing CED requirements that may harm patient access. We further urge the agency to monitor how any CED decisions affect patient access and to reverse any decisions that have a negative impact on patient access.

Finally, Chiron strongly believes that CMS must provide additional information about the CED process, both in terms of when the process will and will not apply, but also in terms of how the evidence generated will be used. We believe that clear and foreseeable coverage and reimbursement rules for new products are necessary to ensure that companies and others that invest in research and development of new therapies will continue to do so. We are concerned that vague and confusing new processes not only will delay access to new therapies but could potentially cause investors in the biotechnology industry to look elsewhere, possibly preventing some therapies from being developed at all.

V. Conclusion

Chiron appreciates the opportunity to comment on this important draft guidance. As we have stated, we support the concept of evidence-based medicine, and indeed are a company dedicated to discovering new therapies and developing evidence that these treatments are safe and effective. We are concerned, however, that the CED process, if not carefully implemented, could serve to hurt patient access to new therapies. We believe that the instances in which the imposition of CED will be useful in the context of new drugs and biologicals will be limited. We urge CMS to ensure that any CED decisions that are imposed are truly necessary and do not harm patient access to new drugs and biologicals.

We are hopeful that our comments will be helpful to CMS as it considers how to proceed with the CED process.

Organization: CIRCARE

(Comment on next page.)

C I R C A R E

Citizens for Responsible Care and Research

24 Indian Lane 410-499-4895

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2005-06-06

Comments RE: Factors CMS Considers in Making a Determination of Coverage with Evidence Development , CMS Draft Guidance

Citizens For Responsible Care and Research, CIRCARE, is the oldest nonprofit research protection advocacy organization in the United States. Our board members are scientists, attorneys, academics, professionals, and laypersons who share a common commitment to effective protection for human subjects in research. CIRCARE has provided invited testimony to FDA, panels of the Institute of Medicine, House and Senate hearings, and federal bioethics advisory bodies. CIRCARE co-founder Adil Shamoo, Ph.D., was appointed to serve on the National Bioethics Advisory Committee, and CIRCARE vice-president Paul Gelsinger serves on the board of advisors for Partnership for Human Research Protection, Inc., the voluntary Institutional Review Board accreditation provider, a collaboration of the Joint Commission on Accreditation of Healthcare Organizations and NCQA. All board members serve without compensation. CIRCARE receives no funding from entities effected by the draft guidance.

CIRCARE appreciates the opportunity to comment on CMS proposed guidance, and we are pleased to submit our recent **CIRCARE InfoMail©** on the proposed guidance for Coverage with Evidence Development (CED) as comment to CMS.

Subject: Proposed Federal Guideline Would Coerce Human Subjects into Clinical Trials Without Informed Consent
Date: 2005-05-25

The Centers for Medicare and Medicaid Services has published draft guidance for Coverage with Evidence Development (CED) that would require Medicare beneficiaries to enroll in research as a condition of coverage for certain new technologies or drugs. The draft guidance violates basic principles of informed consent. (1)

It appears that some Medicare beneficiaries are compelled to participate as a condition of coverage for Implantable Cardiac Defibrillators, anti-cancer and cardio-vascular drugs. This violates the fundamental ethical principle that subjects must give voluntary informed consent: while the wealthy can choose to

forego coverage rather than enroll, finances and fear of death constrain the decision of those with fewer resources.

On page 3, the draft guidance states the following:

"The service is delivered in the context of specific data being collected. Coverage may be limited to providers who participate in and beneficiaries who are enrolled into a defined prospective data collection activity, when this data collection activity constitutes part of the evidence required to ensure the item or service provided to that patient is reasonable and necessary."

We find this recent statement by Dr. Stephen Hammill, MD to CMS about the ICD registry profoundly troubling:

"It would be quite unfortunate to have the informed consent process become a major stumbling block to entering patients and thus preventing patients from receiving primary prevention ICD therapy and being followed in the registry." (2)

We disagree that the fundamental ethical principle requiring subjects give informed consent to participate in research is a stumbling block.

We disagree that the requirement for IRB review and approval of human research is an unresolved issue. Medicare regulations explicitly require compliance with federal regulations for the protection of human subjects as a condition of coverage. The recently published "Summary of Coverage for ICDs" describes how prospective data will be collected through a registry study in which certain Medicare beneficiaries must enroll as a condition of coverage. (3) The study described requires IRB approval according federal regulations. The same federal regulations prohibit IRBs from approving research in which voluntary informed consent is not obtained from research subjects. (4)

Because CMS requires enrollment in the ICD registry as a condition of coverage, Medicare beneficiaries are forced to become research subjects without their consent.

In addition, it appears to us that the ICD registry trial has been confused with Quality Improvement (QI) information collection, with the result that Medicare beneficiaries may be enrolled in research without IRB review and approval as required by federal regulations.

The ICD registry is prospective data collection and so constitutes research. QI, by comparison, is exempt from the requirement of prior IRB review and approval because it collects and analyzes existing data. Moreover, we point out that Dr. Sean Tunis and Dr. Mark McLellan, head of CMS, discussed ICD clinical trial participation as a condition of coverage in the New England Journal of Medicine in February 2005. (5)

We respectfully ask that CMS take notice of the consequences to Medicare beneficiaries as a result of guidelines that conflict with federal regulations for the protection of research subjects. We respectfully suggest CMS consult with the Office for Human Research Protections in this matter, and we ask CMS to clarify the draft guidance document on Coverage with Evidence Development (CED) before moving forward.

The draft guidance on Coverage with Evidence Development (CED) raises serious concerns for the rights and welfare of research subjects. The Nuremberg Code, The Belmont Report, and The Common Rule (45 CFR 46) all unequivocally state that voluntary informed consent of the subject is essential. We reject the idea that seriously ill patients compelled to become research subjects as a condition of Medicare coverage can give voluntary informed consent.

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CIRCARE will post updates to this Infomail at:
http://www.circare.org/medicare.htm

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1. Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development (2005-04-07)
URL: http://www.cms.hhs.gov/coverage/download/guidanceced.pdf

2. Remarks by Dr. Stephen Hammill, MD, President, Heart Rhythm Society, to CMS Council on Technology and Innovation (2005-02-14)
URL: http://www.cms.hhs.gov/providers/cti/odfcomments214.pdf

3. Summary of Coverage for ICDs (2005-01-27)
URL: http://www.cms.hhs.gov/coverage/download/id148a.pdf

4. 45 CFR 46, The Common Rule. Code of Federal Regulations, Title 45: Public Welfare, Department of Health and Human Services, National Institutes of Health, Office For Protection From Research Risks; Part 46: Protection of Human Subjects (13 December 2001)
URL: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

5. Medicare Coverage of ICDs. McClellan M.B., Tunis S.R. N Engl J Med 2005; 352:222-224, Jan. 20, 2005.

Organization: Circular Boot Corporation

Attached are our comments regarding CMS' draft guidance on the Coverage with Evidence Development initiative. We applaud CMS for undertaking this important step to improve the level of care provided to beneficiaries and assuring that coverage determinations are made based upon the compilation of quality scientific data.

We believe that the Coverage with Evidence Development proposal contains significant merit and is entirely in line with two major goals put forward by Administrator McClellan: enhancing the level of medical and scientific data collected by CMS and utilizing new treatment options to improve the quality of care for Medicare recipients.

This initiative will hasten the use of innovative techniques that have the potential to improve quality of care and remove data gathering obstacles that currently impede new treatments from receiving a favorable coverage determination. In this regard, the objectives of CMS reflect those of Circulator Boot Corporation. We remain very optimistic over these developments and are encouraged to begin the process to apply for a National Coverage Determination with Evidence Development for the Circulator Boot™.

Our comments include background information about Circulator Boot Corporation along with ways in which the Coverage with Evidence Development initiative would aid the process by which this innovative treatment could receive a favorable National Coverage Determination.

We thank you for this important proposal and look forward to working with CMS to arrive at solutions that will be of value to Medicare beneficiaries.

Circulator Boot™
Ideal for Coverage with Evidence Development

Background

What is the Circulator Boot?

The Circulator Boot is a system of devices delivering 1.1 to 1.3 pounds per square inch air pressure to prescribed segments of the leg in the end-diastolic portion of the heart cycle. "Long Boots" may be prescribed which encase the leg from the groin to the toes in a hard plastic shell. Within the Long Boot, different pressure bags may be chosen to treat specific portions of the leg: groin-to-toes, groin-to-ankle, low thigh-to-toes or ankle, knee-to-toes, wherever the prescribing physician believes treatment is desirable. A "Mini-Boot" may be prescribed to treat the foot alone or with a canvass sleeve to treat both the lower leg and the foot. The computer in its heart monitor follows the rhythm and pulse rate of the patient and places leg compressions in end-diastole thus allowing each pulse wave to enter the leg unobstructed. Again it releases the leg just before mechanical systole. Release of the big muscles in the upper leg within the Long Boots allows a negative pressure wave (a drop in pressure) to reach the aortic cusps just as the heart begins to expel the stroke volume; afterload is thus reduced and both stroke volume and cardiac output significantly increase.

Why is Circulator Boot Therapy not widely used at present?

Insurance policy makers might be attracted to cover Circulator Boot treatments because of the potential savings: outpatient care versus inpatient care, low risk procedure versus significant operative risks, avoidance of amputations versus amputations and rehabilitation/nursing home costs, etc. Carriers generally rely on published data where the gold standard is a large placebo-controlled prospective study, but no such studies exist justifying the operative revascularization procedures practiced routinely in our hospitals today. There are many studies reporting the patency of various bypasses over time leaving the reader to assume that the leg was preserved because of the bypass.

A prospective placebo-controlled study has not been done by the surgical community in part because it has been deemed unethical. Indeed, the Helsinki ethical research guidelines may be interpreted that such studies may never be done with our Circulator Boot patients either. (http://www.mja.com.au/public/issues/172_06_200300/stockhausen/stockhausen.html). Thus, in the absence of an accepted ethical research protocol and in the absence of research funds, the Circulator Boot Corporation had decided on the slow path to recognition by hoping for slow growth and state-by-state acceptance.

How would Medicare and the public benefit by Coverage with Evidence Development Decision favorable to the Circulator Boot?

Review of our publications and the 200 plus case history illustrations shows the Circulator Boot is a cost-effective vascular support device:

1. We have benefited patients with ASHD and congestive failure both acutely and chronically in our outpatient clinic. Standard care had failed some of these patients. We have restored and maintained the failing circulation in patients with septic shock.
2. Combined with the use of local antibiotic injections, we have cured patients with osteomyelitis and necrotizing cellulitis in either the inpatient or outpatient scene. Treated early, these cures may be rapid occurring in a matter of several days thus avoiding hospitalization, multiple laboratory tests (serum levels of antibiotics), operative procedures and multiple consultations. Many of these patients had failed standard therapies and were at risk of major amputations.
3. We have relieved the pain and markedly improved the walking distance of patients with advanced claudication and/or rest pain due to inoperable arterial occlusive disease. We have benefited the bypass patient by both increasing runoff and the condition of the leg preoperatively and postoperatively.
4. We have cured venous stasis ulcers that had defied many months/years of standard care. (Early treatment would have spared the patient the pain and Medicare the costs of their previous ineffective treatments).
5. We have improved renal function sufficiently in some diabetic patients to avoid the much more expensive and risky dialysis procedures. (This benefit may be limited to diabetics with an element of pre-renal azotemia. Further data is clearly needed but will not be forthcoming until funds are available to enlist the aid of kidney specialists in suitable candidates.

Additional data will be required before the general medical community will be persuaded as to the effectiveness and economic benefit of the above claims. For Medicare to be assured that their investment is justified, the data described below might be required on the clinical record.

While a full complement of studies does not yet exist to document the cost-effectiveness of the Circulator Boot for the Medicare program, the savings are both intuitive and potentially substantial. Use of the Circulator Boot among diabetics has eliminated the need for amputations, increased mobility for patients, and improved circulatory and renal function in patients. The savings to the Medicare program from a reduction in amputations alone would be significant; moreover – and most importantly – such improvements would dramatically enhance the quality of life for beneficiaries.

We believe that Coverage with Evidence Development program for Circulator Boot would be entirely consistent with the goals of the Medicare Modernization Act, namely, reducing Medicare costs by improving the quality of coverage (and the quality of life) for beneficiaries. Coverage with Evidence Development program would enable Circulator Boot to continue compiling the data it needs fully to document the positive effects of this innovative treatment, while broadening the number of patients exposed to this new technique from whom we will be able to collect additional documentary evidence of the Boot's effects.

Factors CMS Considers in Making a Determination of Coverage with Evidence Development / Comments

"In general, CMS will consider requiring data collection as a condition of coverage when additional information is needed for CMS and its contractors to determine if an item or service is reasonable and necessary." / Such is clearly the case with Circulator Boot therapy which has been labeled investigational/ experimental by many insurance reviewers who note the limited number of publications and authors supporting the therapy.

"An initial list of circumstances in which coverage with data collection might be valuable includes:"

- "The item or service is likely to provide benefit, but there are substantial safety concerns or potential side effects that are inadequately described in available clinical literature." / Circulator Boot therapy in the hands of experts is remarkably free of adverse effects. For example, a given arteriosclerotic inoperable patient may present with gangrenous lesions involving a few toes, the heel and perhaps the lateral calf. As booting improves blood flow proximally to distally: the calf before the ankle before the toes, in such a patient, the calf lesion may begin to heal while the toes continue to deteriorate. The inexperienced therapist might interpret the increasing toe pathology to boot failure, but if the treatment continues the calf, then the heel, and finally the toes will heal.
- "The risks and benefits for off-label uses of an item or service have not been adequately addressed in the available clinical literature, particularly when risks are common or potentially common." / Off-label uses have included (1) supporting the failing diabetic kidney to avoid dialysis (possible mechanism: improving cardiac output and renal blood flow, stimulating nitric oxide and prostacyclin), (2) resolving ischemic lesions in the diabetic eye (Improved blood flow and the stimulation of circulating fibrinolysins are perhaps important here. We have added a few such eye cases to the case history section of our website. It may be noted that there are hundreds of ECP centers in China and that in their literature they describe benefit in treating stroke patients.)
- "The available clinical studies may not have adequately described risks and benefits in specific patient subgroups, or in patients with disease characteristics that exclude them from clinical trials, which make up significant segments of the Medicare beneficiary population likely to receive care if covered." / Our publications have described our benefits in patients untreatable by other means. Our literature represents a very small part of that in wound healing and peripheral vascular medicine.
- "Assessment of important outcomes has not been evaluated in the available clinical studies. These outcomes may include, but are not restricted to, long-term risks and benefits, quality of life, utilization, costs, and other real-world outcomes". / While the benefits over various time intervals up to 15 years have been described, the improved quality of life for the patient escaping leg amputation, vascular surgery, or dialysis has not been emphasized. Nor has the relative savings in monetary costs been emphasized (outpatient booting versus in patient care etc.)

- "There may remain questions about the comparative effectiveness of new items and services compared to existing alternatives or to usual care." / Many, if not most, of our patients had exhausted standard care and had the option of an amputation or boot therapy. Leg salvage with boot therapy is obviously a desired outcome. If Boot therapy will work on inoperable (i.e. the most sick) patients, it might easily work on less sick patients who are well enough to undergo reconstruction procedures.
- "The evidence to date shows statistically significant benefits but the clinical significance of the outcomes may not be well understood." / The acute effects of boot therapy are easily seen in the vascular laboratory where they may be affected or stopped with the flick of the switch. The chronic effects of boot therapy include statistically significant changes in vascular tests, healing of legs failing other treatments, healing of legs with vascular tests that predict healing is unlikely, and healing and maintenance of the "sick" leg while the "control" leg fails.

Evidence Development Methods / Comments

- *Databases* – Our published methods of treatment include much of the material above allowing the treating physician to classify degree of ischemia and classify severity of lesions and infection for each patient. These classifications have been associated with likely outcomes with standard treatments. The physical findings described above alert the physician to the nature and severity of the patients' disease, provide guidance as to the need for specific diagnostic tests, and again provide a database. Our published tables for our Method of Treatment provide guidance for the treating physician and require observations from the physician again accumulating data. Thus, we teach important economical and quick means of assessing the vascular status of the patient.

  We provide guidance for hospitalization and immediate care maximizing the benefit of boot therapy while minimizing costs. These guidelines provide a patient tack that can be compared with standard care. Not all patients in a given hospital will be referred to a boot service; these other patients provide a potential "control" group. It would help if Medicare required their beneficiaries to be included in retrospective chart reviews for research purposes. In the Bryn Mawr Hospital, our chief of vascular surgery would not allow his patient charts to be reviewed for comparison with those receiving boot therapies claiming such a review exceeded patient confidentiality policies.

- *Longitudinal or cohort studies* – Patients with vascular disease and neuropathic foot problems do relapse. Thus, there are a lot of "re-do" vascular procedures. Likewise patients benefiting from boot therapy may relapse or develop new lesions. Patients relapsing may merely be pumped again and experience a long symptom-free interval; their outlook differs depending on their overall health habits and status (smoking, dialysis, congestive heart failure, loss of mobility due to stroke, etc). Long term follow-up studies are time consuming and difficult. Access to Medicare data in which patients are tracked around the country by their social security numbers would greatly simplify such studies.

- *Prospective comparative studies* – Helsinki ethical considerations require that patients receive optimal treatments if effective treatment is available. For example, we have designed a prospective study on the “other leg” of diabetic amputees. There is much data to show that the life of the patient and the other leg are at great risk. We proposed randomizing the other legs and comparing those receiving boot therapies prophylactically during their rehabilitation from their first leg amputation with those who did not receive such boot therapy. Because not all potential boot patients in a given hospital will be referred for boot therapy, it would help if Medicare regulations required that their beneficiaries be included in chart reviews as potential “controls” for other treatment studies in their or nearby hospitals. Even then comparative studies would remain difficult as the data on the charts of those following our boot protocols contain much more meaningful data than the charts of physicians not specializing in wound care.

- *Randomized clinical trials (RCTs)* – There are many social and environmental factors that affect the outcome of the patient with a bad diabetic foot: age, degree of obesity, control of the blood sugar, smoking, etc. It is worthwhile noting that boot therapy helps most patients in spite of many of the preceding risks. Still, randomizing such factors would require a large study. Such a study might require the hospitalization of boot patients normally treated as an outpatient so that the advantages of the hospital care and bed rest associated with standard therapies might be equally shared by the boot patients. We would love to have a series of small RCT’s; for example, one could compare the healing rate of osteomyelitis in the diabetic toe in otherwise healthy well-controlled diabetics. One might compare the degree of neuropathy remaining in the foot following boot therapy or bypass surgery. Or, again, compare the fate of patients with inoperable (or operable) rest pain treated by boot or other means.

Organization: Coalition of Cancer Cooperative Groups

(Comment on next page.)

Coalition of
CANCER COOPERATIVE GROUPS

THE VOICE FOR
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June 6, 2005

Steve Phurrough, M.D.
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
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Mailstop: C1-12-28
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Re: Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

Thank you for this opportunity to comment on Centers for Medicare and Medicaid Services' (CMS) "Draft Guidance Document Regarding Factors the CMS Considers in Making a Determination of Coverage with Evidence Development" (CED or Draft Guidance). The Coalition of Cancer Cooperative Groups is a non-profit organization dedicated to increasing awareness of, and participation in, cancer clinical trials. Our membership represents a prolific network of approximately 8,000 physician/researchers nationwide in nearly 2000 hospitals and oncology practices nationwide. Collectively, our members comprise the National Cancer Institute (NCI) sponsored cooperative group system that accounts for more than half of all patients entered onto clinical trials in the United States. In addition, 40 national patient advocacy organizations participate as *Associate Members*, thus assisting us in nationwide efforts to ensure continued access to clinical trials for cancer patients.

We believe that CED has the potential to cause a profound impact on the work of the cooperative group system in establishing the standards of care, based on evidence, for Medicare patients in this country. We applaud CMS for maintaining its commitment to clinical trials, and encourage the agency to continue to embrace the significance of cancer clinical trials as it has done since 2000 when it issued the National Coverage Decision (NCD) requiring coverage of all routine patient care costs in cancer clinical trials.

As CMS considers CED and specific Medicare-wide coverage decisions now and in the future, the 2000 oncology NCD should be part of the landscape. Nothing in CMS's coverage decisions should challenge the fundamental validity of the 2000 decision.

CMS has proposed to use CED as a means to encourage the collection of more clinical data about patients' treatment options. We agree with CMS that clinical evidence is essential for helping patients and physicians make treatment decisions. We find the Draft Guidance to be vague and confusing, however, particularly in its applicability. Regulatory and compliance requirements are a tremendous component of the clinical trials process and there are numerous regulatory and compliance issues which will have to be addressed in order to develop a system and process which meets regulatory requirements and provides useful data relating to evidence based care. It is not clear from the current draft that such issues are being seriously considered or addressed. We will detail other areas of concern below, and it is our belief that CMS, after careful consideration of the current responses from the cancer community, issue a new Draft Guidance, with an additional public comment period.

In preparing such a draft we recommend that the agency include the following points:

1. It is important that the CED guidance explicitly states that it does not in any way abrogate, or in any way weaken, the existing practices regarding the off-label usage of anticancer drugs based upon compendia listings and local carriers' reviews of data.

2. The decision to use CED will be made after consultation with stakeholders, particularly clinical experts with a strong background in clinical trials and other evidence based approaches, such as cancer related Biostatistics

3. CMS will consider CED in a manner that assures no unnecessary costs for providers and patients.

We discuss these recommendations in more detail, as follows:

I. <u>It is important that the CED guidance explicitly states that it does not in any way abrogate, or in any way weaken, the existing practices regarding the off-label usage of anticancer drugs based upon compendia listings and local carriers' reviews of data.</u>

All tolled, only about 4% of adult cancer patients participate in cancer clinical trials. It must be kept in mind that "elderly" patients are a very highly underserved population on both the publicly and privately funded clinical trials system. Therefore, their major access for Medicare patients to new drugs will always be through the existing statuary approaches to the use of off-label drugs.

During the May 9, 2005 Open Door Forum on this subject CMS acknowledged that CED would be used rarely and not for (i) on-label uses of drugs; or (ii) off-label uses of drugs that are used in an anticancer chemotherapeutic regimen and for which the use is listed in a compendia or is supported by peer-reviewed literature. This helpful clarification of CED was not included in the Draft Guidance, yet is an extremely important inclusion to ensure the continuation of existing policies.

II. The decision to use CED will be made after consultation with stakeholders, particularly clinical experts with a strong background in clinical trials and other evidence based approaches, such as cancer related Biostatistics.

The application of CED to a particular item or service will impose significant burdens on providers of that treatment. CMS should decide to use CED only after discussing its usefulness and effects on patient access to care with all relevant stakeholders, particularly clinical research experts who can provide CMS with a full understanding of the applicability of a proposed data collection requirement as an additional regulatory requirement on the current clinical research system. We appreciate that CMS has included medical professional associations, practicing physicians, physician group practices, and hospitals among the stakeholders whose input will be considered when establishing priorities for the use of CED[1] and expect to see that statement included in the final guidance document. It is equally important, however, that the agency consult with clinical research experts about the initial decision to move forward with an NCD and the decision to use CED for specific items or services. Our input can help CMS ensure that the applicability of CED is fully assessed at the outset. We also can help the agency assess whether a specific proposed data collection requirement will expand access to care and whether additional costs will be imposed on beneficiaries and providers, and thus whether opening an NCD is warranted.

We also understand the interest on the part of CMS to encourage, or support, studies having simple designs, endpoints and reporting requirements. But it must be realized and emphasized that all of clinical cancer research and medicine is entering a more complex era where studies and treatments will be based upon key biologic parameters of both the tumor and the patient. We, in the Coalition, have extensive experience with trials of various levels of complexity, but even the most simple survival based study requires additional time and effort on the part of participating sites AND although survival appears to be a simple endpoint it is fraught with confounding variables in cancer patients ranging from the aggressiveness of supportive care, co-morbidities, toxicity issues and the

[1] Draft Guidance, at 11.

increasing availability of effective second and third line treatments for an increasing number of cancers. As research—especially in cancer care—moves into biologically driven trials, clinical questions are becoming more complex, raising a critical question at the outset as to whether the data CMS seeks will be obtainable only via Medicare's likely diverse patient population.

How the data are collected must involve the clinical experts. The Draft Guidance assumes that data collection requirement will be fulfilled by clinical research support staff at the site level, when in fact, data collection will most likely require the expertise of personnel proficient in Medicaid and Medicare reimbursement filings. Will CMS actually be able to collect the CED data it seeks without establishing and funding a large new, nationwide research mechanism?

We agree that a "systematic expansion of practical clinical research efforts to address the needs of health professionals and patients"[2] would be valuable, but we are deeply concerned that CED is neither an appropriate nor effective means to achieve this expansion. CED attempts to satisfy CMS' desire for more data, but does not address the needs of the rest of America's clinical research system. In particular the publicly funded clinical trials system relies on the talent, financial resources, and collaboration of a wide variety of entities, including patients, physicians, researchers, the pharmaceutical and biological industries, and hospitals and other health care providers. Any effort to expand clinical research opportunities must be undertaken with a full understanding of these entities' contributions to the system and the complex relationships among them.

Currently, the publicly funded system reimburses for the research cost of conducting its trials at about $2000/case, which by most estimates is one-half to one third of the costs required to perform the research. It is not reasonable to assume that existing resources can be stretched to add additional reporting requirements at the treatment site level without additional reimbursement.

We urge CMS to bring all stakeholders together to discuss ways to effectively increase support for and use of our clinical research system, and pay particular attention to research by community oncology practices—which account for approximately 60% of all cancer clinical trial accruals.

III. CMS will consider CED in a manner that assures no unnecessary costs for providers and patients.

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[2] Draft Guidance, at 4.

The Draft Guidance explains that evidence development requirements should assure that "no unnecessary costs are imposed"[3] on providers. We share CMS' concern about the cost of clinical research, and we urge the agency to examine fully providers' costs of participating in trials and registries. Providers who participate in clinical research currently are required to absorb considerable uncompensated costs, especially the costs of drug administration, patient counseling, data collection, and the extra staffing required to comply with trials' requirements. Many providers donate their time and resources to support clinical research, but as reimbursement for care outside trials becomes leaner, providers have fewer funds available for these efforts. We agree that CED should use the "least resource-intensive mechanisms possible,"[4] but we also urge CMS to reimburse providers for their necessary costs. In addition to compensation for the costs described above, CMS also must assist providers with the costs of developing the information technology infrastructure needed for data collection. Although an unfortunate reality, the clinical trials system in both the public and private venues is still essentially paper based. Therefore the most experienced personnel who record clinical trials data don't have general access to an easily adaptable or identifiable remote data capture system.

We also believe that CMS must be sensitive to patients' costs of participating in clinical trials. On the public side of the system, no ancillary costs for participation, e.g. travel, home care etc are reimbursed. Currently, other trial sponsors, including pharmaceutical companies, underwrite most of patients' cost of participating in clinical trials. The drug under investigation, as well as many of the other drugs and services involved in the trial, are provided at no cost to the patient. It is not clear how CED will affect this system of trial support. If manufacturers are dissuaded from donating their drugs, patients' costs of participating in trials could increase substantially.

The publicly funded system is heavily involved in performing studies that expand the indications for drugs with an approved indication. In essence the studies rely on the availability of "off-label" use in order to establish new treatments for cancer. If pharmaceutical studies provide drug and NCI studies rely on off label usage there may be an imbalance that might jeopardize the public side of the system. We are particularly concerned that patients would be liable for Medicare's 20% co-payment in a CED trial but would be able to get the drug at no cost in another trial. We strongly recommend that CMS ensure that its coverage proposals do not discourage "off-label" use in publicly sponsored trials or the aforementioned underwritten industry support for clinical trials thereby increasing beneficiaries' costs of care. The agency must clarify in its revised

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[3] Draft Guidance, at 5.

[4] Draft Guidance, at 5,

guidance that CED will be applied in a manner that weighs and minimizes any increased costs for beneficiaries.

On behalf of the Coalition of Cancer Cooperative Groups and the thousands of cancer patients whom we ultimately serve, I greatly appreciate this opportunity to comment on CMS' Draft Guidance regarding the use of CED. Our entire life's work, through our clinical trials, is devoted to developing an evidenced based framework for cancer care. We encourage CMS to address these and others' concerns in the next draft of the guidance document and to allow the public another opportunity to comment on the document. We would be pleased to answer any questions about these comments. Please contact me at 215-789-3609 if we can be of any assistance.

Sincerely,

Robert L. Comis, MD
President and Chairman

Organization: Colorectal Cancer Coalition

(Comment on next page.)

COLORECTAL CANCER COALITION
Research ▪ Policy ▪ Awareness

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June 6, 2005

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Re: Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

The Colorectal Cancer Coalition (C3) appreciates this opportunity to comment on the draft guidance document regarding factors the Centers for Medicare and Medicaid Services (CMS) considers in making a determination of coverage with evidence development (CED). We appreciate CMS diving into this complex topic, and are excited about the potential long-term public benefit offered by CED and related initiatives.

C3 is dedicated to eliminating the suffering and death due to colorectal cancer. Colorectal cancer is diagnosed in approximately 150,000 Americans each year, and kills over 50,000. New drugs – oxaliplatin, bevacizumab, cetuximab – and evolution in treatment of metastatic disease is leading to profound changes in the prognosis of patients diagnosed with metastatic and high-risk colorectal cancer. As these treatments are tested in the adjuvant setting, they may have a similar impact on disease-free survival for more stages of colorectal cancer.

At the same time, the cost of these new treatments is staggering, and point out the need to support research which will help match patients to beneficial treatments.

C3 supports the statements offered by the Cancer Leadership Council (CLC) and Association of Community Cancer Centers (ACCC). Both statements offer specific comments around access to treatment in under CED. In addition, the ACCC comments

raise concerns about the disconnect between the draft guidance and public statements by CMS officials. This disconnect is particularly concerning to us – while we have heard presentations by CMS officials which lay out a bright future, the specifics are not detailed in the draft guidance. The following extract from the ACCC comments is quite explicit (**bolding is ours)**:

> *CMS has proposed to use CED as a means to encourage the collection of more clinical data about patients' treatment options. We agree with CMS that clinical evidence is essential for helping patients and physicians make treatment decisions, and we strongly support efforts to expand research**. We find the draft guidance document to be vague and confusing, however, and to be inconsistent with oral descriptions of CED made by agency staff, as well as CMS' recent application of CED in national coverage determinations (NCDs).** Accordingly, we urge CMS to issue a new draft of the guidance document with an additional comment period. In preparing such a draft, we recommend that the agency include the following points:*
>
> 1. *CED will be used very rarely and never will be used for on-label uses of drugs or off-label, compendia listed uses of drugs used in an anti-cancer chemotherapeutic regimen;*
> 2. *CED only will be used to expand access to care and will not be used to curtail access to therapies currently covered through the local coverage process;*
> 3. *CED will not be used to force patients to enroll in clinical trials;*
> 4. *CMS will apply CED in a manner that minimizes increased costs for beneficiaries; and*
> 5. *The decision to use CED will be made after consultation with stakeholders, including patient groups, and will be made only at the request of trial sponsors who believe Medicare coverage could help a trial move forward.*

In addition, the NCI-CMS task force examining this issue and prioritizing trials has – to the best of our knowledge – no external representation from consumer or professional communities, and its process and deliberations do not seem to be publicly available. We urge CMS to include external stakeholders in these ongoing discussions.

We would like to offer further comments for:

- **Section III – Factors Considered in Applying CED**
- **Section V – Evidence Development Methods**
- **SectionVI – Process for Study Design and Implementation**

Section III states: "*In general, CMS will consider requiring data collection as a condition of coverage when additional information is needed for CMS and its contractors to determine if an item or service is reasonable and necessary.*

"CMS intends to work consultatively and iteratively with external experts and stakeholders in developing the criteria and process for determining when to apply CED. In the short term, we are aiming to identify a small group of high priority pilot efforts on topics for which there is substantial agreement that better evidence would be valuable in expanding access to specific technologies and services while learning more about their risks and benefits to support shared decision making."

As a society, we have chosen to accept high toxicity in cancer therapies because the risk of the disease outweighs the risk of the therapy. In addition, we have chosen to accept incremental improvements in treatments that may be due to small improvements in many people, or big improvements in a few. Until recently, the technology to tell the difference hasn't existed.

Thanks to increasing knowledge and better technology, predictive and prognostic markers are being identified. These markers may help identify which patients will benefit from which treatments. In breast cancer, the OncoType DX test is helping patients with breast cancer understand their risk for recurrence – in consequence, Kaiser in northern California now supports use of this test. Similarly, Herceptin is a targeted therapy with a known target and a valid assay. Patients without the target are not offered the drug – and are spared needless toxicity.

We request CMS to consider this type of correlative research as a factor for CED. Research into predictive and prognostic markers and development of validated assays for these markers are critical pieces of the cancer care puzzle. We need this research sooner rather than later in order to maximize beneficial access to treatment.

Section V states: "*Developing methods for conducting simple, inexpensive clinical studies is essential to optimizing CED.*" Databases, longitudinal studies, prospective studies and randomized controlled trials are called out as supporting CED.

We request CMS to consider removing "randomized" and leave it as "controlled trials". In general, we agree that randomized trials are the correct standard; however, as research into the genetics of cancer is applied to patients, there may be times where non-randomized and/or adaptive trial designs may be appropriate.

Section VI states: ***"****When CMS requires evidence development, we should be assured that there is appropriate oversight of data collection enterprises and an efficient operations system."* At the end of Section VI, many questions to the public are raised about implementation of the specific goals identified in Section VI.

Perhaps inadvertently, CMS's questions to the public for Section VI sound as if the existing system has no oversight. CMS is familiar with NCI's large clinical trial infrastructure which reaches out beyond the clinical cooperative groups into SPORES and academic institutions. NCI's Clinical Trials Working Group has reviewed this

system, and will present recommendations to the National Cancer Advisory Board on June 7, 2005. We suspect that the intent of this section is to fill holes, not add layers. We request that CMS clarify this section of the draft guidance to reflect the existing infrastructure.

In addition, Section VI also states:

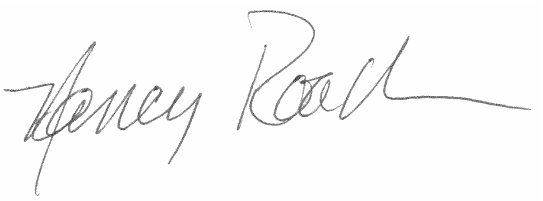
> *"Hypotheses – The data collected should be based on hypotheses integral to the evaluation of clinical safety and benefit of the item or service to the patient and provide information for physician decision making."*

While physicians may recommend decisions, ultimately patients make the decisions. We request that CMS amend the guidance to say "**patient and** physician decision making".

In conclusion, C3 feels that while the broad outlines of CED make sense, and while the details fleshed out in public appearances by CMS officials sound appealing, more specifics are needed in the draft guidance. CMS clearly recognizes the need for specifics due to the number of questions raised in the draft guidance. We respectfully request that CMS offer a new draft with fewer questions and more specifics for public comment. In addition, we suggest additional Open Door forums around future drafts.

We would be happy to answer any questions about these comments. Please contact Nancy Roach at 202-244-2906 if we can be of any assistance as you prepare the next draft of this guidance document. Thank you for moving this important initiative forward!

Sincerely,



Nancy Roach
Chair, Board of Directors
Colorectal Cancer Coalition
4301 Connecticut Ave NW Suite 404
Washington, DC 20008-2369

Nancy.Roach@c-three.org

cc: Board of Directors
Executive Staff

Organization: Community Access Center

I have reviewed the draft guidance on CED for NCD including its questions for the public. While the subject matter is outside my area of expertise, I would like to offer a few thoughts for your consideration.

I would first ask that you be cognoscente of gender specifics in reviewing study data regarding any new technology and/or medications. For example, it is alarming to me that after all of these years of being assured that taking low dose aspirin would reduce my risk of heart attack, to only recently be informed that it only works for men – not women (yet Bayer still has a commercial running inferring the contrary). What else was assumed to be true for women but has only been tested on men?

Then, there's the incidence of a 'lack of sufficient data' to provide evidence of a new technology/medication's efficacy. I ask that you include in your guidance that the individual's opinion and their physician's opinion be evaluated to gain approval for payment of the medication/procedure when there is a potential for quality of life improvement. Frankly, if the individual is willing to accept the risk for a chance at making them more comfortable or functional, they should not be denied due to a lack of substantiating data.

Finally, I am concerned that mental health parity should be required for medications that may improve an individual's brain chemical balance/quality of life. Currently, the law requires parity for medical/mental health services but not medications and Medicare HMO's fail to include these medications in their formularies. I would like to see CMS provide guidance to correct this disparity in care. While this may not be appropriate to this document, I would ask that CMS become sensitive to this issue.

Organization: Cook Group, Inc.

(Comment on next page.)

COOK®

Cook Group Incorporated

May 27, 2005

Steve E. Phurrough, M.D., Ph.D.
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Mailstop C1-12-28
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Dear Dr. Phurrough:

These comments are filed in behalf of the Cook Group Inc. Cook is a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique of angiography, and in techniques for interventional radiology and cardiology. Cook products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells over 15,000 different products which can be purchased in over 60,000 combinations.

We are pleased to submit these comments in response to the CMS request for comments regarding its Draft Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development. The publication of the Guidance and request for comments is another positive step in an extensive dialogue that CMS has conducted with stakeholders about Medicare coverage of items and services. This discussion has been a healthy one, and we commend Dr. McClellan and the CMS staff for taking so much of their time to consider input from those who are vitally interested in this subject. We set out our thoughts on this recent publication below.

First, we think it is absolutely critical that development of policy in this area be conducted with an understanding of the differences in device, drug, and biological product innovation. Medical device innovation is a fast moving process, fueled by practitioner feedback and rapid iterative changes. Compared with drugs, medical devices are short-lived. The product life of most devices averages only 18 months. The market for even widely used medical devices is quite small compared to the market for most

drugs. Indeed, there are tens of thousands of devices with markets of less than $1 million. We need to recognize these facts and tailor our observations and data gathering accordingly. For the vast majority of devices, evidence development as envisioned in the guidance is both unneeded and inappropriate. When it is required, we need to make certain that information collection techniques are designed so that they do not dampen the development of new medical technologies and procedures.

We are pleased to see that the agency states in the Guidance that it does not anticipate many new coverage decisions that require data collection. We are also pleased that the agency notes the importance of local coverage decisions as a "pathway by which new technologies are made available in the Medicare program." Yet, CMS states that all national coverage decisions (NCDs) will be made subject to conditions in the future. This implies to us that, indeed, national coverage decisions with evidence development (CED) will become increasingly common. In our view this would be inappropriate as it pertains to development of devices. The Food and Drug Administration is adding more and more requirements for data, both pre- and post- market, in its device approval process. In all but the rarest cases, coverage decisions can and should be made at the local level. Requirements for additional evidence development or other conditions will not be essential and will add significantly to the cost of bringing new products to market and ultimately to the cost of health care, as well as stifle product evolution.

There are other issues raised by the Guidance that cause additional concern for us. First of all, there are several references to CED being used to develop information regarding "safety." It is our understanding that determinations of safety fall solely within the purview of FDA, and the repeated use of this word may indicate an intent at CMS to expand its role beyond deciding what is "reasonable and necessary."

Similarly, the Guidance states on page one, "The primary purpose of obtaining additional evidence through CED is for the agency's use in making *payment* determinations..." (Emphasis added). And on page four, it says that "care provided under these protocols generally involves greater attention to appropriate patient evaluation and selection, as well as the appropriate application of the technology." Is the agency intending to use CED as a pricing mechanism? A means to control utilization or the practice of medicine?

It is also unclear how the evidence collected for a particular product "will also assist doctors and patients in better understanding the risks, benefits, and costs of alternative diagnostic and treatment options" (page four), and how it will be determined that "the service is reasonable and necessary for the individual patient." (page six). As CMS revises the Guidance, we hope that it will speak clearly on these issues and those raised in the preceding paragraphs. It is important for all to understand what is truly intended.

More positively and importantly, we commend CMS for stating the goal of providing prompt access to new medical technologies by collecting data during coverage. Dr. McClellan and other CMS officials have mentioned in public forums that Medicare's intent is to lower the initial evidence threshold to establish coverage, while then gathering additional evidence under "Coverage with Evidence Development." This, indeed, is much better than delaying coverage until more definitive studies are completed. If we move wisely towards this goal of providing prompt access, the device industry will be able to continue in its tradition of innovation, and patients will reap the benefits of exciting new technologies. If, on the other hand, CED merely adds an additional measure of clinical evidence needed to determine coverage, then this approach will ultimately fail those who stand the most to gain from medical innovation, its beneficiaries.

We also commend CMS for noting that the "potential value of information generated through coverage linked to evidence development must be carefully considered in the context of the burden associated with the collection of this data." The Guidance refers to a "value of information analysis" as a formal approach to assessing burdens vs. benefits. The Guidance stops short of defining what the elements of a value of information analysis might entail, however, and we recommend that the agency provide further clarification in this important area.

The Guidance also makes clear that CED should only be used to gather essential data and that data collection should only continue as long as important questions remain. Evidence development "should assure that no unnecessary costs are imposed." These statements appear to embody the concept of "least burdensome," which is a critical component of FDA's regulation of medical devices and should be given the highest emphasis by CMS.

We also believe the statements by CMS about the importance of the agency using routinely collected data from administrative sources are sound. We assume this includes Medicare claims data, and we encourage the agency to open a high level dialogue on how such data can be most effectively used and shared. If we proceed wisely, claims data and other databases could be used to examine the outcomes associated with a range of products and procedures in various treatment settings or facilities. If, for example, CMS has questions or concerns about endograft procedures for treating abdominal aortic aneurysms, it could use this sort of data to gather information on the reliability of the various products used in the procedure, the impact of practitioner training and experience, and facility performance. Similarly, claims data could help us ascertain the impact of antibacterial catheters. Their use could be compared to what should be an excellent historical database that reflects rates of infection and associated problems arising from the use of catheters that are not coated with antibiotics.

Clearly, this type of analysis is not an easy process, but instead of focusing on the problems that exist with respect to existing claims databases, CMS should look forward--to explore how changes can be made to produce the information we need for decision-making.

In a recent article, Dr. Sean Tunis of CMS called for the establishment of a system that is "simple," "inexpensive," and "reliable" to answer questions about medical therapies. If we develop smart ways to analyze existing and future databases, we will have a system that has those qualities and will also be self-executing.

We recommend that this effort be given the highest priority by CMS and that it use all available resources, including expertise in the private sector. The Regenstrief Institute in Indiana, for example, can assist the agency in finding ways to use existing and future databases built upon electronic medical records to enrich claims data and further our understanding of many therapies.

An important element in developing and utilizing data is the rapid development of a system of electronic medical records. We encourage CMS to continue its efforts in this area. Effective, governmental leadership is absolutely essential.

In the shorter term, we make the following recommendations to CMS as it considers CED:

--Because it will take time to develop systems to collect evidence in particular cases, attention should be given to ensuring patient access to newly covered medical technologies until registries or other data collection exercises become fully operational.

--CMS coverage should not be limited to those participating in post-coverage data collection efforts—i.e., those participating in post-coverage registries or observational trials. If the questions CMS might have with respect to the technology can be answered with a sample of those covered, coverage to others for a therapy should not be denied.

--Finally, all stakeholders need to be brought together to discuss ethical, privacy and other regulatory issues associated with the collection of patient data. Medical ethics, HIPAA requirements and IRB approval procedures will cause problems for post-coverage data collection efforts, and we need to find ways to solve those problems while still protecting essential patient interests. We have yet to realize "methods for conducting simple, inexpensive clinical studies" (page 11) for collecting useful data of adequate quality to address the issues described in the guidance.

To conclude, we thank CMS for the very hard work it has done in this very difficult area. We are grateful for the agency's vision and for the opportunity to share our views.

Sincerely,

Stephen L. Ferguson /RSV

Stephen L. Ferguson
Chairman of the Board

Organization: Elan Corporation

(Comment on next page)

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June 6, 2005

By Electronic Delivery to: CAGInquiries@cms.hhs.gov

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Dear Drs. Straub and Phurrough:

On behalf of the Elan Corporation ("Elan"), I thank you for the opportunity to submit the following comments on the Centers for Medicare and Medicaid Services' ("CMS") draft guidance regarding the factors CMS should consider in making a determination of coverage with evidence development (the "Draft Guidance"). Elan is a neuroscience-based biotechnology company that is focused on discovering, developing, manufacturing and marketing advanced therapies in neurology, autoimmune diseases, and severe pain.

Elan commends CMS for its ongoing efforts to promote evidence-based medicine and the collection of information that will assist patients, physicians, and payers determine when a medical treatment or technology is appropriate for a specific patient. Elan is committed to these same ideals and expends vast resources to test the clinical efficacy of our products. We also support the dissemination of this evidence to further clinical knowledge and enhance and

improve the clinical decision-making process. Nevertheless, Elan is concerned that coverage with evidence development ("CED") could reduce access to innovative drugs and biologicals, harming patient care both now and in the future.

While Elan recognizes the complexity of drafting the guidance, we feel that the Draft Guidance does not offer sufficiently detailed direction and conflicts with some of CMS's statements about CED during the May 9, 2005, Open Door Forum and the agency's recent uses of CED. We urge CMS to consider issuing a second draft of the guidance, with an additional comment period, that incorporates the feedback the agency receives on the current version. We believe strongly that such a process is necessary and would help to bolster stakeholder confidence in CED.
Our comments address specific concerns with the Draft Guidance, as well as respond to some of CMS's questions. Although we recognize that CED could apply to many items and services, we have limited our comments to the use of CED for drugs and biologicals, since this is the area where our company is experienced. We hope our comments are useful to you.

Clarify the Scope and Application of CED

Manufacturers' evidence development processes combined with the Food and Drug Administration's evaluation of product safety and efficacy and Medicare's current coverage and payment policies allow beneficiaries timely access to new therapies and encourages innovation. Despite this, the CED is proposing to change Medicare's role as payer into one of payer and research organization. Elan is concerned that CED could, if not applied narrowly, slow technology diffusion and innovation by limiting physicians' choice of therapies and freedom to use cutting-edge regimens. It could deny many beneficiaries who do not meet CED trial criteria access to critical therapies. It also could create uncertainty about reimbursement and could interfere with private market research priorities and funding, thus, slowing the development of new therapies.

The Draft Guidance states that CMS "does not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirement,"[1] and during the Open Door Forum, CMS said that it would use CED infrequently and in narrow circumstances. Despite these indications that CMS intends to limit the application of CED, the Draft Guidance lists broad circumstances in which CED will be considered and could encompass many uses of

[1] Draft Guidance at 2.

innovative therapies.[2] The agency's claims of the narrow use of CED are further put into question by CMS' recent national coverage determination (NCD) on anti-cancer chemotherapy for colorectal cancer. These conflicting and vague statements and actions make it difficult for stakeholders to truly understand how CMS plans to use CED. We ask CMS to provide a more detailed description of the circumstances in which CED will be used.

The Draft Guidance also is not clear as to the amount of evidence CMS needs about an item or service before deciding to use CED. During the Open Door Forum, CMS stated that the agency would use CED when the evidence is not complete to support full coverage and additional data would help CMS be confident about providing full coverage. The description provided during the Open Door Forum also does not correspond perfectly to the Draft Guidance's descriptions of the evidence required to reach any of the three possible coverage decisions.[3] It, therefore, is not clear when CMS would determine that enough evidence exists to apply CED instead of making a non-coverage decision or concluding that no national coverage decision is needed to inform coverage determinations made by local contractors.

CMS also provides little insight into the extent to which it intends to consider cost and utilization in deciding whether to apply CED. While cost and utilizations may be appropriate parameters for CMS to take into account when it is deciding whether to undertake a national coverage decision or entertain the need for a CED, cost and utilization should not, in our view, be considerations when a particular CED is being designed. CMS should clarify the role of cost and utilization in the next draft of the guidance document.

Finally, the draft guidance also suggests that CMS is positioning itself to creep into the Food and Drug Administration's jurisdiction. On page 9 of the Draft Guidance, CMS states that CMS may use CED when an " . . .item or service is likely to provide benefit, but there are substantial safety concerns. . .." CMS does not have the internal expertise for determining safety or for carrying out post-approval safety monitoring. FDA is the agency best positioned for this role and is being revamped to improve and expand its post-marketing safety surveillance activities. If CMS believes that safety issues are not adequately being dealt with, then the agency should work with the FDA to address its concerns. CMS also should articulate its concerns to Congress and the Administration to ensure that the FDA has the funding to finance the type of program that will

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[2] Id. at 9-10.
[3] Id. at 3.

protect Medicare beneficiaries. The answer is not for CMS to use its resources to take on this task.

Apply CED Only to Expand Access to Care and Without Interfering with the Local Coverage Process

CMS must provide clearer guidance as to the relationship between CED and local carrier authority. Elan is concerned that CED will curtail access to drugs and biologicals currently available through the local coverage process. As intended by Congress, this process allows beneficiaries to receive anticancer chemotherapy drugs and biologicals for off-label indications, when the use is supported by citation in certain compendia or peer-reviewed literature, or when the contractor determines that the use is medically appropriate.[4] It also permits beneficiaries to receive other categories of drugs and biological – not just anticancer chemotherapeutics – when the local contractor finds medical necessity. If medially necessary therapies are available only through clinical trials or other evidence gathering methods, many patients could be denied access to critical treatments. As CMS must be aware, many Medicare beneficiaries are ineligible for clinical trials due to age, comorbidities, or complications. Others may choose not to participate if the trial would require them to travel, change physicians, or experience other substantial inconvenience. This may be particularly true for patients in rural areas, minorities, and women, who traditionally have been under-represented in clinical trials. The local coverage process must remain intact to allow patients who do not qualify for clinical trials or who choose not to participate to receive appropriate therapies.

In the Draft Guidance, CMS says that it does not "anticipate circumstances under which CED would represent a net reduction in coverage available under local coverage policies."[5] To ensure that CED does not harm access to care, we ask CMS to commit to specifying precisely how the application of CED is expected to increase patient access. We also urge CMS to provide clearer instructions to carriers that a NCD with CED does not affect their discretion to cover uses of these therapies outside the CED requirements. CMS then should monitor and report on access to care after a CED decision is implemented both to verify that access is expanded as expected and that patients continue to receive the care prescribed by their treating physician, regardless of their participation in the evidence development exercise. Access monitoring also should be done for the CED activities currently underway.

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[4] Social Security Act § 1861(t)(2).

[5] Draft Guidance at 6.

Patient access analysis should be part of a comprehensive evaluation that CMS should be required to conduct whenever it proposes to use CED. All interested stakeholders then should have the opportunity to respond to the evaluation report. Such treatment is consistent with the Regulatory Impact Analyses and Regulatory Flexibility Analyses prepared for major rules and rules impacting small entities. CMS would be required to spell out the potential costs, burdens, and expected benefits of CED clearly before it implements each CED determination. These requirements should be incorporated into the next draft of the Guidance Document.

Distinguish the Application of CED to Drugs and Biologicals from Its Application to Devices

The application of CED to drugs and biologicals should be distinguish from its application to devices, particularly those devices that only are cleared for marketing under the 510(k) process and not approved through the pre-marketing approval (or PMA) process. Specifically, application of CED to products that undergo more rigorous evaluation by the Food and Drug Administration should be less common and less burdensome and should allow greater flexibility. This distinction would be consistent with CMS's past practices.

CMS historically has treated coverage of drugs and biologicals differently than other items and services, particularly devices approved under section 510(k) of the Federal Food, Drug, and Cosmetic Act. Indeed, in 1989, the agency said that its national policy is that drugs or biologicals approved for marketing by the FDA are safe and effective for on-label indications, but that FDA approval for marketing of a medical device does not necessarily lead to a favorable coverage recommendation, especially when the FDA approval is under section 510(k).[6] CMS should continue to acknowledge the different amounts and types of data required to approve these technologies by providing separate descriptions of its plans to use CED for drugs and biologicals as distinguished from devices. The agency also should separately describe the application of CED to procedures that do not require FDA approval. This approach would permit CMS to describe its plans and requirements with greater specificity.

[6] 54 Fed. Reg. 4302, 4306-07 (Jan. 30, 1989). See also, 52 Fed. Reg. 15560, 15561 (Apr. 29, 1987) ("Medicare coverage of drugs and biologicals is treated differently" than other item and services).

Clarify that CED Will Not be Applicable to Drugs Covered under Part D

CMS must clarify that CED will not apply to drugs and biologicals covered under Medicare Part D. CMS and the Administration have spent considerable effort to institute assessment procedures to assure the public that beneficiaries will have access to medically necessary medications under the new Part D program. For example, CMS has agreed to review every plan's (i.e., Medicare Advantage – Prescription Drug Plans ("MA-PDPs") and other Prescription Drug Plans ("PDPs")) formulary and to impose a defined exceptions and appeal process so beneficiaries may challenge plan coverage determinations. Elan is very concerned that the Part D plans will view or try to make the claim that drugs subject to a CED are experimental, and, therefore, not eligible for coverage under Part D. Such a consequence would be unfair and potentially financially devastating to a beneficiary who already will be paying considerable out-of-pocket dollars for Part D coverage. CMS must be clear about the relationship of CED to Part D and vigilantly monitor treatment denials by MA-PDPs and PDPs, which appear to be related to the inclusion of a drug in a CED trial.

Take Steps to Ensure that Proposed Evidence Collection Method Will Achieve Stated Goals with Minimal Burdens on Patients, Providers, and Manufacturers

When CMS uses CED for an item or service, it must take care to ensure that its chosen research methods can achieve specific goals with minimal burdens for patients, providers, and manufacturers. We agree with the agency that (1) the value of the information gathered must be carefully balanced against the burden of collecting it; (2) all CED requirements must be aligned with the FDA's clinical study requirements and with other research priorities to ensure that research resources are used efficiently; and (3) data collection only should continue as long as important questions remain and the effort and resources required to collect this data are justified by the potential value of the information to be collected.[7] The Draft Guidance does not, however, describe CMS's process for ensuring that these criteria are met.

We are especially concerned about how CMS will determine what hypothesis will be examined, when sufficient evidence has been gathered, and when CED will be brought to a close. Unless the research question is clearly defined from the outset, we cannot be confident that the study will produce data to satisfy CMS' needs or that coverage decisions will be made in an efficient and timely manner. Good quality research starts by asking the correct research question. Clear

[7] Draft Guidance at 5 and 14.

articulation of the research question informs all other aspects of research, including study design, enrolment criteria, sampling methods, power calculations, ethical considerations, and analytical plan. The consequences of a poorly articulated research question are development of faulty or biased data, or engagement in data dredging exercises with the inherent risk of making spurious inferences.

To ensure that an application of CED fulfils these criteria, we urge CMS to consult stakeholders at each stage of the process. Before beginning any evidence development process, CMS must work with stakeholders to assess the need for more evidence about a drug or biological, the value of the information to be collected, and the burdens on stakeholders of collecting it. With input from stakeholders, CMS must clearly articulate the specific research questions, goals, and limitations of the intended research design. As the evidence is gathered, CMS should consult with stakeholders about the data and its analysis. We support CMS's plan, described during the Open Door Forum, to release aggregate data to the public for additional analysis, but we emphasize that this is not a substitute for initial consensus about the trial's design and purpose.

In the Draft Guidance, CMS asks, "how should the costs of study design, data collection, analysis and other activities associated with these programs be fairly allocated to various stakeholders?"[8] In addition to minimizing these costs as much as possible, we urge CMS to pay particular attention to the costs imposed on beneficiaries and providers. Beneficiaries' cost of care under CED should not be greater than under coverage without evidence development. If beneficiaries are forced to incur greater costs for receiving care in Medicare-covered clinical trials or other evidence development programs, they may choose other, potentially less appropriate, care options.

CMS also must minimize the resources utilization related to CED. As we all are learning from the chemotherapy quality demonstration projects initiated under the 2005 Physician Fee Schedule, there are some considerable difficulties and costs related with collection and interpretation of diffuse registry data. Providers who participate in data collecting activities expend considerable amounts of time and resources to evaluating patients' eligibility for trials, data collection, and drug administration services that frequently are not fully reimbursed by trial sponsors, particularly public-sector trial sponsors. With Medicare's recent changes to reimbursement for drugs and drug administration and its pending reimbursement cuts for all physician services, many physicians are less able to afford to participate in under-funded clinical

[8] Id. at 15.

research. We must be sure that the data collected under CED is worth the costs of its collection, calculated considering the potential impact on participation in other clinical research activities involving more scientifically robust protocols and having greater potential to yield meaningful data. Certainly, the quality of data collected to date through CMS-initiated activities is not particularly robust and of questionable utility. CMS in conjunction with stakeholders must carefully weigh the cost and benefit of any CED activity. In addition, CMS should develop reimbursement codes and rates for these services to make participation in the CED research more financially feasible.

Conclusion

We hope our recommendations help CMS to apply CED in a predictable manner that ensures beneficiary access to innovative drugs and biologicals.

In summary, we encourage CMS to address the concerns articulated above by:

- Adding a "scope" section to the next draft of the CED Guidance that sets forth with particularity the types of situations in which CMS might use CED. The revised draft also should memorialise CMS' intention (as articulated publicly) to limit use of CED to a narrow set of circumstances.

- Explaining whether and how CMS intends to incorporate issues of cost and utilization into the CED process.

- Articulating in the revised draft that CED:
  - Will be used only when it serves as an expansion of coverage;
  - Will not be used for on-label use of drugs or biologicals;
  - Will not be used where there are statutory provisions setting out the Congressionally mandated evidence standard, e.g., for off-label uses of drugs or biologicals used in anti-cancer chemotherapeutic regimens that are listed in the compendia or supported by peer-reviewed literature;
  - Will not supplant local carrier discretion. Include examples of how local carrier's authority may be exercised in relationship to a CED.

- Distinguishing drugs and biologicals from devices and instituting different CED procedures for each the two categories.

- Clarifying that CED does not apply to drugs and biologicals covered under Part D and that MA-PDPs and PDPs will not be permitted to deny coverage as experimental just because a CED applies to coverage of a product under Part B.

- Stipulating that each CED will state the question(s) driving the CED decision, explain why the required study design is appropriate to the question(s), and clarify the amount of evidence CMS expects to collect to answer the question(s) underlying the CED.

- Taking steps to work routinely with stakeholders to ensure that a proposed evidence collection method will achieve its goals with minimal burdens on patients, providers, and manufacturers.

* * *

Thank you for your consideration of our comments. Elan looks forward to working with CMS to protect Medicare beneficiaries' access to innovative drugs and biologicals. If you have any questions regarding our comments, please contact me at (858) 320-7681.

Sincerely,

Nick Poulios, Ph.D.
Vice. President, Pricing and Reimbursement

Organization: Eli Lilly

(Comment on next page)

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June 6, 2005

ELECTRONIC SUBMISSION

Steve Phurrough, M.D.
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Dear Dr. Phurrough:

Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Eli Lilly and Company (Lilly) appreciates this opportunity to respond to selected questions for the public posed by the Centers for Medicare and Medicaid Services (CMS) in the April 7, 2005, draft guidance document (Draft Guidance) regarding factors CMS considers in making a determination of coverage with evidence development (CED).

Eli Lilly and Company is a leading, innovation-driven corporation committed to developing a growing portfolio of best-in-class and first-in-class pharmaceutical products that help people live longer, healthier and more active lives. Lilly products treat depression, schizophrenia, attention-deficit hyperactivity disorder, diabetes, osteoporosis, and many other conditions. We are committed to providing answers that matter - through medicines and information - for some of the world's most urgent medical needs.

V. Evidence Development Methods – Questions for the public (page 13)

- **What other study designs should be considered?**
- **What type of questions is each study design best able to answer?**
- **What are the limitations of each study design?**
- **Under what circumstances should CMS require a database? A longitudinal data collection? A prospective study? A clinical trial?**
- **How should CMS determine whether the evidence collected suggests patients are either harmed or not benefited by the item or service?**

Comments

Databases:

Retrospective analysis of administrative claims data carries with it several distinct strengths. Because they were not captured under conditions of a study protocol and therefore not subject to sentinel effects associated with study participation, these data are the most naturalistic, particularly regarding patterns of care. Retrospective research is generally much less costly than prospective research, especially when considered on a per subject basis. Analytic and design techniques, such as episode of illness algorithms, instrumental variable analysis, and propensity scoring, have advanced over time to mitigate some of the well known biases and gaps in data associated with such datasets. These studies can therefore be made to be analytic, although the intent in producing the dataset was not for research purposes at all. A final consideration is that retrospective analysis can be a good complement to prospective designs, both in generating hypotheses for prospective research and in exploring numerical trends from prospective studies that may require a larger dataset in which to confirm those trends at a statistically significant level.

Retrospective datasets also have numerous drawbacks. Many of these are well know, such as selection bias issues and gaps in data, particularly high quality clinical and health outcomes data. A less well recognized drawback of retrospective analysis is a practical one that emerges in the context of new technology assessment. Depending on the disease state being examined, construction of an episode of illness may require data for a period of eighteen months. Since new technologies often initially draw treatment failures from existing technologies, it is advisable not to use data from the first six months of availability of a new technology. Add to these times a window of a year in which to select eligible patients and a year to analyze and

disseminate, and it may well be four years past the introduction of a new technology before a database can deliver high quality data on which to make decisions.

Longitudinal or cohort studies:

From the description provided in the draft guidance, the assumption is that these studies do not have a comparison group and so by design are not analytic. By this strict definition, these studies would not be very useful for making choices between alternatives. However, in much the same way that administrative datasets can be made to fit a retrospective analytic design, so can descriptive studies that have a broad disease focus and that collect detailed data on exposure to treatments (Ascher-Svanum. Ann Gen Hosp Psychiatry, 3, 2004:11). These studies have the advantage over database studies of having a more complete set of clinical and health outcomes measures. However, they would be more expensive to conduct, more obtrusive than database studies, and have the same issues around selection bias and episode of illness construction. If such studies had to be started de novo and if they are in the same range of per patient cost as an analytic observational study, one would question why a descriptive study would be chosen.

Prospective Comparative Studies (also called 'practical clinical trials'):

While this section of the draft guidance includes practical clinical trials and analytic observational studies together, we believe there are important characteristics of the two that are often overlooked and little understood and that each deserves separate review.

1. **Practical Clinical Trials**

   In practical clinical trials (PCTs), the design supposedly allows us to enjoy the best of both worlds: to mitigate selection bias we have introduced the random assignment that is a hallmark of randomized controlled trials and we have allowed usual care and usual patients to permit the generalizability associated with observational studies. By mitigating selection bias, we also believe that we can employ statistical models on the basis of random sampling theory. However, such designs aim at understanding how a technology interacts with patient, provider and health plan characteristics to produce an outcome (Simon. JAMA, 275, 1996:1901.) In so doing, questions about the direct role of the technology in producing outcomes independent of the effects of other characteristics can be tricky to answer, particularly under standard intent-to-treat analysis schemes.

Our experience suggests that in disease states characterized by individualistic response to therapy where there are apparent prognostic factors, clinicians will rapidly alter treatments so that the PCT design becomes a defacto observational design, sometimes before the first follow-up visit from baseline can occur. In these instances, and most of our experience with PCTs is derived from studies of mental disorders where arguably these conditions exist, neither the assumption of random allocation nor the consequent use of standard statistical approaches can be argued with much conviction. Tightening treatment flexibility to compensate jeopardizes the generalizability of the results. Another approach taken by the NIMH in their usual care trials of mental health conditions has been to re-randomize after treatment failure and to introduce an element of choice into the selection of treatments in the second stage randomization. While intriguing, such approaches certainly are more intrusive than naturalistic and risk the same questions about ability to generalize as apply to randomized controlled trials (RCTs.)

What we are currently experimenting with in these situations are alternative analytic approaches that model the change in treatments as time-varying covariates. Consider a PCT involving comparison of conventional and atypical antipsychotics that experienced early and frequent switching of medications (Faries, APA Presentation, May 23, 2005: Atlanta). In Table 1 are the results of the analysis of schizophrenia symptom scores using five approaches: intent-to-treat (ITT, the current standard), an analysis of only the time period on monotherapy ('On Drug'), an analysis of the subpopulation that completed the trial on monotherapy (Completers), an epoch/episode analysis that treats each new drug switch as a new baseline and then 'adds' up results (Epoch), and a marginal structural modeling approach that treats switching as a time-varying covariate (MSM).

Table 1: Comparison of Results Across Methods

	Predicted Treatment	
	Difference	P-value
ITT	-0.0	.980
'On Drug'	-3.0	.010
Completers	-0.9	.593
Epoch	-3.1	.034
MSM	-3.6	.030
Summary Statistics	-4.8	

As you can see, predicted treatment differences and their associated p-values differ substantially. 52% of the time 'in response' in the typical antipsychotic arm was accounted for by atypicals. If you had used the standard ITT analysis to answer the question about the difference in treatments, you would miss the substantial role of the atypicals in patient outcome in both arms of the PCT. We believe that the MSM approach best answers the question about the direct impact of the two technologies on clinical outcomes. As this example illustrates, we are concerned that ITT approaches increase the likelihood of failing to detect important contributions to the improvement of health status.

However, the ITT approach does answers an important question from an administrative perspective. It tells a health system what the clinical and economic impacts would be if it introduces a new technology randomly to patients with the target disease and does nothing else. What can be much more difficult to tease out of PCTs are the how and why questions associated with the observed results.

A final practical consideration is the cost associated with doing PCTs. If a pharmaceutical manufacturer sponsored these studies, for instance, they would be considered interventional and would need to be conducted under Good Clinical Practice (GCP) processes associated with the Investigational New Drug (IND) authority from the FDA. As such they would be 5-10 times more expensive than an observational study of comparable size that would be conducted using good research principles but not under the requirements of GCPs.

2. **Analytic Observational Studies:**

Analytic observational studies (AOS) share many of the characteristics of PCT designs that are at the more naturalistic end of the RCT-PCT research spectrum. For example, like PCTs they are amenable to the application of statistical techniques (like marginal structural modeling or time to event analysis) that attempt to describe and account for variability introduced by changes in treatment strategy.

Unlike PCTs, AOSs would likely have a larger sample size for a given expenditure, irrespective, in all probability, of the requirements of GCPs. A larger sample allows a more normal distribution across characteristics of interest that may be less frequent.

The design would therefore be more amenable than a PCT in exploring subpopulation issues, safety issues, and the like. The design would also be less intrusive than PCTs, particularly those that range toward the RCT end of the trial design spectrum.

A novel application of observational studies in the context of the introduction of new technologies is to begin a study prior to the introduction of a new technology to provide baseline information on utilization patterns, adverse advents, disease comorbidities, and health outcomes. One can then monitor changes in parameters of interest once the technology is introduced from an interrupted time series design and analysis perspective. PCTs and RCTs, in particular, are not well suited to this approach.

Selection bias remains a major obstacle in drawing causal inference from AOSs, although as we have argued above, it is also not a straightforward exercise for PCTs either. We have already discussed some of the analytic approaches–instrumental variables, propensity scoring, marginal structural models—that can be applied to mitigate this bias. Some also advocate design features, particularly around inclusion/exclusion criteria, that would help to further mitigate selection bias (Vandenbroucke. Lancet, 363, 2004:1728). In part, physicians use observed prognostic factors to make decisions about what treatments to recommend. In the absence of these factors, recommendations for treatments may be more random in nature. Therefore, excluding such patients with recognized prognostic factors could help mitigate selection bias in AOSs. Surveys of physicians in preparation for an AOS could help identify important prognostic factors.

Consider a simple example of a patient being treated for arthritis. At the end of the examination the physician may ask whether the patient has ever had a peptic ulcer or gastrointestinal bleeding. The answer to that question may determine whether the patient gets a prostaglandin-sparing NSAID or even a COX-2. In the absence of other controls, results might indicate, spuriously, that prostaglandin-sparing NSAIDS and COX-2s were associated with greater GI adverse events, given the prior history of the patient. However, if such patients were excluded from the study, the physician might recommend treatments in a more random way. Patients with a prior GI history are certainly of interest, but it might be more fruitful anyway to investigate them using a more controlled design, such as an RCT or PCT.

Randomized Controlled Trials (RCTs):

The positives and negatives of this design selection are well known. What is vital to recognize is the absolute role that RCTs and efficacy results play in planning and interpreting the results from an agenda of effectiveness research. RCTs tell us whether an intervention has the potential to change health outcomes in usual care. Moreover, they give us an effect size estimate that some believe represents the best or maximum effect that can possibly be achieved in usual care (Streiner. Can. J. Psych., 47, 2002:552).

If a technology fails to achieve its potential in an effectiveness study, then decisions around its adoption are critically related to why and how this failure took place. If, for example, a side effect of the treatment that was manageable in the context of protocol driven care with motivated patients proves to be unmanageable in usual care, then the prospects for the technology should be marginal. If, however, compliance with the intervention is poor for reasons associated with patient, provider, or health plan characteristics, then with an appropriate compliance program the technology may yet realize its potential to affect beneficial change in health status in usual care.

Without an estimate of the upward bound of its potential via RCTs, it is much more difficult to interpret the results from effectiveness studies. Of course, as argued earlier, PCTs and other effectiveness studies, as traditionalized analyzed, may be hard pressed to supply adequate answers to questions of how and why. In addition to new analytic or design features, PCTs may need to be supplemented with qualitative work performed to help in interpreting results. In a PCT involving patients with unrecognized anxiety and depression, we used qualitative interviews with site investigators to understand that the failure of the intervention, a mental health lab slip, was related to the unique characteristics of those with unrecognized mental illness thus calling into question the appropriateness of screening programs alone in primary care (Mathias. J. Gen. Intern. Med., 49, 1994:606).

Conclusions and Recommendations:

The renewed interest in PCTs notwithstanding, there is no gold standard research design for studies aimed at facilitating coverage decisions. A comprehensive research agenda composed of several studies that supply pieces of evidence that accrue over time is the best strategy for decision-making. Uncertainties will always exist and the best evidence available will likely be at the end of the lifecycle of a new technology when its use for coverage decisions is already

moot. Our best sense of a minimally adequate research agenda for decision-making, understanding that many of the sponsors of such research may be small firms, would be: 1) at least one well designed RCT to determine potential usual care impact; 2) at least one moderate in size AOS, hopefully starting before launch of the technology; and, 3) at least one large retrospective database study performed as soon as administrative databases contain sufficient data for research purposes. Other studies could follow depending on the results from the recommended set. It may also be useful to use predictive models with the results from the RCT to estimate some of the uncertainties of translation of a new technology into usual care and to help prepare the AOS. Assuming that RCT's have been conducted prior to the introduction of a technology, then the AOS would be the study specified under Coverage with Evidence Development.

PCTs hold promise for administrative decision-making, but the experience base in conducting, analyzing, and interpreting them is small relative to that of RCTs. Moreover, they have a greater propensity to fail to detect an important intervention effect when one exists and they are often not examined rigorously enough to understand important characteristics of how and why intervention effects occur or fail to occur. CMS and other organizations that wish to promote or use the results from PCTs should therefore support symposia, fund methodological research, and develop appropriate analytic techniques that would serve to mature the application of this design. For now we would recommend using a well thought out and designed AOS rather than a PCT for the reasons noted above.

Finally, if technologies perform poorly in usual care for reasons not associated with the characteristics of the technology, CMS may want to consider other types of scope conditions for coverage analogous to coverage limitations to subpopulations associated with clinical status or biomarker level. For example, if compliance is critical to achieving large incremental clinical improvements as compared to usual care alternatives and poor compliance not associated with the characteristics of the intervention is revealed in an AOS, then coverage might be extended in conjunction with an approved compliance program. While this suggestion raises a host of questions, it relates decision-making directly to the types of questions about how and why technologies work that we believe need to be addressed as part of an agenda of effectiveness research.

We look forward to working with CMS to protect Medicare beneficiaries' access to innovative drugs and biologicals. If you have any questions regarding our comments, please contact Diane Flickinger at 850-914-9848 or d.flickinger@lilly.com.

Sincerely,

ELI LILLY AND COMPANY

Diane Flickinger, Federal Health Outcomes Liaison
Outcomes Research, US Medical Division

Organization: Enteral Nutrition and Wound Care Manufacturers

I appreciate the opportunity to submit comments on behalf of the Coalition of Enteral Nutrition Manufacturers, Coalition of Respiratory Care Manufacturers, Coalition of Wheelchair Seating Manufacturers and Coalition of Wound Care Manufacturers regarding CMS's draft guidance on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development." We appreciate CMS's efforts to improve the transparency of the coverage policy decision-making process through issuance of the Draft Guidance, along with your earlier draft guidance documents addressing factors CMS considers in opening a national coverage determination ("NCD") and in referring topics to the Medicare Coverage Advisory Committee or in commissioning external technology assessments.

The Coalitions share your commitment to promoting access to effective medical technologies and services for Medicare beneficiaries. It appears, however, that the approach outlined in the new draft guidance documents could set unreasonably high evidence standards, and impose unnecessary and inappropriate barriers to patient access to certain types of technologies. Specifically, we are concerned that the guidance documents: (1) exceed CMS's statutory mandate with regard to coverage policy; (2) impose an essentially unitary standard of evidence for all technologies; and (3) would undermine the value of local coverage determination process. We seek to ensure that in establishing the final guidance documents, CMS:

- Distinguishes evidence requirements for different types of technologies;
- Recognizes the hurdles associated with evidence collection for existing products;
- Defers to well-established policies by the Durable Medical Equipment Regional Carriers
- Recognizes the appropriate role of the Food and Drug Administration (FDA) in medical product/service safety, effectiveness, and post-market surveillance determinations; and
- Provides an opportunity for public comment on the final guidance framework.

Recognize the Statutory Mandate for Coverage Determinations

As CMS has pointed out, the Social Security Act charges CMS with covering items and services that are "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Yet, CMS proposes to expand this mandate to require that for Medicare coverage, a technology "improve net health outcomes." The Medicare statute –"reasonable and necessary" for diagnosis or treatment -- should not be narrowed so much as to limit coverage. Likewise, CMS's expansive guidance proposals would establish extremely low thresholds for triggering lengthy coverage review processes and complex, costly, ongoing evidence requirements, again without a clear statutory basis.

Rather than diverting limited CMS resources and imposing inflexible new approaches to evidence collection and outcomes research that risk delaying Medicare beneficiary access to new technologies, CMS should concentrate on speeding coverage, coding, and payment decisions that will bring these medical advances to Medicare beneficiaries in a more timely fashion.

Long-term Evidence Collection is Not Needed for Many Technologies

Clearly, long-term evidence gathering may have some value for policy making on technologies where a major dispute exists. We urge that long-term evidence gathering be the exception rather than the rule, however, in Medicare coverage policy. If not, CMS will transform medical innovation into a lock-step process that expects evidence gathering as a condition of Medicare coverage for a potentially unreasonable time frame, and at costs to the device manufacturer that are not commensurate with the Medicare policy-making need.

Calibrate Evidence Requirements to the Technology

CMS coverage decisions impact a wide range of medical technologies, ranging from the most basic disposable medical supplies to complex implantable devices to pharmaceuticals with potentially serious side effects. CMS must ensure that its evidence requirements recognize these tremendous variations and do not impose a "one size fits all" evidence standard on all medical technologies.

While CMS notes that it "will avoid stipulating the use of a particular design" for clinical studies because data collection protocols could vary according to the use of the item or service being provided, CMS does not recognize that there may be classes of products for which the cost and burden of ongoing evidence collection requirements simply would be inappropriate. Instead, CMS potentially could subject all types of medical technologies, including DME and supplies that pose little risk to Medicare beneficiaries and that have long been successfully used by Medicare beneficiaries, to complex evidence requirements. A unitary standard of evidence for all technologies risks increasing costs to the Medicare program and its beneficiaries while delaying or even preventing access to important products. Instead, CMS should distinguish evidence requirements for different types of technologies, based on the complexity of the product and associated beneficiary risks.

Protect the Local Coverage Determination Process

Medicare coverage policy should be responsive to patient and provider needs. Whenever possible, coverage decisions should be made at the local or regional level, where carrier medical directors have working relationships with physicians and clinicians and can more closely monitor the medical needs of the community. In particular, the Durable Medical Equipment Regional Carriers have long used evidence-based decisionmaking in close cooperation with providers, suppliers, and manufacturers.

CMS should not jeopardize this successful local decisionmaking process by routinely nationalizing coverage decisions. Instead, CMS should defer to the local carriers except

in rare cases where significant conflicts exist among carrier policies that threaten beneficiary access to technology and services, or in cases of serious quality of care or program integrity concerns.

Recognize Hurdles for Evidence Collection for Existing Products

CMS asks whether CMS should focus on new technologies and services, or the entire spectrum of technologies and services. New evidence gathering requirements for technologies that have been previously covered by Medicare could disrupt care for beneficiaries already using the item or service and impose unnecessary burdens on manufacturers and suppliers of proven technology. Thus, in the absence of a compelling reason for reconsidering coverage of an existing technology (i.e., significant quality of care concerns or program integrity issues), CMS should concentrate on medical technologies and services that are new to the Medicare market.

Recognize the Appropriate Role of the FDA in Safety Monitoring

In the draft guidance, CMS states that it will review items with "substantial safety concerns or potential side effects that are inadequately described in the available clinical literature." However, CMS apparently fails to recognize that the FDA is the federal agency charged with ensuring medical product safety, effectiveness, and post-market surveillance determinations. In fact, the FDA already uses postmarketing study commitments from product sponsors when appropriate to gather additional information about a product's safety, efficacy, or optimal use.

CMS should not impose a duplicative and possibly contradictory requirement on manufacturers and clinicians that could hinder access to need medical products and services. Instead, CMS should defer to the FDA in product safety, effectiveness, and postmarketing determinations.

Provide Comment Opportunity

CMS's recent draft guidance documents include numerous unanswered questions, and how CMS responds to those questions will have an important impact on the coverage determination process and associated evidence collection requirements. The public should have a further opportunity to review and comment on CMS's answers to its many outstanding questions before the guidance documents are finalized.

Distinguish Coverage Decisions from Coding

We are troubled that CMS coding decisions have appeared to import coverage criteria. Coding, while important for coverage, should use different criteria. We urge the evidence needs of the coverage process to remain properly within the coverage and analysis group, and for coding determinations to continue to reflect product, technology, clinical indications, distinct patient populations, costs, and features considerations.

* * * * *

In short, the Coalitions urge CMS to seek to minimize the burdens and information collection hurdles associated with the Medicare coverage process in order to ensure that Medicare beneficiaries have access to effective medical technologies.

Organization: Federation of American Hospitals

The Federation of American Hospitals ("FAH") is the national representative of investor owned or managed community hospitals and health systems throughout the United States. Our members include teaching and non-teaching hospitals in urban and rural areas of the United States. FAH appreciates the opportunity to comment on the draft guidance document issued on April 7, 2005 regarding Coverage with Evidence Development.

FAH offers the following general comments:

- It is logical to assess new technology or services in the "real world", e.g., actual medical practice, rather than in a clinical trial. However, is it necessary to establish a new process that requires hospitals to do data collection and CMS to do the data analysis and follow-up? Would it be more prudent to change or add to the clinical trial process instead of creating an entirely new one? Those who do clinical trials are more skilled at data collection and study design and would perhaps be better able to answer the questions CMS poses as to the reasonableness of the technology or service.

- Data collection should not be burdensome to the hospital. While the EHR is being touted as a means to capture the additional clinical data being requested, it will be years before this is mature or widespread enough to ease the hospital's data collection burden. In addition, the data must still be re-entered into the system (i.e., QNET) for transmission to CMS.

- Even if the data collection does not appear to be burdensome for the particular coverage decision to which it applies, if there are many data collections a provider has to contend with, that will add to the burden.

- The companies who have developed the technology or service to which the CED applies should bear responsibility for the cost of the data collection not the providers.

- Companies with new technology or services should not be allowed to use this process as a substitute for or a shortening of a clinical trial.

- The data collected by the hospital is a just a snapshot in time which will not be useful for long term outcomes reporting. Is this data being used simply to identify patients who will need additional follow-up and data collection or simply as a means to show that the product was used for the appropriate medically necessary reasons? If follow-up data collection is required, how will it be done?

- Data should not be collected "forever" for the CEDs. CMS should implement a timeframe and/or a number of patients where the data collected should be sufficient to draw conclusions about the CED effectiveness.

- CMS should seek comments from the providers who will be collecting data so that the operational issues associated with the data collection can be identified and taken into consideration.

- Data elements need to be clearly defined. For example when including data elements that occur multiple times within a stay, such as vital signs, the data collection form should be specific as to which vital signs are required – those at admission, those on the day of the surgery, etc – or if it doesn't matter, then state that it does not.

- Data collection should be relevant to the services rendered during the stay. For example, according to instructions received from CMS, the ICD Implant Data Form is to be used for initial implantations as well as replacements. Clearly, the data captured for the initial implantation should be different from that for re-implantations. Would it not be important to know why the re-implantation was done – did the device fail, did the patient have an infection, etc? Why would a hospital be required to submit essentially the same information for 2 very different admissions?

- Before implementing additional CEDs, CMS needs to assess the results of the first one to determine if changes need to be made.

We appreciate the opportunity to submit these comments.

Organization: GE Healthcare

(Comment on next page)

GE Healthcare

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June 1, 2005

Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mailstop: c1-12-28
7500 Security Boulevard
Baltimore, MD 21244

Dear Sir or Madame:

GE Healthcare appreciates the opportunity to submit comments in response to the CMS draft guidance document, dated April 7, 2005, entitled ***Factors CMS Considers in Making a Determination of Coverage with Evidence Development***.

GE Healthcare is a $14 billion unit of General Electric Company that is headquartered in the United Kingdom with expertise in medical imaging and information technologies, medical diagnostics, patient monitoring systems, disease research, drug discovery and biopharmaceuticals. Worldwide, GE Healthcare employs more than 42,500 people committed to serving healthcare professionals and their patients in more than 100 countries.

GE Healthcare supports the development of better evidence to inform physicians and their patients regarding appropriate medical care. We believe that evidence-based decision making is a key component of a rational health care system, thereby avoiding draconian measures to contain rising health care costs. GE Healthcare supports the agency's efforts to provide flexible mechanisms, such as Coverage with Evidence Development (CED), to facilitate the development of evidence that is critical for medical and coverage decision making.

In refining and implementing its policy for Coverage with Evidence Development, we strongly urge CMS to consider the following principles:

- **The CED policy should provide a mechanism for timely patient access to promising new medical advances.** CED should not inhibit or control the diffusion of quality-enhancing improvements in care, but rather should provide expedited patient access to important medical advances.

- **Evidence requirements should reflect important differences in health care interventions that have an impact on patient management and health outcomes.** Study objectives and parameters need to reflect the unique differences between device and pharmaceutical

products, as well as diagnostic and therapeutic interventions. This will require that CMS consider the full range of evidence development methods, tailored to specific needs.

- **CMS should ensure the systematic involvement of all stakeholders in the implementation of the CED policy.** CMS needs to institute a rigorous process for determining and engaging interested and affected parties.

- **CMS implementation of CED should leverage advances in health information technology, a key to development and dissemination of evidence for clinical decision making.** GEHC strongly agrees with CMS that advances in health information technology offer greater efficiency and accuracy in collecting and analyzing data, as well as ensuring patient privacy. As a leader in the development of health information technology, GEHC would appreciate the opportunity to explore with you the proper design solution for the proposed data management process.

- **CMS must preserve its local coverage process – the optimal approach for addressing the vast majority of coverage decisions.** The implementation of CED should not inhibit or in any way replace Medicare's local coverage process.

GEHC supports the comments submitted by our representative trade organizations regarding the CMS draft guidance document. These organizations include the National Electrical Manufacturers Association (NEMA), and the Pharmaceutical Manufacturers Association (PharMA).

We urge CMS to consider the comments provided by these organizations and we welcome the opportunity to further explore these important issues. Should you have any questions, please contact me at (262) 548-2088

Sincerely,

Mike

Michael Becker
General Manager, Global Reimbursement
GE Healthcare

Organization: Genetech

(Comment on next page)

Genentech
IN BUSINESS FOR LIFE

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June 6, 2005

Steve Phurrough, MD, MPA
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Department of Health and Human Services
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Re: Draft Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

Genentech, Inc. is pleased to provide the Centers for Medicare & Medicaid Services (CMS) with comments regarding the CMS Draft Guidance on Coverage with Evidence Development (CED Draft). Genentech is a leading biotechnology company, headquartered in South San Francisco, California. We currently market 14 products designed to treat patients with serious or unmet medical needs, ranging from cardiovascular disease to cancer. Genentech has discovered and developed a number of products made available to Medicare beneficiaries and reimbursed under Part B of the Medicare program, including Rituxan® for Non-Hodgkin's Lymphoma, Herceptin® for breast cancer, and Avastin® for colorectal cancer. As such, Medicare policy relating to both coverage and reimbursement of our products directly impacts patient access to these life-saving therapies.

While Genentech supports CMS' efforts to promote the use of evidence in making treatment decisions, we are concerned that the CED Draft, as currently written, does not accomplish this goal. In fact, the draft guidance may unintentionally result in limiting beneficiary access to and physician choice of medically appropriate and life-saving therapies by reducing the level of access to innovative drugs and biologics already achieved through the local coverage process.

As currently written, the CED Draft is unclear in its scope and mission, and raises more questions than it answers. Recent public statements by CMS to clarify or modify the intent of CED have further confused and complicated what was stated in the draft guidance regarding the role CED would play in fulfilling the goals of CMS. As such,

Genentech respectfully requests that CMS convene a series of public stakeholder[1] meetings to discuss, in detail, the many issues raised within the CED Draft, and then publish another draft of the guidance for additional public review and comment prior to publishing new CED requirements. Without engaging in detailed and constructive public discussions, we are concerned that moving forward with a broad guidance document for CED will adversely impact Medicare beneficiaries' access to care and create unnecessary barriers to medically necessary treatments.

CMS' Authority to Condition Coverage on Data Collection

CMS cites its authority to mandate significant and costly data collection efforts as an outgrowth of its discretion to cover only products which it deems "reasonable and necessary."[2] Furthermore, CMS implies throughout the CED Draft that its mission extends beyond that of a payer for items and services under the Medicare program. Genentech appreciates the need for CMS to be a judicious steward of Medicare funds; however, we do not believe CED is an appropriate and effective use of CMS' authority. Public health agencies such as the Food and Drug Administration (FDA), Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the National Institutes of Health, are better positioned and have the capacity, resources, and, most importantly, authority to respond to the health and clinical concerns of all Americans, including Medicare beneficiaries.

As a state-of-the-art research organization, Genentech develops clinical evidence for evidence-based decision-making by providers and patients. We support CMS' interest in the appropriate dissemination of evidence to help physicians make the most effective treatment decisions for their patients. We are concerned, however, that the CED Draft is premised on the flawed assumptions that (1) physicians currently are not basing decisions on the best available evidence; and (2) sufficient evidence to make treatment decisions is not being produced by public or private sector researchers. In reality, market incentives demand that manufacturers develop as much evidence as is necessary and appropriate to answer physician and patient questions on possible uses and benefits of marketed products. In particular, in 2004, Genentech alone invested 21 percent of its operating revenues into research and development activities.[3] Genentech recommends that CMS focus its resources on disseminating existing clinical evidence to providers and patients regarding innovative products and treatments, including compendia-listed indications for drugs, as we describe further below.

It should be noted that existing Medicare coverage policy provides a significant incentive for companies to pursue additional research of potential off-label uses of products, particularly anti-cancer products. Without sufficient clinical evidence, physicians will not prescribe products for uses beyond the FDA-approved label. Similarly, Medicare carriers have little incentive to cover off-label uses of anti-cancer

[1] Public stakeholders include physicians, patients, provider and patient specialty societies, public and private researchers, and manufacturers.
[2] Social Security Act (SSA) 1862(a)(1)(A).
[3] http://www.gene.com/gene/pipeline/status/. Accessed June 1, 2005.

therapies that are not supported in the medical literature. Thus, to ensure patient access to medically necessary therapies, manufacturers must generate sufficient evidence to justify a product's use. Ultimately, manufacturers also must secure an expanded FDA label or a listing in one of few recognized medical compendia or peer-reviewed journals to ensure off-label use of a product is covered by Medicare.

Genentech does not believe that CMS establishes a sufficient rationale in its CED Draft to justify a change in Medicare's existing coverage policy for labeled and off-label uses of drugs and biologicals, particularly anti-cancer products. In addition, if the goal of the CED Draft, as CMS states, is to enhance the quality of care given to patients by ensuring physicians have the necessary evidence to make appropriate clinical decisions, it is unclear whether CED is the best method to do so. CMS must state in the next version of Draft Guidance the basis for why CED is the best method to obtain such information. The Agency may be premature in assuming that linking evidence collection to Medicare coverage decisions automatically will improve the quality of patient care.

CED Interferes with the Local Coverage Decision-Making Process

As mentioned above, Medicare currently covers uses of anti-cancer drugs and biologics that are within the FDA-labeled indication, as well as uses which are recognized within select medical compendia or peer-reviewed scientific journals. Decisions regarding coverage of uses that are outside the FDA label and not listed in a compendium or scientific journal are left to the discretion of local Medicare carriers. Local Medicare carriers routinely make coverage decisions for drugs and biologics, often with the advice of local Carrier Advisory Committee members, who typically are physicians practicing within the community. Presumably, these decisions are based on the most recent and accurate evidence available to the medical community.

Although the CED Draft states that CMS does not intend to interfere with the current local decision-making process, the trend in CMS coverage decisions over the last several years has been toward increased national decision-making, which by definition, overrides local coverage policies. CMS has stated that CED should be used in cases where the may not be sufficient evidence to conclude that an item or service is "reasonable and necessary." Therefore, contractors should have discretion to make coverage decisions based on the standard of care in their area. Limiting Medicare coverage to circumstances where data are collected may disadvantage beneficiaries unable to participate in associated clinical trials or those whose physician is unwilling or unable to collect the required information.

CED Interferes with the Doctor/Patient Relationship

CMS also has stated on a number of occasions that the CED Draft will not interfere with the physician/patient relationship. Were that the case, there would be no need for the Agency to tie evidence collection efforts directly to Medicare coverage. Rather, the CED Draft is based on an incorrect assumption that in certain cases, physician decisions are not evidence-based and thus, require intervention by CMS. Although the CED Draft neglects to describe how the information will be used by CMS once it is

collected, presumably it will be used to make decisions regarding which treatment options are most appropriate and in which circumstances, and that these decisions will be enforced through Medicare coverage policy. Inevitably, this will lead to CMS establishing a set of standardized treatment guidelines that may not be medically appropriate for many Medicare beneficiaries.

Any type of conditional Medicare coverage interferes with the physician/patient relationship by substituting CMS' judgment for that of the practicing physician. CMS' influence in physicians' decision-making is likely to limit patient access to needed and promising therapies. CED is the most egregious type of conditional coverage because it limits physician and patient choice by restricting payment for certain products and services. Such proscriptive medicine ignores patient-specific needs and differences, like co-morbidities, present at the time of treatment. In order to ensure the highest quality of care is provided, physicians must be allowed to determine the most medically appropriate course of treatment for each patient, based on evidence available and each patient's unique characteristics. Broad practice guidelines developed at the national level cannot and will not be sufficiently nuanced to reflect important patient differences.

Rather than focus on ways to control physician decision-making, Genentech encourages CMS to focus on ways to ensure physicians access to the best medical resources. Specifically, Genentech encourages CMS to expand the existing list of CMS-recognized compendia since physicians rely heavily on medical compendia when making treatment decisions. Currently, CMS recognizes very few compendia in making coverage decisions, and recent changes in law and circumstance have narrowed the list further. Expanding the list of compendia sources CMS recognizes in making coverage decisions would be a more efficient and flexible way to disseminate clinical information about accepted uses of products to physicians. Moreover, compendia listings allow for more timely and consistent application of "best practice", and most importantly, would retain critical physician discretion in treatment decisions. CMS should develop educational materials or work with professional societies to inform physicians on updates to the compendia in order to assist physicians in remaining abreast of the newest therapies. We believe that this type of education effort, rather than restricting coverage through CED requirements, would best meet CMS' goal to improve the quality of care delivered to Medicare beneficiaries.

CED is Inconsistent with Personalized Medicine

The direction of the CED Draft departs significantly from the overall direction of modern medicine, particularly in the area of biotechnology. Biomedical research is focused more on personalized medicine—targeting treatments to particular patients and patient populations—which has been show to lead to greater efficacy and higher treatment success rates. The intent of CED to link coverage with evidence development may be a barrier to the type of evidence already being collected by limiting the clinical trials performed to those only recognized by CMS for coverage.

Suggested Methods are Not Appropriate for Long-Term Data Collection

The CED Draft relies on the use of patient registries and practical clinical trials as the primary mechanisms for evidence development. These tools are unlikely to yield the type of information or evidence CMS is interested in a timely manner. Furthermore, the CED Draft does not clarify who will be required to pay for the trials or registries, or who will be deciding exactly which research questions need to be answered. The CED Draft also does not indicate how CMS will determine when a sufficient amount of evidence to make coverage decisions has been collected under CED. Both clinical trials and patient registries are long-term tools, typically not conducive to reaching answers in the short-term. As such, it is unclear whether these suggested tools are the most appropriate ones for CMS to use to gather additional evidence for the purposes of making coverage decisions.

One rationale given in the CED Draft is that its application will encourage greater Medicare beneficiary participation in clinical trials if coverage is linked directly with data collection. If, however, CMS is concerned that Medicare beneficiaries have insufficient access to clinical trials or are not adequately represented in medical research, then it should focus on more direct ways of enabling and encouraging beneficiaries to participate in such trials. For example, although CMS published a national coverage determination (NCD) in September 2000 addressing Medicare coverage of routine medical costs incurred by Medicare beneficiaries enrolled in clinical trials, we understand the policy is used minimally within the Medicare program.[4] Many physicians remain unaware of this particular NCD and rarely suggest that Medicare beneficiaries enroll in available clinical trials. At a minimum, CMS should focus more attention and resources toward educating providers and beneficiaries on the availability of Medicare coverage of these routine health care costs, consistent with the existing NCD.

CED Draft Interferes with Research Agenda of Manufacturers

The clinical research agenda of manufacturers is driven largely by societal demand and decisions regarding how limited research dollars are best invested. The CED Draft does not take into consideration who will decide what additional research is needed from industry for CMS' purposes, nor does it address the critical question of who should or will be required to bear the costs of sponsoring CED-mandated activities. Genentech is concerned that redirecting limited research resources away from pursuing scientific questions established by manufacturers and the medical community, and forcing manufacturers to bear the financial burden of CED initiatives, will mean less investment will be made in researching and developing therapies for unmet medical needs. In addition, providers likely will be concerned about the costs associated with CED. Without additional reimbursement provided for CED collection efforts, providers may be forced to compromise patient care to adhere to collection requirements, thereby jeopardizing patient access to needed treatments.

[4] Medicare Benefits Policy Manual. Section 310.1. (NCD for Routine Costs in Clinical Trails)

The CED Draft proposes the creation of a committee charged with reviewing research and deciding the research questions it feels can or should be answered through the CED mechanism. CMS is not a research entity and should not establish a national research agenda. Similarly, Genentech is concerned with CMS' statements that another rationale for CED is to collect data on products that will be used to assess the safety of products. Again, evaluating a product's safety is not the role of CMS. Rather, assessing the safety and efficacy of drugs and biologics placed on the market for public use falls within the purview of the FDA. As a public health agency, the FDA has authority to work directly with manufacturers in designing clinical trials to prove a product's safety and efficacy, as well as in requiring additional post-approval research to monitor safety once the product is on the market. We believe that CMS' mission and jurisdiction is limited to that of a payer of items and services provided to Medicare beneficiaries; we do not believe that CED or Medicare coverage policy should be used generally to expand the scope and mission of the Agency.

Appropriate Application of CED

Although we question CMS' authority to mandate manufacturers engage in additional research in order to secure coverage of our products for the Medicare population, we offer the following suggestions for the more appropriate application of the CED mechanism.

Specifically, Genentech supports CMS' recommendation that the application of CED in national coverage decisions be used rarely.[5] As such, we encourage CMS to limit application of CED to situations in which (1) a national non-coverage policy exists, or (2) CED would serve as an alternative to the Agency issuing a national non-coverage determination. By applying CED only in circumstances of national non-coverage, the Agency truly will be expanding coverage and improving beneficiary access to important therapies.

Moreover, in order for CMS to justify the application of CED initiatives, the Agency must first demonstrate that a gap in existing research currently exists and is preventing physicians and patients from making the most medically appropriate decisions. Without illustrating that a research gap exists, CMS risks duplicating time and resource-intensive data collection efforts already ongoing within the industry. If CMS sufficiently illustrates a disparity in evidence, the Agency should bear the burden of publicly defining the particular research question it believes needs answered to improve the quality of care provided to Medicare beneficiaries. In such cases, CMS should work directly with product manufacturers to determine whether ongoing research is being conducted that will provide answers to appropriate questions, or to determine the best methods for gathering the necessary evidence.

CED initiatives should compliment, not duplicate, efforts being conducted by researchers (both public and private), professional societies, providers, and

[5] CMS. Draft Guidance for the Public, Industry and CMS staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED). Issued April 7, 2005.

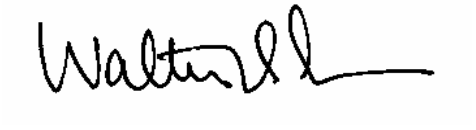
manufacturers. For example, Genentech currently is engaged in conducting a large number of clinical trials (both prior to and after FDA approval). Such research is intended to investigate potential new indications for a product, including the safety, effectiveness and economic impact of the product in "real world" settings. Before CMS engages in any CED initiatives, the Agency should actively engage with a product's manufacturer to determine the type of data already being collected in order to ensure that CMS is not repeating current research efforts.

Finally, as indicated in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress intended for CMS to allow for an open coverage process that encourages public input and participation. Only through a collaborative and open process will the Medicare program be able to enhance the body of research needed for physicians and patients to determine treatment decisions. The CED Draft does not explicitly define the process the Agency intends to follow when implementing CED. Specifically, the draft guidance does not define exactly how patients, providers, and manufacturers will be involved together in the data collection process. Additional clarification from the Agency is needed to ensure that CED is implemented in appropriate circumstances, and an efficient and transparent manner, that encourages public input.

In summary, the initial CED Draft is likely to have unintended consequences on patient access, the quality of medical care delivered to Medicare beneficiaries, and the ability of physicians to offer appropriate and medically necessary therapies. Genentech encourages CMS to ensure that CED initiatives are not redundant and do not detract from existing research efforts. We also urge the Agency to focus data collection efforts on expanding, not limiting, coverage for and patient access to needed treatments. By preserving the physician/patient relationship and encouraging individual patient decision-making, CMS will help foster biomedical innovation and improve the quality of care delivered to Medicare beneficiaries. Due to these concerns, Genentech urges CMS to conduct a series of stakeholder meetings and provide additional versions of the CED Draft before finalizing the guidance.

Thank you for the opportunity to provide comments on the CED Draft. Please contact me directly at (202) 296-7272 should you have any follow-up questions.

Sincerely,



Walter K. Moore,
Vice President, Government Affairs

cc: Dr. Mark McClellan
Dr. Barry Straube

Organization: GlaxoSmithKline

(Comment on next page)

GlaxoSmithKline (GSK) appreciates the opportunity to offer our comments on the recent draft guidance pertaining to Coverage with Evidence Development (CED). GSK is a global pharmaceutical company with major products in the oncology, HIV, vaccine, and general pharmaceutical areas. We continue to have an extensive list of drug therapies in development. That development process includes the design and implementation of clinical trials to demonstrate the safety and efficacy of our products in appropriate populations. We are, therefore, especially interested in how others, including CMS, view the development of evidence for drug therapies.

To begin, we are encouraged by CMS' intent to make the technology evaluation process more transparent and more open to input from all relevant stakeholders. Ensuring that medical technology advancements are available to Medicare beneficiaries is important. We view this draft guidance as one more step in developing an open coverage process and are optimistic that this trend will continue.

Because the Medicare law requires that a treatment be "reasonable and necessary" as a condition for payment, and because of our interest in ensuring that patients receive an effective treatment most appropriate to their medical needs, we understand the need for a robust technology evaluation process, and the related coverage process, when used to determine whether a particular treatment is "reasonable and necessary" for treatment purposes. We have concerns, however, that the approach in this draft guidance could be misused to mandate research protocols in addition to those already appropriately required by the FDA. Further, we are concerned that this type of approach could be misconstrued as an attempt by CMS to influence, or control, how physicians treat their patients.

Our concerns would be ameliorated if CMS would follow this draft guidance with a revised draft guidance with greater detail about the criteria that would be used to initiate, structure, and evaluate CEDs.

Areas Requiring Clarification

Initiation of CED.

The Draft Guidance should provide clear examples of when CED will be considered or used. Although in the Draft Guidance, CMS says that it "does not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirement,"[1] the Guidance also lists broad circumstances in which CED will be considered.[2] It would be helpful to patients and to manufacturers who are developing products if CMS were to clarify the amount and type of evidence it needs before requiring CED to an item or service as a condition of coverage.

For example, GSK is in the process of developing an intravenous cardiovascular drug that would cause atherosclerotic plaque regression. For FDA approval, cardiovascular events including mortality based outcomes study is likely to be necessary. Imaging data alone

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1 Draft Guidance, at 2.
2 Draft Guidance, at 9-10.

will not alone afford full approval. The FDA may require that a link between plaque regression and decreased mortality is clearly established.

Because mortality based outcomes trials are based on counting specific data points (for example, numbers of deaths, heart attacks or number of months of additional life), often only patients with a history of cardiovascular (CV) events are studied because they are at high risk for developing another event and can yield the necessary evidence to show a difference between treatment and control within a 3-5 year period. These secondary prevention studies (preventing a second event) often require 10,000 - 20,000 patients and can cost $300-400 million.

Patients who do not have a history of CV events but have occlusive atherosclerotic plaque could also benefit from this therapy to prevent the 1st CV event (primary prevention). But because the event risk in this patient population is lower (within a certain period), it takes 3-5 times more patients and twice as long to collect the necessary events to show a difference between control and treatment. A study of this patient population would, therefore, be extremely costly.

If, in the absence of specific data, CMS were to cover the product only for patients with a history of CV events, but deny coverage or require that evidence be available for at risk patients without such a history, many patients could die needlessly. There would be significant logistical and economic burdens associated with collecting and analyzing the required data, making the study impossible to implement. In a situation such as this, we are hopeful that CMS would accept the established linkage between atherosclerotic plaque and CV events as sufficient to allow coverage without the need to collect additional data.

We also encourage CMS to clarify that CMS intends for this process to be supplemental to the statutory provisions setting out the Congressionally mandated coverage standard (requiring coverage for off-label uses of drugs or biologicals used in anti-cancer chemotherapeutic regimens that are listed in the compendia or supported by peer-reviewed literature) and is not intended to supplant these existing standards

To clarify statements in the Draft Guidance about the use of CED to assist CMS and its contractors,[3] the agency also should state explicitly that CED is to be applied as a national policy only and is not to be initiated by local contractors.

Impact on Patient Access

We have significant experience working with oncologists and, less directly, with cancer patients. We know that for some patients, an off-label use of a product may, literally, be the difference between life and death. We encourage CMS to clarify that CED will not curtail access to drugs and biologicals currently available through the local coverage

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3 See Draft Guidance, at 5, 9 ("In general, CMS will consider requiring data collection as a condition of coverage when additional information is needed for *CMS and its contractors* to determine if an item or service is reasonable and necessary.") (emphasis added).

process. As intended by Congress, this process allows beneficiaries to receive anticancer chemotherapy drugs and biologicals for off-label indications when the use is supported by citation in certain compendia or peer-reviewed literature.[4] If these therapies are available only through clinical trials or other evidence gathering methods, many patients could be denied access to critical treatments.

The draft guidance discusses the use of clinical trials to assess off-label use. Medicare beneficiaries, however, may be ineligible for clinical trials due to age, comorbidities, or complications. In addition, many patients do not live close to the trial study sites and may not be able to participate if the trial would require them to travel, change physicians, or experience other substantial inconvenience. Requiring participation in a trial as a condition of coverage may be implementing systematic discrimination among Medicare beneficiaries based on disease and location. These problems could be addressed by continuing an active, intact local coverage process that allows coverage decisions to be made by local carriers.

We were pleased to read in the Draft Guidance that CMS does not "anticipate circumstances under which CED would represent a net reduction in coverage available under local coverage policies."[5] Because of the importance of this issue, and the anxiety it can provoke in patients, we encourage CMS to provide more specific instructions to carriers that a NCD with CED does not affect their discretion to cover uses of these therapies outside the CED requirements. CMS also should monitor access to care after a CED decision is implemented to verify that patients continue to receive care, regardless of their participation in the evidence development exercise.

Application of CED to Drugs and Biologicals

To establish clear expectations for patients, providers and manufacturers, we encourage CMS to specify that the CED process for drugs and biologicals will be different than for devices and procedures. In recognition of the FDA's rigorous drug approval process, CMS historically has treated coverage of drugs and biologicals differently than other items and services, particularly devices approved under section 510(k) of the Federal Food, Drug, and Cosmetic Act.

For example, in 1989 the agency stated that its national policy is that drugs or biologicals approved for marketing by the FDA are safe and effective for on-label indications, but that FDA approval for marketing of a medical device does not necessarily lead to a favorable coverage recommendation, especially when the FDA approval is under section 510(k).[6] CMS should continue to acknowledge the different amounts and types of data required to approve these technologies by providing separate descriptions of its plans to use CED for drugs and biologicals and for devices. The agency also should separately

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4 SSA § 1861(t)(2).

5 Draft Guidance, at 6.

6 54 Fed. Reg. 4302, 4306-07 (Jan. 30, 1989). See also, 52 Fed. Reg. 15560, 15561 (Apr. 29, 1987) ("Medicare coverage of drugs and biologicals is treated differently" than other item and services).

describe the application of CED to procedures that do not require FDA approval. This would permit CMS to describe its plans and requirements with greater specificity.

Implementation of the CED

If CMS determines the use of CED for an item or service, it must take care to ensure that the chosen research methods can achieve specific goals with minimal burden for patients, providers, and manufacturers. The Draft Guidance notes that the value of the information gathered must be carefully balanced against the burden of collecting it; any CED requirements must be aligned with the FDA's clinical study requirements and with other research priorities to ensure that research resources are used efficiently; and, data collection only should continue as long as important questions remain and the effort and resources required to collect this data are justified by the potential value of the information to be collected.[7]

We are especially concerned about how CMS will determine the issues that will require the collection of additional information, what type of data or level of evidence that will be sufficient to respond to those issues, and when the required studies would be brought to an end. Unless the study design, including data collection and variables under study, are clearly defined from the outset, we cannot be confident that the study will produce the appropriate data.. To be partners in this process, we need assurance that coverage decisions will be made in an efficient and timely manner, and that such studies will be feasible from both a logistical and economic standpoint.

Further, it would be helpful if CMS accepted alternative research methods (e.g., claims data, modeling, meta-analysis) to clinically based studies. In addition, depending on the technology under study, and the number of patients who might make use of an off label use of the technology, we encourage CMS to allow evidence based studies as envisioned in this draft guidance with a sample of patients, instead of the universe of patients.

In the recent NCD on colorectal cancer, CMS required that studies be performed under the auspice of the NCI. We are not clear what additional organizations might also conduct acceptable studies. Assuming there would be other acceptable organizations, CMS should clarify whether there will be a single standard for submitting results of studies or multiple acceptable formats

In the Draft Guidance, CMS asks, "how should the costs of study design, data collection, analysis and other activities associated with these programs be fairly allocated to various stakeholders?"[8] GSK recommends that CMS explore the creation of new reimbursement codes that would reimburse physicians for the added burden associated with patient recruitment and recordkeeping. We also recommend that CMS provide reimbursement for the non-routine costs of clinical trials, such as drug administration services, where such costs are not reimbursed by trial sponsors.

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7 Draft Guidance, at 5, 14.
8 Draft Guidance, at 15.

We would also suggest that these new codes not require a copayment by the patient. Beneficiaries' cost of care under CED should not be greater than under coverage without evidence development. If beneficiaries are forced to incur greater costs for receiving care in Medicare-covered clinical trials or other evidence development programs, they may choose other, potentially less appropriate, care options.

Thank you again for the opportunity to provide our perspective on CED. Please feel free to contact us if you have questions or require additional information.

Organization: Guidant Corporation

(Comment on next page)

June 6, 2005

Stephen Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore, MD 21244-1850

Re: Comments on Draft Guidance Entitled "Factors CMS Considers in Making a Determination of Coverage with Evidence Development"

Dear Dr. Phurrough:

Guidant Corporation, a sponsor of landmark clinical trials and an advocate of evidence-based medicine, commends the Centers for Medicare and Medicaid Services (CMS) for its efforts to help patients, providers and policymakers make healthcare decisions based on clinical evidence. We support the agency in its examination of multiple approaches to achieve this objective, and believe that a transparent and open evaluation of coverage with evidence development (CED) is appropriate in this context.

Headquartered in Indianapolis, Indiana, with manufacturing and/or research and development facilities in the states of Minnesota, California and Washington, as well as in Puerto Rico and Ireland, Guidant Corporation is a leading designer and manufacturer of medical technologies used primarily to treat cardiovascular and vascular illnesses. Guidant's products save and enhance lives throughout the world.

We welcome the opportunity to comment on the draft guidance entitled "Factors CMS Considers in Making a Determination of Coverage with Evidence Development." In our comments, we will note principles fundamental to CED that we support, and also raise issues of concern. The draft guidance is complex and its potential impact on patients, providers and the healthcare system overall is significant. Therefore, we suggest that following review of comments received in response to this draft, the agency explore remaining questions through a series of stakeholder meetings and then issue another draft for further comment. Such a process will help ensure that the objectives of the agency are met and that patients, providers and the healthcare system benefit from, and are not unnecessarily burdened by, change.

A brief summary of our comments follows.

Summary of Comments

CMS has proposed the adoption of several principles to ensure the successful and appropriate application of CED. Guidant supports the following principles and recommends that they guide the use of CED:

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- CED should promote Medicare beneficiary access to new therapies and services;
- CED should be applied only rarely;
- The benefits of data collection associated with CED should always outweigh its cost and burden;
- Data collection associated with CED should address a specific unanswered question regarding health outcomes, and should employ the least burdensome data collection methodology over the shortest amount of time appropriate to answer that question;
- CED should not be used to reduce the importance or frequency of local coverage determinations; and
- CED efforts should not be duplicative of existing or future data collection efforts by the FDA or other public or private entities.

Adoption of and adherence to these principles will enable Coverage with Evidence Development to be successfully implemented, thereby enhancing beneficiary access to new therapies.

Guidant believes that the following provisions of the draft guidance should be revised to address concerns noted below:

- Authority to Use CED Within the NCD Process;
- Circumstances Appropriate for Application of CED;
- Outcomes Appropriate to Use of CED; and
- Types of Possible Coverage Decisions.

Authority to Use CED Within the NCD Process

Guidant supports evidence-based medicine and believes that the quality of care can be improved by the dissemination to patients and providers of clinical evidence associated with new and existing therapies. We believe that the application of CED may advance this objective. However, questions have been raised as to whether CMS has the legal authority to incorporate CED within the national coverage determination process for the purpose of developing evidence and measuring quality. The authority for linking the determination of what is reasonable and necessary care to data collection on provider quality or on outcomes remains vague, and the agency should provide greater clarity before proceeding with this approach. A failure to do so could render CED subject to challenge in the future.

Circumstances Appropriate for Application of CED

CMS describes two circumstances in which the application of CED is appropriate. We disagree with CMS' assertion that CED can appropriately be applied to "a particular medical intervention (that) may have been demonstrated to improve health outcomes in a broad population of patients, but the evidence would only be adequate, and the services therefore reasonable and necessary for the individual patient, when specific data is

collected…" Technologies approved or cleared by the FDA that have demonstrated improvement in health outcomes in a broad population of patients should be covered. CED does not add value to the evidence on these types of therapies and could impede beneficiary access.

The second circumstance set forth by CMS for the use of CED is when "a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit." In general, we believe the use of CED in this circumstance would be appropriate when it provides beneficiary access to a technology that otherwise would have resulted in a non-coverage decision.

Outcomes Appropriate to Use of CED

The draft guidance states that CED could be used to address questions of safety. The assessment of safety of medical therapies is the purview of the FDA, and not within the authority of CMS. Further, the draft guidance states that CED could be used to assess outcomes associated with costs, utilization, and quality of life. Though issues surrounding these types of outcomes may justify the initiation of a national coverage determination, they should not be considered in the context of a NCD. Therefore, CED cannot be used to evaluate outcomes other than improvement in health. Recently, the CMS administrator stated that cost-benefit analysis will not be considered in coverage decisions.[1] We suggest that the guidance be consistent with this position.

Types of Possible Coverage Decisions

In the draft guidance, CMS states its intent to render three types of coverage determinations: non-coverage, coverage with conditions, and coverage without conditions. CMS fails to note, however, that there are circumstances in which a technology may be addressed in the context of a NCD but a national determination is not made owing to insufficient evidence. CMS should clarify in the draft guidance that such technologies may be considered through the local coverage determination process.

Further, CMS states that it is unlikely to issue additional NCDs that are "coverage without condition" decisions. We question the appropriateness of stating that there will be no further national coverage decisions that do not include conditions. We suggest that there will be circumstances in which technologies have an evidence base that indicates positive health outcomes for all patients with a specific clinical condition, and that coverage with conditions will not be appropriate. In such cases, CED would be unnecessarily burdensome and costly while providing no additional value to the beneficiary or the program.

[1] *The Gray Sheet*. May 23, 2005. "Cost-Benefit Decisions Will Reside with Docs/Patients, Not CMS – McClellan"

Detailed Comments

Key Principles Essential to Successful Implementation of CED

The adoption of and adherence to fundamental principles is essential to the successful implementation of CED.

First, the agency states, "CMS is committed to ensuring that advances in medical technology are available for its beneficiaries while also ensuring the care they receive is reasonable and necessary." We agree that beneficiaries must be provided timely access to technology innovations and that the NCD process, possibly including CED, offers one approach to achieving this objective. We believe that the application of CED, in those narrow circumstances in which coverage would otherwise be denied, could improve beneficiary access and clinician choice. We note that some agency officials have stated publicly that the application of CED would be limited and narrowly focused. This would appear to indicate that the use of CED will be limited to situations where coverage would otherwise be denied and thus, in fact, will provide improved access to technology for beneficiaries. An indiscriminate use of CED would have the reverse impact, i.e., it would deny beneficiaries' access and would be opposed by Guidant.

Second, CMS states, "… any evidence development requirements should not only assure that the expected benefits outweigh the costs, but also assure that no unnecessary costs are imposed." CMS further states that questions should be specific and only the minimum amount of data required should be collected. Adherence to these principles will be essential. Data collection will be unnecessarily costly if questions and data collection methods are not determined prospectively. To address this concern, Guidant recommends that CMS describe in future draft guidance how the cost vs. benefit analysis will be conducted. We also urge that the agency examine its application of CED to date, and apply lessons from early data collection experiences to any future NCDs with CED. Appropriately planned CED should result in data collected over a short period of time that specifically addresses a previously unanswered question about the health outcomes or change in treatment decision resulting from a technology.

Third, the agency states that data collection through CED will not be duplicative of data collection required by the FDA or of any "ongoing publicly and privately funded clinical studies." We commend the agency for stating clearly that any application of CED will take into consideration evidence development efforts by other relevant entities. Following this principle will ensure evidence development is not unnecessarily costly and does not create a barrier that impedes technology adoption.

Finally, we appreciate CMS' assurance that CED will not "reduce the importance or frequency of local coverage determinations." The local coverage process is important to ensuring continued access by Medicare beneficiaries to new technologies. Providing for local coverage also enables physicians to gain real world experience with new

technologies that may facilitate efficient decision-making at the national level if warranted.

Guidant commends the agency for proposing principles to guide the use of CED. We recognize there is more work to be done to ensure the successful application of these principles, and look forward to working with the agency toward that end.

Authority for Use of CED within the NCD Process and the Definition of Reasonable and Necessary

In the draft guidance, CMS details its authority for CED. However, questions have been raised as to whether in it is appropriate to address evidence collection and quality of care in the NCD process. Sec 1862(a)(1)(A) of the Social Security Act states that items and services paid for by the Medicare program must be reasonable and necessary. The statute also makes it clear that a given service should be reasonable and necessary for a particular beneficiary at that time. The linkage between determining if an item or service is reasonable and necessary for a given patient and collecting data is somewhat tenuous and is the subject of concern.

Historically, the definition of reasonable and necessary as applied in coverage determinations has meant that when a therapy or technology is provided it has to be reasonable and necessary for that specific patient at that specific time. However, the draft guidance seems to associate reasonable and necessary with the quality of the evidence as when CMS states, "the core consideration in determining when an item or service is reasonable and necessary is the quality of the evidence available to assess whether it improves net health outcomes." Further, CMS seems to believe that reasonable and necessary can be defined by the collection of data and not by what is appropriate for the patient at that specific time when it states, "In some cases, CMS will determine that an item or service is only reasonable and necessary when specific data collections accompany the provision of a service." We do not believe that it is appropriate to render an individual patient care decision based on whether or not data will be collected. A therapy is either reasonable and necessary for a patient or it is not, particularly when the data collected will be used to impact future coverage decisions and does not impact the patient being treated today. We understand CMS' desire to collect prospective data and to build an evidence base, but such data collection is not consistent with deciding whether or not a proven therapy is reasonable and necessary for a given patient.

Given the discrepancy in the application of the reasonable and necessary standard, CMS may want to consider how to standardize and clarify the definition of reasonable and necessary care, and also review the statutory authority for the Medicare program to link data collection to coverage decisions. Though collecting evidence to facilitate better decision-making and developing methods to measure quality of care are important goals for the Medicare program, it must be clear whether the NCD process allows for such an effort. A failure to clarify this now will significantly weaken the efforts of the agency to move forward.

Circumstances Appropriate for Application of CED

In the draft guidance, CMS sets forth circumstances in which a therapy or service would be considered reasonable and necessary only if provided within the context of data collection. The first circumstance is "a particular medical intervention may have been demonstrated to improve health outcomes in a broad population of patients, but the evidence would only be adequate, and the services therefore reasonable and necessary for the individual patient, when specific data is collected." Coverage with evidence development should not be applied in this circumstance. If a technology has received FDA approval or clearance and there is evidence demonstrating positive health outcomes in a broad population of patients, there is no justification for additional data collection and the therapy should be covered. It is difficult to understand how the collection of data for a single Medicare beneficiary through CED helps "to ensure that the care provided to individual patients is likely to improve health outcomes" more effectively then a prospectively designed clinical study used for FDA clearance or approval.

The second circumstance set forth by CMS for the use of CED is where "a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit." In general, we believe the use of CED in this circumstance would be appropriate when it provides beneficiary access to a technology that otherwise would have resulted in a non-coverage decision.

Outcomes Appropriate for Use of CED

In the draft guidance, CMS sets forth the potential outcomes of a therapy that might appropriately be addressed by CED. We suggest that some of these outcomes may be inappropriate when addressed in the context of the NCD process. In the draft, CMS states multiple times that CED could be used to evaluate the safety and benefit or the safety and effectiveness of an item or service. Within the Department of Health and Human Services, the FDA is specifically designated as the agency responsible for evaluating and ensuring the safety of medical technologies and products. In recognition of the safety-related responsibilities of the FDA, Guidant recommends that CMS, within the CED process, defer to the FDA on determinations of safety and restrict the use of CED to address unanswered questions pertaining to the clinical effectiveness of a therapy, not to its safety.

In the draft guidance, CMS notes that CED could be applied in circumstances where "assessment of important outcomes has not been evaluated in the available clinical studies" including "quality of life, utilization, costs and other real-world outcomes." We understand that questions pertaining to the cost, expected utilization or lack of utilization of a technology could justify the initiation of a NCD on that technology if these outcomes demonstrate a potentially significant impact on the Medicare program. However, questions on these types of outcomes are only related to whether a NCD should be

initiated and should not be considered in the context of the NCD. Therefore, CED is not appropriately applied to these types of outcomes. The definition of reasonable and necessary care is applied as a determination of whether or not a therapy is clinically reasonable and clinically necessary; it does not provide for a consideration of economic outcomes. Thus, coverage decisions, and any associated CED should be focused on the clinical outcomes of a technology and not on economic value. We appreciate and agree with Dr. McClellan's recent public remark that evaluation of cost-effectiveness and cost-benefit will not be addressed by CMS and is more appropriately applied at the physician-patient level.[2] We encourage CMS to reiterate this position in future draft guidance on CED.

Types of Possible Coverage Decisions

In the draft guidance, CMS notes that there are three types of coverage decisions: non-coverage, coverage with conditions, and coverage without conditions.

Guidant suggests this represents an inappropriate limitation. We believe CMS should clarify in the draft guidance that there are circumstances in which items and services originally subjected to the NCD process can be addressed through the local coverage determination (LCD) process. We believe the LCD process often represents the best mechanism to allow beneficiary access while at the same time increasing real-world experience with a technology that might assist CMS in a future NCD.

In addition, the agency states "CMS does not anticipate additional decisions" that would be considered "coverage without conditions." We believe this statement is inappropriate because there may be circumstances in which technologies do have an evidence base that indicates positive health outcomes for all patients with a specific clinical condition and coverage with conditions would be perceived as erecting barriers to beneficiary access. Indeed, if CMS' vision of evidence based medical decisions at the physician-patient level is successful, there will likely be many technologies that should be covered without conditions.

Questions for the Public

In the draft guidance, CMS seeks input from the public on how to specifically implement CED. By posing these questions, CMS is providing an opportunity for stakeholders to assist in developing the CED the process. However, because there continue to be a number of unanswered questions associated with the CED process, we can at this time address only a few of these questions. We look forward to providing further guidance at a later date.

[2] *The Gray Sheet*. May 23, 2005. "Cost-Benefit Decisions Will Reside with Docs/Patients, Not CMS – McClellan"

- What procedures and forums would be most effective for obtaining public input in this decision making process?

To determine how and when CED should be applied, CMS should engage key stakeholders in a series of meetings specifically focused on establishing priorities and criteria for when the application of CED is appropriate and valuable. These stakeholder meetings should be used to define the process and assess the cost vs. the benefit of conducting CED for a specific item or service. A revised draft open for public comment should be issued at the conclusion of these meetings.

- Should there be a process for requesting national coverage decisions with evidence development and how should such requests be prioritized?

Stakeholders, when requesting a national coverage determination, should be able to also request CED within that NCD. However, that request for CED should be open to comment from the public since the stakeholder making the request may not have access to evidence on the technology available to other stakeholders. There should be a process in place to assess whether CED is warranted regardless of whether the request for CED is internally or externally generated.

- What other study designs should be considered? What type of questions is each study design best able to answer? What are the limitations of each study design? Under what circumstances should CMS require a database? A longitudinal data collection? A prospective study? A clinical trial? What process should CMS use to evaluate the quality of a proposed study design? How should CMS determine whether the evidence collected suggests patients are either harmed or not benefited by the item or service?

Designing and conducting evidence development within the context of coverage decisions is an entirely new area for CMS as well as for providers, patients and other stakeholders. When contemplating CED for a technology, CMS should engage stakeholders in a series of meetings to establish research questions, evaluate study designs and complete a cost vs. benefit analysis of any proposed data collection methodology. Discussions with stakeholders should include the relative strengths and weaknesses for various study designs and the ability to address various types of evidence questions including tradeoffs involving internal and external validity, cost vs. benefit, duration of data collection and maintaining data quality. Engaging stakeholders in developing data collection methodologies will ensure proposed study designs meet universally accepted principles for data collection, including qualified scientific oversight, patient confidentiality, patient protection and informed consent, provider training, statistical analysis and development of sample size, hypothesis selection, data security, quality assurance and patient safety and monitoring. We caution the agency that developing effective data collection strategies takes time but beneficiary access to a therapy should not be hindered as a data collection methodology is developed. If a data collection methodology is not defined at the time when a NCD decision is effective,

coverage should be granted in the interim and beneficiary access to a therapy should not be hindered.

Guidant Corporation supports CMS' efforts to encourage the use of evidence-based medicine. Physicians and patients need information to make the best decision on medical care. The conduct of thoughtfully designed prospective clinical studies adds to the evidence base and helps ensure physicians and patients make the best choices in medical technology and services. In general, we feel this evidence is sufficient for coverage. However, we acknowledge that in rare cases there may be a need for the collection of additional evidence to support Medicare beneficiaries' continued access to a therapy. This draft guidance of Coverage with Evidence Development initiates a formal explanation of this subject but it fails to fully clarify the purpose of CED, when its use is justified and the implementation process. This guidance should be revised and then subjected to further discussion with stakeholders.

In conclusion, Guidant Corporation believes CMS has embarked on a path that represents significant change. It is imperative that the process is thoughtful, transparent and, for the benefit of today's seniors and those of the future, that the structure put in place for CED provides value to patients, providers and the healthcare system. We encourage the agency to continue its efforts and will look forward to further dialogue.

Sincerely,
Ann Gosier
Vice President, Government Affairs
Guidant Corporation

Organization: H. Lee Moffitt Cancer Center

The following are collective comments from clinicians from our Center to some of the questions that you asked to be addressed in the Draft guidance document:

Overall we believe that the intent of CMS is good and we are encouraged that CMS is trying to find innovative ways to improve healthcare.

The opening statement is perhaps the most important "The purpose...is to describe factors CMS may consider in a decision to extend national coverage....linked to a requirement for prospective data collection." We propose that a cancer registry of the NCI centers be supported to develop usage data.

Page 6 states that CMS will pay for what is "reasonable and necessary" under 2 conditions. 1) ... intervention has been demonstrated to improve outcomes... and 2) ...intervention has yet to conclusively demonstrate an improvement...may provide an important benefit. Once again these statements support out proposal to use a patient registry because, as NCI centers we use evidence based support, or we use peer evaluation of the unique patient circumstances and in the collaborative opinion of experts determine if the patient might benefit.

It is of the opinion that CMS should survey the NCI centers to determine what compendia the national experts consider worthy to support the use of therapy.

CMS should develop an advisory board, and this board can advise them what is appropriate (or who to ask) in the case of rare disease therapies.

CED technology should be applied to both old and new drugs, because, if it is being used for an unapproved indication for a new drug, it is essentially a "new drug for that indication".

Regarding paying for drugs used in clinical trials. I might be missing something, along with several other people, but most of us believe that drugs used in clinical trials are provided free by NCI or another sponsor, so why would CMS pay for them??? Perhaps they are talking about phase 3 or 4 trials, but those aren't usually of any significance. I really don't understand this point.

What stakeholders should be involved? I believe they should have an advisory board comprised primarily of MDs, but also pharmacists and nurses.

Effective method of obtaining public input? I think they should have a couple of lay people on the advisory board. They can also tap into patient advocacy organizations, and patient support organizations.

Who shoud be responsible for CED oversight? The advisory board, and it should be driven by the NCI cancer centers.

How can burden of data collection be minimized? Link it to the existing national cancer registry. In that way, both efforts are improved.

Organization: Hemophilia Federation of America

(Comment on next page)

Hemophilia Federation of America

Advocacy For Persons With Clotting Disorders

June 3, 2005

Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail Stop C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

Re: Draft Guidance Factors CMS Considers in Making a Determination of Coverage with Evidence Development, April 7, 2005

To Whom It May Concern:

Your proposed guidance on "coverage with evidence development (CED)" has come to us for review and we have some concerns. At first glance, a concern is that this seems to be creating a duplicate of effort and expense within the federal arena where budgets are already tight. It is difficult to understand why CMS would want to oversee clinical trials including their implementation and their initial evaluation while there are several federal agencies that are already doing these things and have a long history of experience and depth of knowledge in carrying out these functions. The agencies that come to our attention immediately are NIH, FDA, AHRQ, and VA to name a few.

It is our understanding that, for instance for drugs and devices, the FDA has the responsibility for requesting and monitoring post-approval trials. The FDA has a significant number of staff members who are trained to differentiate good and bad designs, they are knowledgeable about IRB and other ethical requirements, and are capable of determining whether study results are satisfactory, flawed, generalizable, etc. If the FDA is not exercising this responsibility to the best of their ability, perhaps this should be addressed and corrected instead of reinventing the wheel and starting from scratch in another department with personnel who are not in the habit of handling this very complex process.

In regard to the draft guidance for orphan drugs, we are again concerned about duplicating efforts already in place at the FDA. As advocates for the blood clotting disorders community, we are acutely aware of the role played by the FDA in approving orphan drugs, especially in the areas of efficacy and safety.

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Web Site: www.hemophiliafed.org

Some of the clinical trials overseen by the FDA are for orphan drugs for rare diseases that may not result in massive statistics due to the small numbers of patients available for the trials as compared to drugs for larger populations. HFA respectfully requests that CMS re-consider bringing these clinical trials under their umbrella and leave them within FDA.

Hemophilia Federation of America is a national nonprofit organization that assists and advocates for the blood clotting community and we have the vision that the blood clotting disorders community has removed all barriers to both choice of treatment and quality of life. We work on some of the same issues that The National Hemophilia Foundation does but mostly they handle research and medical matters with great expertise and HFA deals more with one on one matters of support for community members. We try not to duplicate efforts where resources are limited and feel this is a good premise to be followed in the instance of clinical trials, as well.

Thank you for listening to our concerns and reading our comments. If you have any questions regarding these comments, feel free to call me at 337-984-6446.

Sincerely,

Jan Hamilton

Jan Hamilton
Advocacy Director
Cc: HFA Executive Committee

Organization: ImClone

(Comment on next page)

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June 6, 2005

Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mailstop: C1-12-28
Department of Health and Human Services
7500 Security Boulevard
Baltimore, Maryland 21244

Re: Draft Guidance on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development"

Dear Coverage and Analysis Group:

ImClone Systems Incorporated ("ImClone") is pleased to submit these comments in response to the Draft Guidance ("Draft Guidance") on Factors CMS Considers in Making a Determination of Coverage with Evidence Development ("CED") issued by the Centers for Medicare and Medicaid Services ("CMS") on April 7, 2005. ImClone is a biopharmaceutical company dedicated to developing breakthrough biologic oncology medications. The Company has utilized advances made in the fields of molecular biology, oncology, genomics, and antibody engineering to develop a novel pipeline of product candidates designed to address specific genetic mechanisms involved in cancer growth.

In summary, ImClone presents the following suggestions for consideration:

- CMS should explicitly provide coverage to all similarly situated persons meeting the applicable CED study protocols, regardless of whether or not they are involved in a study;
- Randomized clinical trials should be the appropriate CED study design;
- CED approach should have a defined timeframe that promotes rapid expansion of coverage once a clinical endpoint is achieved in a clinically significant manner; and
- Medicare carriers are best positioned to establish a means to report data.

The Company's first approved product, Erbitux® (cetuximab), has been approved by the Food and Drug Administration ("FDA") for the treatment of irinotecan refractory or intolerant metastatic colorectal cancer. Earlier this year, CMS issued its first national coverage determination ("NCD") based on the CED approach for Erbitux and three other anti-cancer drugs approved for colorectal cancer in National Cancer Institute-clinical trials identified by CMS for off-label use.[1] Accordingly, we believe that we have an important and useful perspective to bring to the discussion of the Draft Guidance document.

[1] Department of Health and Human Services Centers for Medicare and Medicaid Services, Change Request 3742, March 29, 2005.

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We welcome this opportunity to comment on the Draft Guidance in light of the fact that our company, our customers, and their patients are so directly affected by the CED for anti-cancer drugs against colorectal cancer. At the onset, as a matter of consistency and fairness, we note that it is critically important that any changes in guidance that result from this notice and comment procedure and that improve the coverage offered through the CED process should automatically apply to the CED to which Erbitux® is subject.

We applaud CMS for circulating this Draft Guidance to stakeholders, like ImClone, in an effort to ensure that the CED approach both improves beneficiary health and serves to facilitate the adoption of new and expanded medical technologies and services. Further, we appreciate the fact that the Agency does not anticipate the frequent use of the CED approach going forward. We believe that the use of the CED Guidance should be rare, as the creation of coverage for only portions of an affected Medicare population can create disturbing issues.

We frame our comments based upon our ongoing Erbitux® CED experience and offer the following specific suggestions.

I. Patients Should Be Treated Equitably under the CED Guidance

On the colorectal cancer CED, CMS determined that off-label, unlisted uses of four approved drugs would be covered by all contractors, providing coverage to the extent that the patients receiving these drugs were enrolled in one of nine National Cancer Institute-sponsored clinical trials. As the Draft Guidance indicates, CMS hoped that CED represented a net expansion of coverage because it ensured that all contractors would provide coverage for any patient enrolled in the NCI trials. Unfortunately, that was not the case. Because ImClone intends to use the data from the NCI trials in FDA approval submissions, the Erbitux™ used in the CED trials cannot be reimbursed by any third party, including CMS. According to 21 C.F.R. § 312.7(d) "[c]harging for an investigational drug in a clinical trial under an [investigational new drug application] is not permitted without the prior written approval of FDA." Accordingly, for Erbitux®, the NCD supplies coverage, but no reimbursement, a fact that has created more frustration for beneficiaries.

The colorectal CED left in place the discretion available to contractors to cover off-label, uses of the affected anti-cancer drugs for patients not enrolled in certain NCI trials. ImClone was disappointed, however, that the CED did not encourage the local contractors to provide expanded coverage even where non-trial patients are subject to the same protocol measures as trial participants and have demonstrated an inability to access and enroll in the NCI trial. Accordingly, we were pleased that the Draft Guidance states: "[i]t is not the intent of this approach to reduce the importance or frequency of local coverage determinations as a pathway

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by which new technologies are made available in the Medicare program."[2] We and the rest of the cancer care community were delighted by the suggestion in the Draft Guidance that the CED approach and contractor's discretion to make local coverage determinations on new technologies will continue to coexist.

ImClone, therefore, wholeheartedly agrees that coverage should be available for all patients who are treated in accordance with the protocols developed for the nine NCI-sponsored clinical trials, whether or not they are in an NCI trial or any trial. The Draft Guidance states: "NCI trials provide rigorous safeguards for patients, and ensure patient evaluation and selection and reasonable use of cancer chemotherapy. Trial designs include an adequate plan for data and safety monitoring and ensure individualized analysis and evaluation of patients' response to chemotherapy and their health status."[3] Where measures are present, regardless of the context in which they are present, there is no basis to discriminate among patients. To do so would be to deny coverage to similarly situated beneficiaries.

We believe that the best means of ensuring equitable treatment under a CED for all beneficiaries who meet the protocol for the specified data collection is for CMS, in its CEDs, to explicitly provide coverage to all similarly situated persons meeting the applicable study protocols, regardless of whether they are involved in a study or not, and they can not reasonably access the sponsored study. Although it would be significantly less attractive as a policy because of the delays that it would involve, CMS might also protect its CED determinations from criticism that they otherwise discriminate among beneficiaries by strengthening the language regarding what should be a clear presumption that local contractors should expand coverage to patients not in CED covered trials to the extent that the patients meet the applicable protocols and can not participate in the trial. In any event, only one of these two approaches will create any real coverage for Erbitux®. As indicated above, the colorectal CED should be immediately changed to reflect increased coverage commitments or opportunities adopted through this CED process.

II. Evidence Development Methods

ImClone agrees that study designs linked to CED should adhere to scientific, medical, and ethical principles. ImClone is committed to rigorous study design and oversight. Because the CED policy represents a lesser standard in assessing what is "reasonable and necessary" than might otherwise apply, CMS should set an appropriately high bar with respect to the evidence that it seeks to accumulate.

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[2] *Draft Guidance for the Public, Industry, and CMS Staff, Factors CMS Considers in Making a Determination of Coverage with Evidence Development, April 7, 2005* at 6.
[3] *Id.* at *8.*

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Accordingly, randomized clinical trials should be the appropriate CED study design. As the Draft Guidance acknowledges, they often provide the best evidence of effectiveness. If the CED initiative is intended to enable Medicare to provide payment for items and services under conditions that help assure significant net benefits of the treatment for beneficiaries, then CMS should rely on the high bar provided through randomized clinical trials to ensure adequate support for a finding of a likelihood of improved health outcomes is present.

III. Process for Study Design and Implementation

We applaud CMS for recognizing the importance of appropriate oversight of data collection enterprises and an efficient operations system. Within this section of the Draft Guidance discussing Process for Study Design and Implementation the Agency raises significant issues regarding timeframe and data collection. ImClone offers suggestions as to both issues. First, the CED process should have a defined timeframe that promotes rapid expansion of coverage once a clinical endpoint is achieved in a clinically significant manner. Second, Medicare carriers are best positioned to establish a means to report data.

A. Timeframe

ImClone agrees that there should be a defined timeframe for the CED process. At that point, a requestor, including the manufacturer, should be able to formally request full coverage, with no limits based on enrollment in the CED study or application of the CED protocol, that is consistent with the clinical endpoint that has been achieved. CMS should have 90 days to consider the request. If the Agency fails to act, automatic coverage expansion to all Medicare beneficiaries should result at that time.

Expansion should be rapid once the predetermined clinical endpoint is achieved that CMS determined would and should be significant to the coverage question. In the absence of rapid expansions, unacceptable and unjustified discrimination among beneficiaries will occur. Indeed, even those patients who originally had coverage will now be denied it, as the underlying study will have ended.

This approach to the timeframe and endpoint issues allows CMS to partner with the industry to ensure that sufficient evidence is available to assess whether an item or service improves net health outcomes while remaining faithful to the principles of evidence-based medicine and judiciously expanding coverage to beneficiaries.

B. Data Collection

ImClone is sensitive to the Agency's need to fairly allocate the costs of study design, data collection, analysis and other activities associated with these programs among the

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various stakeholders. To that end, we believe that Medicare carriers are best positioned to establish a means to report data. Based on their integral place in the program and their pre-existing relationships with providers and beneficiaries, carriers are best suited to act as a repository of the data collected through CED. While this may be an added burden to these entities, the Agency's own recognition that CED process will be used sparingly weighs against the costly creation of an alternative mechanism for data collection, where one already exists through the carriers.

IV. Conclusion

Thank you for the opportunity to participate in the development of the CED approach. We look forward to working with you in the future to ensure that Medicare beneficiaries have access to emerging and existing drug therapies and future innovations.

Sincerely,

Eric Rowinsky, M.D.
Senior Vice President, Chief Medical Officer

cc: Herb Kuhn
Steve Phurrough, M.D.
Barry M. Straube, M.D.
Greg Mayes, ImClone Systems Incorporated
William A. Sarraille, Sidley Austin Brown & Wood LLP

Organization: Indiana Medical Device Manufacturers Council
Name:

(Comment on next page)

June 3, 2005

Steve E. Phurrough, M.D., M.P.A.
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail Stop: C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

Re: Comments on Draft Guidance Document concerning Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

The Indiana Medical Device Manufacturers Council (IMDMC) appreciates the opportunity to submit these comments on the CMS draft guidance document on Coverage with Evidence Development (CED).

IMDMC is an association that represents Indiana-based manufacturers of medical devices and diagnostics products. One key objective of IMDMC is to improve the access of Medicare beneficiaries to innovative, high-quality health care. Medicare's national coverage process can bear directly on this objective. We therefore appreciate the opportunity to submit these comments.

CED Vision is Compelling

IMDMC, in comments submitted in advance of the draft CED guidance, reviewed a number of thoughtful CMS and AHRQ suggestions for producing and using medical evidence more effectively. We noted the remarks of Dr. McClellan, Dr. Clancy, Dr. Tunis, and yourself at a February 14 Open Door Forum. We cited a cogent article authored by Dr. Tunis (to which Dr. McClellan contributed) that described a strategy for increasing the supply of "real-world" information on health care interventions.[1]

[1] S.R. Tunis, "A Clinical Research Strategy To Support Shared Decision Making," *Health Affairs*, January/February 2005; 24(1): 180-184.

From these remarks and materials we discerned a vision of a health care system that identifies gaps in evidence; that sets priorities for filling those gaps; and that develops and deploys simpler techniques for collecting evidence to address these "gap filling" priorities.

As we said in our comments, this vision is compelling, and it is one to which IMDMC subscribes. IMDMC believes in evidence-based medicine; it believes that the availability of better information would improve health care decisions and help patients secure access to higher quality care.

Subsequent to the time we submitted these comments, we acquired much more detailed information on CED. This information included the discussion at a May 9 Open Door Forum, as well as the text of the draft CED guidance itself. Based on these materials, we find the vision of Dr. McClellan and his colleagues no less compelling, and we alter the depth of our support for it not one iota.

As noted in our March comments, however, we have questions about how this vision can properly be reflected in Medicare national coverage decisions. Specifically, as described below, we are concerned that some might interpret the agency's implementation of CED to be inconsistent with the applicable statutes. We also have a number of technical critiques and suggestions on the draft CED guidance.

Before addressing these topics, however, we would like to reiterate a key point from our previous comments: the need for CMS, as it moves forward on the CED draft, to encourage meaningful interaction with stakeholders.

Meaningful Interaction with Stakeholders

IMDMC noted in its March comments that CMS should not proceed at an artificially rapid pace to issue a final CED guidance, but should instead allow stakeholders the time to genuinely deliberate and provide meaningful input.

As we noted in those earlier comments, there are at least two reasons for CMS to take special care to ensure that, in developing the CED guidance, it has the benefit of multiple perspectives. First, this guidance, when finalized, will be among the first coverage guidances that CMS will issue, suggesting that the agency should err on the side of discussion and feedback in order to minimize the possibility of unintended consequences. And second, CED is not a well-known, long-discussed concept; it represents a potentially far-reaching change not yet fully understood -- and thus one deserving of more focus than might be accorded familiar topics.

IMDMC appreciates the opportunity to comment on this first draft of the CED guidance, and, as indicated in our March comments, we recommend that CMS issue additional drafts, with appropriate opportunities for stakeholder comments on all such subsequent drafts. However, we also believe that written comment opportunities are not alone sufficient for the CMS-stakeholder dialogue that CED requires.

Specifically, we would like to reiterate a recommendation made in our March comments: that CMS convene public meetings in a workshop-type format. Meetings like these would be consistent with FDA's Good Guidance Practices,[2] and they would allow more time for in-depth discussion than is possible in a CMS Open Door Forum. Moreover, such "real-time" dialogue can be especially valuable when, as with CED, there is substantial ambiguity and uncertainty. Finally, CMS-stakeholder interaction in this type of format would allow a careful review of two areas that IMDMC believes warrant particular attention.

The first area concerns the learning that is becoming available as recent CED decisions are implemented. In the last few months, CMS has applied CED (if not by that name) to such health care interventions as implantable cardioverter defibrillators and PET scanning. It would be valuable to use a workshop-type session to review the "real world" experience being gained as these decisions are implemented. From a review of these "case studies," CMS and stakeholders could understand more fully the implications of CED decisions and the practical issues that a thoughtful implementation plan should address. CMS could then draw on this knowledge in future instances in which application of CED is being considered.

The second area – one that to date has garnered relatively little attention – concerns the potential effects of CED on small manufacturing companies. Many of these companies are IMDMC members, and we are keenly aware of important role these small enterprises play in developing innovative medical devices and diagnostic products.

Because small companies are often modestly capitalized, and may derive little or no revenue until their first commercialized technology reaches market, we fear that CED might inadvertently act as a barrier to innovation. In the short term, a small company might find it impractical to bear the evidence-gathering costs necessary to introduce a new health care innovation into the Medicare market. In the longer term, CED might inadvertently threaten not just innovations themselves, but also the very *incentive* to innovate.

In sum, CMS should structure opportunities for direct and meaningful interactions between the agency and stakeholders – to address the topics noted above, as well as other issues that CED implicates.

Relationship of CED to Applicable Statutes

We are concerned that the draft CED guidance, in molding a potentially expansive health care vision to a specific government program, might be viewed by some as taking Medicare into areas that the Medicare statute does not allow. This is perhaps a commentary more on the statute than on the vision. Indeed, it has become clear over the

[2] *See* 21 C.F.R. §10.115(g)(iii)(A). The Medicare statute requires that coverage guidances be developed in a manner similar to that used by FDA. Social Security Act § 1862(l)(1) (42 U.S.C. §1395y(l)(1)).

years that Medicare, a program of the mid-1960s, has not always been able to keep pace with the quickening cadence of modern medicine.

Please know that IMDMC supports the vision of a health care system that encourages the practical and swift production of better medical evidence – and that seamlessly transports that evidence to physicians and patients for use in their day-to-day clinical decisions. Therefore, our comments, below, are offered constructively, in the interest of ensuring that CMS has available to it the full range of views that might be put forward on the relationship of CED to the applicable statutes. Should CMS conclude that CED requires adjustments in light of statutory concerns, IMDMC would be happy to work with CMS to fashion any changes that are needed, while still preserving the agency's vision.

- *"Reasonable and Necessary"*

  The Medicare statute entitles a beneficiary to specified categories of reimbursable benefits, but allows the HHS Secretary to exclude from these benefits any items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member . . ."[3] This statutory language could be interpreted to provide that an item or service must be "reasonable and necessary" for a *particular* beneficiary in order for the item or service to be covered for that beneficiary.

  In the draft guidance, CMS acknowledges this interpretation of the statute. In the draft's third sentence, the agency states:

  > "The primary purpose of obtaining additional evidence through CED is for the agency's use in making payment determinations, i.e., that a treatment is reasonable and necessary."

  Other passages in the draft guidance, however, might be read to suggest that additional purposes underlie CED. On page 4, for example, the draft guidance describes CED as contributing to "a systematic expansion of practical clinical research efforts to address the information needs of health professionals and patients."

  To be clear, expanding research and providing information to physicians and patients are laudable objectives, and IMDMC certainly supports them. But some might argue that while the production and distribution of new clinical knowledge can be valuable in guiding physician and patient decisions *in the future*, they are not usually pertinent to the coverage decisions being made for beneficiaries *in the present* – i.e., for the beneficiaries with respect to whom the evidence is actually being collected. According to this reasoning, the collection of evidence, to be consistent with the statute, must confer a clinical

[3]."Social Security Act §1862(a)(1)(A) (42 U.S.C. §1395y(a)).

advantage that, if not present, would preclude a service from being "reasonable and necessary" at the time a beneficiary receives it.

- *Protection of Research Subjects*

  Under the interpretation of "reasonable and necessary" described above, "current" Medicare beneficiaries could be viewed as effectively participating in a research program aimed at producing evidence to inform clinical care decisions that will affect "future" beneficiaries.

  CMS acknowledges in the draft guidance that participants in research are protected by confidentiality and privacy requirements. These protections, in and of themselves, are very important. Beyond them, however, "if there is any element of research in an activity, that activity should undergo review for the protection of human subjects."[4]

  Specifically, the value of "informed consent" in a CED research protocol might be questionable. This is because the voluntary nature of informed consent can be assured only when "refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled . . ."[5] In at least most instances of CED's application, declining to participate in a research protocol would result in loss of health care benefits. Thus, it would be ethically problematic for CMS to deny Medicare coverage to a beneficiary on the basis that the beneficiary has declined to participate in a CED research protocol.

- *"Safety and Effectiveness"*

  In several passages, the draft guidance cites "safety and effectiveness" as a type of issue that may precipitate or be the object of a CED evidence-production initiative. On page 5, for example, the draft states that post-coverage evidence development –

  > "may help address important questions of safety and effectiveness that otherwise would be very difficult to address in the premarket setting, or in the postmarket setting in the absence of CMS support."

  As IMDMC has commented on other draft coverage guidance documents, we believe the law vests in FDA exclusive responsibility within the Department of Health and Human Services for ensuring the safety of products subject to FDA regulation. We therefore submit that the draft exceeds the authority of

[4] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (April 18, 1979), available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm, at Part A, Section A, para 4.

[5] 45 C.F.R. §116(a)(8).

CMS because it intrudes into areas for which Congress has provided exclusive authority to FDA.

We note that CMS has previously said that in making Medicare coverage decisions it "adopts FDA determinations of safety and effectiveness."[6] We urge the CMS to use the CED guidance or another coverage guidance to make clear that it not only accepts those safety determinations that FDA renders, but that it abstains from itself attempting to resolve any *additional* safety issues that it perceives may exist. "Effectiveness," we recognize, may have different meanings in the regulatory and reimbursement contexts. We suggest that CMS explain more precisely the "effectiveness" questions to which it believe CED might appropriately be applied.

- *"Cost" and "Cost-Effectiveness"*

  In several instances, the draft guidance cites "cost" and "cost effectiveness" as outcomes that might be identified as a result of a CED protocol. IMDMC concurs in the importance of cost and cost effectiveness as outcomes measures. We question their role, however, as an element of CED.

  We make two specific points. First, we believe "reasonable and necessary" encompasses only clinical considerations and does not permit an inquiry into economic factors. Our second point is that cost and cost-effectiveness are more easily understood and applied at the focused physician-patient level, rather that at the broad Medicare programmatic level. We note that in recent reported remarks, Dr. McClellan offered a thoughtful observation:

  > "There are so many opportunities to get better quality or lower costs without us or anybody else having to make explicit judgments about whether a technology is really worth it or not . . . [But] just because we are not taking account of cost-effectiveness in our coverage decisions . . . does not mean that [these]consideration are not going to matter. They are going to matter . . . increasingly from the standpoint of doctors and patients, when they are weighing treatment options."[7]

  We agree with Dr. McClellan's remarks, and we urge that the content they convey be integrated into the draft CED guidance.

Additional Technical Comments

- *Frequency of CED Use*

[6] Notice, "Medicare Program; Revised Process for Making Medicare National Coverage Determinations," Centers for Medicare and Medicaid Services, 68 Fed. Reg. 55,634 (Sept. 26, 2003), at 55,636
[7] "The Gray Sheet," Medical Devices, Diagnostics & Instrumentation (May 23, 2005).

CMS states in the draft guidance, on page 2, that "[w]e do not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirements." Moreover, the agency notes on page 9 that limited pilot studies will precede any broader CED implementation. Consistent with these views, we understood you, Dr. Phurrough, to say at the May 9 Open Door Forum that CED will be used infrequently.

IMDMC agrees with CMS that CED should be used sparingly and at first only on a pilot basis. As you noted at the May 9 Forum, drawing on existing Medicare claims data may serve as an alternative or supplementary evidentiary tool to CED.[8] IMDMC supports use of claims data as a potentially fertile means for better understanding the outcomes of Medicare-covered services under actual clinical conditions.

- *Analyzing Costs/Benefits of CED Use*

  One method for limiting CED's use to appropriate circumstance is to apply a disciplined cost/benefit analysis to any proposed deployment of this tool. We acknowledge the agency's helpful statement, on page 5 of the draft, that the expected benefits of collecting evidence through CED should outweigh the costs.

  We suggest that this concept be implemented through a defined methodology and process, with opportunities for stakeholder involvement and comment. Pilot applications of CED (see above) might be used to test cost-benefit models. Without a clear, defined model, CMS will have no basis for concluding that a given CED protocol is or is not cost-beneficial.

- *Coverage "With Conditions"*

  We are concerned about the draft guidance's broad statement, on page 4, that "CMS does not anticipate additional decisions" that do not attach conditions to coverage, such as conditions associated with particular patient characteristics or particular qualifications for professionals and facilities.

  We believe this statement is so sweeping as to verge on being imprudent. It seems particularly inapt with respect to services utilizing FDA-cleared products. If implemented literally, the statement would seriously damage beneficiary access to needed health carte services.

- *Study Design and Implementation*

[8] *See* Decision Memorandum, "Reconsideration of Ultrasound Stimulation for Nonunion Fractures," Centers for Medicare and Medicaid Services, CAG-00022R (April 27, 2005) (approving coverage, with post-coverage analysis of claims data).

There are a number of very detailed comments that could be offered on the topic of design and implementation of CED-required studies. The overarching point, it seems to us, is that CMS needs to understand – and to publicly make clear – the exact questions that a study is intended to answer. If these questions are not clearly articulated -- at least by the time a final coverage decision memorandum issues -- CED will not only sow confusion and uncertainty, but it will undercut the credibility of the evidence-production objectives that CMS seeks to foster.

***

IMDMC very much appreciates the opportunity to submit these comments. We look forward to continuing to work with CMS as the agency develops this and future guidance documents on Medicare's national coverage process.

Respectfully submitted,

Bradley Merrill Thompson
General Counsel

BMT/slb

Organization: ISPOR
Name:

(Comment on next page)

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June 6, 2005

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Re: Draft Guidance for Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

Thank you for the opportunity to comment on the proposed Factors CMS Considers in Making a Determination of Coverage with Evidence Development.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) is an international organization promoting the science of pharmacoeconomics and health outcomes research. The International Society is organized to act as a scientific leader relevant to research in pharmacoeconomics, health outcomes assessment, and related issues of public policy. The International Society represents healthcare researchers and practitioners including pharmacists, physicians, economists, nurses and researchers from academia, pharmaceutical industry, government, managed care, health research organizations, and purchasers of healthcare. The mission of the International Society for Pharmacoeconomics and Outcomes Research is to translate pharmacoeconomics and outcomes research into practice to ensure that society allocates scarce healthcare resources wisely, fairly, and efficiently.

ISPOR members have been following the CMS CED guidance with great interest. We share CMS's goal of ensuring that advances in medical technology are available for its Medicare beneficiaries while also ensuring that the care they receive is reasonable and necessary. We appreciate the need for CMS to carefully consider evidence issues surrounding the coverage of items and services for Medicare beneficiaries, and welcome the guidance as an opportunity to have a dialogue on this critical issue.

The science of establishing clinical evidence outside of RCTs and for establishing evidence of value has evolved considerably in recent years. ISPOR has interest in ensuring that all existing knowledge, expertise, and best practices are utilized by CMS. We believe that is it critical that dollars for research be used in most efficient way possible.

We acknowledge many difficult challenges in determining evidence for purposes of coverage and payment, and we commend CMS on identifying many of salient issues and key questions to be addressed in this guidance.

Among the critical issues:

- **Good research practice**. It is important that CED follow good research practices (e.g., posing well-defined questions, specifying timeframes for duration of data collection, periodic monitoring to ensure quality and responsiveness to research questions, limiting sample sizes to the minimum necessary, and so forth).
- **Prioritizing decisions**. It will be important to prioritize CED decisions so that they focus on cases in which the benefits of collecting additional information are expected to outweigh the costs of data collection.
- **Process**. It is vital that considerable attention be paid to the process implemented for prioritizing and enacting CED decisions, and for disseminating information after data collection. The process should be as transparent as possible, should allow opportunity for public and stakeholder participation, and should spell out clearly issues and potential concerns related to informed consent and human subjects protections. It will also be critical to develop a systematic and transparent process for disseminating evidence collected to a wide range of stakeholders identified. The evolving processes used by the UK National Institute for Health and Clinical Excellence are worth reviewing for lessons learned.

- **Value of information**. The draft guidance cites the tool of "value of information analysis" as a more formal approach to deciding when and what types of data to collect following a coverage decision. Our members are among the most experienced practitioners in applying this approach, which provides both a cost-benefit framework for addressing these questions systematically. We urge explicit consideration of this tool, and, in particular, explicit consideration to the potential positive health outcomes forgone due to delays in coverage as well as the potential adverse consequences of too rapid uptake when the risk-benefit ratio is highly uncertain.
- **Types of study design.** The draft guidance appropriately recognizes that several different study designs can provide useful information for coverage decisions. Randomized controlled trials (RCTs) remain the gold standard for demonstrating clinical efficacy in restricted trial setting, but other designs—such as observational registries, claims databases, and practical clinical trials—can contribute to the evidence base needed for coverage decisions. The level of evidence required will relate to the question at hand.

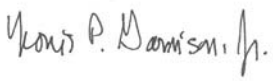
Finally, we would urge that the CED be seen as a starting point for debates about coverage and evidence. We would encourage CMS to think about CED alongside larger questions about appropriate incentives for the Medicare program.

The signees of this letter represent ISPOR's Task on Using "Real World" Data in Coverage and Reimbursement Decisions, ISPOR Special Interest Group on Health Technology Assessment, ISPOR Patient Registry Special Interest Group and the US Medical Device and Diagnostics Council and do not necessarily reflect the views of the broader ISPOR membership. However, there is broad consensus that ISPOR members have considerable expertise to help focus on methodological issues. Please see the attached document for detailed responses to individual questions. These responses reflect the suggestions of the SIG's listed below.

We look forward to follow up to this guidance and the opportunity to contribute on specific implementation issues. Thank you again for this opportunity. If you have any questions regarding our comments, please contact Marilyn Dix Smith, Ph.D. directly or the ISPOR office at mdsmith@ispor.org .

Sincerely,

Peter J. Neumann ScD, ISPOR Using Real World Data Task Force Co-chair & Associate Professor of Policy and Decision Sciences, Harvard School of Public Health , Boston, MA, USA



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cc: Marilyn Dix Smith RPh, PhD, ISPOR Executive Director [Email: mdsmith@ispor.org], and ISPOR Board of Directors

V. Evidence Development Methods

What other study designs should be considered?

Comments from Health Technology Assessment Special Interest Group - Methodology Working Group

RCT'S, Prospective Registries, Administrative Databases

Comments from the Health Technology Special Interest Group: HTA in Reimbursement Economics Working Group

The study design recommended here should be considered in case CMS decides that the focus of the CED will be on the entire spectrum of technologies and services and not only on new technologies and services. Depending on the question (safety, benefits, etc.) being asked about older technologies that are being covered by Medicare it may be worthwhile in terms of time, cost, and efficiency to first consider a retrospective claims database analysis (using Medicare claims data). Depending on the findings of the retrospective claims database analysis, CMS may decide if further data collection using a different study design may be required. If additional clinical detail (not available in Medicare claims) is required then patients identified as having received the older technology can be identified from the claims data and recruited for a study involving medical record review, clinical examination, or personal interview.

Comments from ISPOR Patient Registry Special Interest Group comments

A study's structure is, of course, a critical aspect in achieving its objectives. That said, inasmuch as CMS seeks actual practice or 'real world' information, it may want to consider incorporating into its categorizations an acknowledgement of study designs that would be more likely to produce such findings. RCTs, for example, rarely can describe actual practice conditions with a degree of accuracy since, through the imposition of randomization and protocol-driven activity, an unnatural situation is created. Analyses derived from observational studies — databases and longitudinal cohort studies or "registries" — are most appropriate for describing actual practice conditions. Post-randomization, practical clinical trials can also be designed to be relatively naturalistic.

What type of questions is each study design best able to answer?

Comments from ISPOR Health Technology Assessment Special Interest Group - Methodology Working Group

RCT: Efficacy, +/- Effectiveness (Medical Effectiveness Trial)
Prospective Registries: Effectiveness

Admin Databases: Safety Issues

Comments from ISPOR Patient Registry Special Interest Group

RCTs are, appropriately, the gold standard for proving or disproving, within statistical tolerances, a specific hypothesis. Inclusion criteria and procedural controls are established to eliminate extraneous variables impacting the clarity necessary to answer a specific question. By contrast, observational studies are uncontrolled and include "all comers." Hence, the ability to assess the impact of extraneous variables may be compromised. As such, RCTs can generally be considered more definitive in answering specific questions that can be framed as hypotheses (e.g., A achieves better outcomes than B).

Observational studies can provide important insights into relationships between variables and outcomes, trends, and sub-populations. Statistical techniques can be employed to achieve between group comparability and to facilitate the evaluation of hypotheses in a fashion similar to a RCT, albeit with a potentially lower level of definitiveness (since all extraneous variables must be identified and their impacts statistically evaluated).

As compared to RCTs, observational studies can better address longer-term outcomes, as naturalistic research is generally easier to sustain than the artificial conditions of a RCT.

Although they, intrinsically, lack the controls of RCTs, observational studies and, to some extent, practical clinical trials, provide the best possible means for understanding treatments and outcomes in actual practice settings.

What are the limitations of each study design?

Comments from ISPOR Patient Registry Special Interest Group

Simply stated, RCTs cannot generally reflect actual medical practice conditions.
Observational studies lack the design features that would result in a truly definitive answer to a question.
Taken together, RCTs and observational studies can be considered highly complimentary.

Comments from ISPOR Health Technology Assessment Special Interest Group

RCT'S: Generalizability, Costs
Prospective Databases: Patient Selection, Confounding

Admin Databases: Confounding of Outcomes, Chanelling

Under what circumstances should CMS require a database? A longitudinal data collection? A prospective study? A clinical trial?

Comments from ISPOR Patient Registry Special Interest Group

Databases (claims, EMRs) can be useful in providing illumination about a particular issue, but retrospective analyses are limited to the data collected and to the peculiarities imposed (e.g., motivation to code a particular procedure so as to maximize reimbursement). Rarely can Patient-Reported Outcomes (PRO) data be expected in a retrospective database. Database analysis can be useful in generating a hypothesis. Rarely should CMS "require" a database…

Passive, longitudinal data collection can be appropriate and even desirable when specific data elements and outcomes can be incorporated into the data collection process.

Prospective, observational studies are most appropriate when there are concerns over post-approval uses of a particular product. An Analysis Plan must be part of any prospective initiative.

A (randomized, controlled) clinical trial is appropriate when an answer to a specific condition is needed, and the conditions imposed by the trial are relevant.

Comments from ISPOR Health Technology Assessment Special Interest Group

Clinical Trial: To Assess Efficacy Of New Medications, And I Also Feel To Assess New Medical Devices (With perhaps an exception for solely diagnostic technologies that are harder to evaluate in this setting)
Prospective Study: Assessment Of Emerging Diagnostic Technologies

Admin Databases/Specialized Registries: Long Term Safety of New Meds And Devices

Comments from the Health Technology Assessment Special Interest Group: HTA in Reimbursement Economics Working Group

Note: In addition to a list of specific circumstances, the "value of information" analysis may potentially help CMS identify what type of study design may be worth pursuing on a case-by-case basis.

Additional Comments
Data collection requirements should be established after:
Review of all existing and planned private and public research efforts in a consistent and comprehensive manner to ensure that these mechanisms are leveraged in an efficient manner and that CMS data collection efforts are complimentary to existing research.
Agreement on a protocol with well-defined research questions, timeframes for the duration of data collection, and periodic monitoring to ensure quality and responsiveness to research questions;
Limiting the sample size to the minimum necessary as defined by the agreed upon protocol.

What process should CMS use to evaluate the quality of a proposed study design?

Comments from the ISPOR Health Technology Assessment Special Interest Group

Panel of experts; established criteria of quality with recognized grading of the level of evidence they generate (using all study methodologies applicable to the question at hand).

How should CMS determine whether the evidence collected suggests patients are either harmed or not benefited by the item or service?

Comments from the ISPOR Health Technology Assessment Special Interest Group

Adequate powering of clinical trials/registries, or adequate follow-up time of admin databases/registries based on biological plausible considerations of safety/harm.

Comments from the ISPOR Patient Registry Special Interest Group

CMS should establish *a priori* parameters and thresholds that would indicate, within statistical tolerances, either that safety or effectiveness is diminished relative to the use of an alternative item or service. Outcome measures must be relevant.

Before concluding that evidence from an observational study suggests (definitively) that patients are either harmed or not benefited, a more formal controlled study should be undertaken to prove or disprove the hypothesis generated from the observational study.

Further analysis should be undertaken to determine whether incremental harm or lack of benefit is associated with a particular subgroup.

Although "increased harm" is clearly undesirable in any respect, CMS may want to consider incorporating economic and/or humanistic measures into studies to further inform situations in which there is little or no apparent incremental clinical benefit. Clinical parity achieved at a lower overall cost and/or in association with improved patient satisfaction and/or quality of life, may indicate items or services of potentially increased value.

Miscellaneous comments

How can CMS best ensure that these studies are implanted in a way that is compatible with current public and private efforts to promote effective and consistent adoption and use of health.

VI. Process for Study Design and Implementation

Who should participate in study oversight and implementation?

Comments from the ISPOR Health Technology Assessment Special Interest Group: HTA in Reimbursement Economics Working Group

In addition to individuals with clinical, scientific, and technical expertise, a committee comprising of representatives of pertinent stakeholders (e.g. CMS, manufacturer, etc.) should be designated for overall study oversight.

Comments from the ISPOR Patient Registry Special Interest Group

Study oversight in design and execution should be under the auspices of a multi-disciplinary committee consisting of clinical experts, practicing physicians and other health care professionals, outcomes research specialists, and statisticians familiar with specific study designs.

Comments from the ISPOR Health Technology Assessment Special Interest Group

Third party, independent experienced group of individuals

How should CMS determine the qualifications of investigators involved with coverage evidence development?

Comments from the ISPOR Patient Registry Special Interest Group

Investigators participating in trials, registries, etc. (i.e., any prospective research initiative) should be bound by a formal legal contract stating their obligations and expectations for contributing accurate data from actual patients. Study designs should be sufficiently transparent for CMS to understand the limitations of findings. Data managers should be bound by legal contracts and/or certifications, as well as professional ethics.

Comments from the ISPOR Health Technology Assessment Special Interest Group

Based on training, publication profile, work experience, and letters of reference from recognized evaluative organizations/acknowledged peers.

What are other important oversight and operations issues?

Comments from the ISPOR Patient Registry Special Interest Group

IRB approval is critical. In many cases, central IRB review and approval of study protocols and procedures is adequate.

Independent Scientific Advisory Boards, comprised of clinicians and outcomes researchers, also provide critical oversight relating to study findings.

Comments from the ISPOR Health Technology Assessment Special Interest Group

Funding issues need to be determined; operationalizing the entire process needs to be carried out in a timely and transparent manner; a pool of contributing overseeing organizations/individuals need to be created as does the corresponding administrative infrastructure.

Comments from the Health Technology Assessment Special Interest Group: HTA in Reimbursement Economics Working Group

In addition to minimizing data collection burden, processes should be put in place to reduce administrative burden associated with implementing a study. For instance, a structure should be put in place to ensure efficient human subject reviews for all studies conducted as part of the CED initiative.

What are the major oversight and implementation issues?

Comments from the ISPOR Health Technology Assessment Special Interest Group

Funding issues need to be determined; operationalizing the entire process needs to be carried out in a timely and transparent manner; a pool of contributing overseeing organizations/individuals need to be created as does the corresponding administrative infrastructure.

What approaches to study design and implementation would be least costly and most efficient? What are some specific ideas for minimizing the resources required for conduction these studies, while generating the maximum amount of useful information?

Comments from the ISPOR Patient Registry Special Interest Group

Different study designs have different implications in terms of rigor and data quality. Certain aspects of GCP may not apply in the case of observational studies (in which Good Epidemiological Practices should be considered).

"High tech" approaches, such as EDC via the Internet, can often improve the overall cost-efficiency of a study.

Comments from the ISPOR Health Technology Assessment Special Interest Group

Existing ongoing administrative databses, if already maintained by other organizations would be most cost-efficient Propsective studies could be piggy-backed ont the assessment of each new drug/device.

Establishing a network of investigators to be used repeatedly for such initatives and funding a related infrastructure could be expensive upfront but would allow a cost-efficient use of resources in time (see below).

What parameters are needed to evaluate operational issues?

Comments from the ISPOR Health Technology Assessment Special Interest Group

Assessment of the quality of data entry, and quality control of source documentation would need to be verified (both electronically, by informatics, and by manual sampling of data); cross-linking with other existing databases could also be considered as independent source documentation.

What criteria should CMS use to assess the appropriateness of the above operational issues involved in evidence development?

Comments from the ISPOR Health Technology Assessment Special Interest Group

Not sure; perhaps a literature review would be helpful to identify what others probably have identified with regards to this area.

How should CMS determine what the data collection should end?

Comments from the ISPOR Health Technology Assessment Special Interest Group

See above: variable - it depends on the biological rationale hypothesized for positive and negative outcomes on the particular study population concerned by the device/drug/service under consideration.

Comments from the ISPOR Health Technology Assessment

Collection periods may be predetermined by study goals (e.g., cross sectional data or longitudinal collection phases). For example, in the area of allergic rhinitis, our data collection periods are typically one year to correspond with seasonal rhinitis. In our recent study, we found that patients who undergo diagnostic testing (either specific ige blood testing or skin testing) experience better quality of life - forthcoming in the annals of allergy asthma & immunology. Thus, appropriate study length may be contingent on disease state, data availability, type of technology.

Our study findings suggest..... From the standpoint of evidence based medicine -- instead of prescribing antihistamines to determine if the patient responds to them -- it may be better to test (diagnostic evaluation) the patient first, then prescribe medications according to test results -- that is -- whether the patient is truly allergic.

Who should have access to the data and in what form?

Comments from the ISPOR Health Technology Assessment Special Interest Group

The data should be made available to the overseeing organization, the concerned federal bodies, any industrial or organizational partner that has an interest in brinign this forward, and subsequently (ideally) should be made available at some time on a website to lay groups.

Comments from the ISPOR Health Technology Assessment SIG's HTA to Support Marketing Initiatives Working Group

Access to data should be provided within established guidelines -- hipaa -- protected health information.

Comments from the ISPOR Patient Registry Special Interest Group

Whoever is funding/sponsoring collection of data, and their agents, should have access to the data. It is also crucial that independent Scientific Advisory Boards have access to data and that any published findings must be reviewed by these bodies.

How will evidence collected through CED be disseminated?

Comments from the ISPOR Health Technology Assessment Special Interest Group

Ideally one would try and create a large infrastructure of primary care based investigators with whom both evaluative reserch could be done as well as assessment of knowledge transfer and diffusion/dissemination-type research. This infrastructure would include an entire it network allowing for real time at the point of care data collection.

Comments from the HTA SIG: HTA in Reimbursement Economics Working Group

While several avenues for dissemination may be used, all evidence collected through CED should be available as technical reports in a central repository that can be accessed from the CMS website. Each time a new report is posted on the website an e-mail can be sent to members subscribing to a list-serve and all relevant stakeholders. Scientists/investigators involved in the study may also be interested in disseminating the results of the study in scientific publications. Given that various stakeholders may be funding the CED data collection, issues related to publication rights will need to be ironed-out upfront. Also all scientific publications should undergo internal review by a committee before submission to journals to ensure a fair presentation of the study results.

Comments from the ISPOR Health Technology Assessment SIG's HTA to Support Marketing Initiatives Working Group

Probably an unlimited number of channels here -- i would suggest disseminating through channels with the greatest impact / perspective.

How should the costs of study design, data collection, analysis and other activities associated with these programs be fairly allocated to various stakeholders?

Comments from the ISPOR Health Technology Assessment Special Interest Group

On a sliding scale based on ability to pay, level of interest and responsibility for generating the information.

Comments from the ISPOR Health Technology Assessment SIG's HTA to Support Marketing Initiatives Working Group

I believe these parameters would be determined largely by the perspective of the study.

Comments from the ISPOR Patient Registry Special Interest Group

CMS should encourage stakeholders — product manufacturers in particular — to design and execute studies that will be acceptable in CED. In this manner, CMS can be assured of an on-going supply of evidence, provided parameters for what constitutes "acceptable" are promulgated. This would tend to avoid the complex issue of fair allocation.

How can CMS best ensure that these studies are implanted in a way that is compatible with current public and private efforts to promote effective and consistent adoption and use of health IT?

Comments from the ISPOR Health Technology Assessment Special Interest Group

See above; ideally one would try and create a large infrastructure of primary care based investigators with whom both evaluative research could be done as well as assessment of knowledge transfer and diffusion/dissemination-type research. This infrastructure would include an entire it network allowing for real time at the point of care data collection.

Comments from the ISPOR Health Technology Assessment SIG's HTA to Support Marketing Initiatives Working Group

Again, dissemination through appropriate channels -- as a suggestion -- a tier or phase approach may be possible -- where certain groups can be targeted for each phase. Strategies may involve reaching early adoptors and/or changing guidelines/protocals in managed care organizations regarding the use of diagnostics and new technolgoies. In addition to the importance of evidence-based medicine and the impact that these studies could have in this area -- various consumer groups might be important as well.

Comments from the Health Technology Assessment Special Interest Group: HTA in Reimbursement Economics Working Group

Miscellaneous comments

CMS should focus its initial efforts on developing and refining CED requirements for items and services where the evidence of an intervention's effectiveness is inconclusive. CMS should not expand CED to circumstances where the technology has already demonstrated improved health outcomes in a broad population until the potential value of CED is clearly established. As CMS suggests in the guidance document they should consider beginning the CED initiative by identifying a small group of high priority pilot efforts on topics for which there is substantial agreement that better evidence would be valuable in expanding access to specific technologies and service that would otherwise remain non-covered. Once the potential value and operational and implementation issues related to CED are identified from these pilot projects CMS may consider extending the CED initiative to other circumstances.

The CED draft guidance provides limited understanding on how information collected under CED will be eventually applied in the evaluation of health technologies.

Organization: Johnson & Johnson

(Comment on next page)

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June 6, 2005

By Hand Delivery

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Department of Health and Human Services
Mailstop: C1-12-28
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Re: Draft Guidance for the Public, Industry, and CMS Staff – Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

On behalf of Johnson & Johnson (J&J), we are providing the following comments and recommendations in response to the draft guidance issued by the Centers for Medicare and Medicaid Services (CMS) regarding implementation of the Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED), issued on April 7, 2005.

J&J is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical and medical devices and diagnostics markets. J&J has more than 200 operating companies in 57 countries around the world employing approximately 109,000 employees and selling products in more than 175 countries. The fundamental objective of Johnson & Johnson is to provide scientifically sound, high quality products and services to help heal, cure disease and improve the quality of life.

Summary of Recommendations

We recognize that CMS seeks to improve the quality of evidence about the use of Medicare-covered therapies, medical technologies, and pharmaceuticals, in order to improve patient care and to contribute to better quality, value, and efficiency of the health care system. The document implies tension between broader access to technologies and treatments versus more appropriate usage, which would limit access. Though the tone of the proposal favors the former, there are several suggestions of the latter (e.g., “risks and

benefits of off-label uses" and "comparative effectiveness of new items"). We are concerned that CED could lead to targeting a narrower and narrower group of patients, rather than making important treatments more widely available. The draft guidance is at a very early stage, lacking answers to basic operational questions of what, when, who and how. CMS has sought input on many questions, and how the agency chooses to answer those questions is critical to building a CED process that stakeholders can support. If the agency proceeds too quickly, without clarity about the selection criteria, the use of data , industry's and physicians' responsibilities in data oversight, coordination with FDA, and other key issues, the CED effort could create access problems for beneficiaries and opposition by stakeholders. In order to achieve CMS's objectives, we recommend:

- **CMS should issue another draft guidance**, which answers many of the questions raised in this guidance and provides more precise information about the specific criteria for and extent to which CMS will apply CED to national coverage decisions.

- **CED should be the "exception" rather than the "rule," in national coverage decisions.** It should be used to expand coverage and should not be applied to on-label use of drugs or PMA-approved medical devices.

- **CMS needs to clarify which circumstances call for which types of evidence-gathering methods, for example registries or practical clinical trials.**

- **CMS should begin using CED in a few pilot cases,** in order to build confidence in the process and selection of coverage decisions that will be affected by CED. Priority should be given to new therapies that would otherwise not be available quickly to Medicare beneficiaries, without the additional evidence requirements.

- **The selection should be made in collaboration with physician groups and industry and should use an inclusive and transparent process for arriving at selection of treatments, study methodology, and objectives.** CMS should consider creating a "study design oversight" group that can provide input on the validity of study designs prior to any analysis of data or results.

- **CMS should identify the process and timetable for implementing a CED and for using data upon completion of a CED** to reassure patients, physicians, and industry that the process does not create an additional barrier to entry or delay access to new treatments.

- **In addition to considering the cost burden of requiring additional evidence development, CMS needs to address whether only innovator companies, first with a new technology, will support CED data collection or whether "fast followers" will have the same requirements.**

- **Before implementing the CED approach nationwide, CMS should seek notice and comment rulemaking** on the methods, use of data, selection criteria, and process for implementing CED.

- **CED should not result in delaying the assignment of a new technology or drug to a reimbursement rate,** particularly since Medicare reimbursement decisions are made on a cycle, with often a narrow window for adding new treatments. This would not preclude CMS from requiring additional evidence development if appropriate.

- **As detailed below, we believe there are several important questions that CMS must address** before implementing CED, including how CED fits into the kinds of coverage decisions the agency makes. For example, will CED primarily apply to new and innovative treatments, can it apply to new uses of existing treatments, and will the study requirements be more or less rigorous than CMS's current standards for National Coverage Decisions? Will CMS and FDA require different post-marketing studies or can the same studies serve both agencies' objectives?

Below is a section-by-section analysis of CMS's approach and Johnson & Johnson's position.

I. Purpose of this Guidance Document

CMS Approach

- The objective is of CED is to improve the health of beneficiaries by enhancing access to medical technologies and services that improve health outcomes.
- CMS will work with all affected stakeholders to meet the objective.
- CMS will use CED in specific cases, where better evidence is needed to determine if Medicare should cover the item or service.

J&J Position

We support CMS proceeding to provide "coverage with evidence development (CED)" but believe it is critical that CMS use the approach in a balanced way in order to meet the following objectives:

- CED should stimulate development of better information for physicians and other healthcare providers, in order to improve treatment of patients.

- One of the principal objectives of CED should be to lead to faster access to new treatments and technologies for patients, reducing the delays that currently result from lack of data.

- CED should result in higher quality and more efficiency in use by beneficiaries of Medicare resources and services.

- CED should not create a hurdle to coverage that will reduce access to important treatments.

- CED should not be so rigidly applied that it creates a barrier to physicians' ability to develop new uses of treatments for individual patients, e.g., off-label uses of approved drugs.

- CMS should assess the impact of using CED on incentives for innovation, since Medicare is the major payer for health care services in the U.S.

- CED should be used selectively, where it can provide the greatest benefit.

- CED should be very cognizant of minimizing the cost of the methods used and reporting burden.

While we recognize CMS's underlying statutory authority to determine which items and services are "reasonable and necessary" for Medicare beneficiaries, it is important to note:

- There are no regulations that define "reasonable and necessary." CMS should recognize that a guidance document does not have the same standing as a regulation promulgated under the Administrative Procedure Act.

- This guidance has the potential to have a significant negative impact on the development, research protocols, and availability to patients of drugs, devices, and other technologies, rather than the hoped-for positive outcome, if it is not judiciously applied. The impact may be most marked on smaller manufacturers if the additional costs of CED have to be borne by the manufacturer.

- Beneficiaries and providers have limited ability to appeal CMS decisions on Medicare coverage because of statutory exemptions.

- In light of the above, CMS's processes and criteria should take into account concerns of stakeholders and clarify that the CED process is not a new "hurdle" designed to contain costs.

- The CED approach should be implemented in a transparent way. CMS should develop notice and comment rulemaking to ensure that criteria and methods reflect public input.

II. Background

A. The National Coverage Determination (NCD) Process

CMS Approach

This section describes the current NCD process and the broad types of coverage decisions that CMS issues. However, in this section, CMS also states:

> There are a number of older national coverage decisions that do not provide any conditions for coverage. CMS does not anticipate issuing additional decisions of this type.

J&J Position

- We oppose CMS eliminating the option of issuing a coverage decision that does not include conditions of coverage. Some treatments may be useful in diagnosing or treating beneficiaries but CMS and physicians may not know of all possible uses at the time of the coverage decision. In effect, this statement could be read as saying that CMS will never cover off-label uses of drugs or technologies that are reviewed for an NCD.

- Since we believe that CMS does not intend to restrict coverage through CED of all off-label uses of drugs and devices, the agency should clarify that fact. CMS should reiterate that Medicare policies have allowed carriers to cover off-label uses approved in compendia. The agency should clarify that it will continue to allow local carriers discretion in the coverage of off-label uses. The CED approach should not erode the policy set out in the Medicare statute that acknowledges the acceptability of off-label uses referenced in the U.S. Pharmacopeia.

B. **Purpose of linking coverage with a requirement for data collection**

CMS Approach

CMS emphasizes its commitment to making advances in medical technology available while ensuring that the care is "reasonable and necessary," that protocol-driven data have potential to increase the likelihood of improved health outcomes, and that rapid adoption of promising new technologies can be promoted by linking technology diffusion to demonstrations of the value of technologies in actual practice. CMS says that the benefits of technologies are often demonstrated in a specific population – additional studies may help target those patients who benefit most or identify additional patients who benefit beyond those originally studied.

CMS also acknowledges the potential costs and burden of collecting additional information, refers to "value of information analysis," and alignment with FDA clinical studies. The agency also refers to other studies that will be considered, in deciding whether to require collection of evidence in an NCD. Lastly, CMS states that the CED approach will not reduce the importance or frequency of local coverage determinations as a way for new technologies to be covered by Medicare. They also do not expect CEDs to represent a net reduction in coverage when issued.

J&J Position

- We applaud CMS's objective of potentially accelerating the availability of new medical technologies, while gathering data on use in actual practice. CMS should clarify in its final guidance that CED should not create the opposite effect – actually slowing the availability of important technological or therapeutic advances because CED becomes an additional hurdle.
- CMS should follow the same discipline in its CED approach as is used in good study designs. That is, the agency should specify entry criteria and exclusions from CED. We recommend that CMS be clear about the kinds of coverage decisions that will be subject to CED and those that will not. The list on pages 9 and 10 is so broad that most coverage decisions would be candidates for CED, for example, the second

generation of covered medical devices, Part D drugs, and on-label uses of approved Part B drugs.

- The section points out that CED might be especially useful for patients with chronic conditions because side-effects or complications can be evaluated over time. Will CED be skewed to chronic conditions?
- We oppose using" value of information analysis" until the methodology has been vetted with stakeholders. We recommend CMS be more specific about the methodology in a second draft guidance, so stakeholders can comment on the use of this approach for setting priorities for use of CED.
- CMS should specify the kind of "information from other studies" it will use. For example, information from AHRQ, NICE, and others may take into account different criteria and thresholds than would be appropriate for Medicare.
- We agree that the CED approach should not reduce the importance of local coverage determinations. The local coverage determination process allows new therapies to be reviewed against local practice norms and covered at early stages of diffusion. If CMS were to drive all new therapies through the CMS national coverage process, the coverage process would take too long and Medicare beneficiaries would not have expedited access to new therapies.
- CMS should clarify that it does accept clinical trials, used as the basis for FDA approval, to establish the safety and effectiveness of drugs and medical devices. In general, Medicare coverage should be at least as broad or narrow as the approved label, unless CMS believes more evidence is needed to gather more information about use in the Medicare population.
- Until the recent decision to cover off-label use of colorectal cancer drugs, CMS's policy on off-label uses was to leave the determination to its local carriers. Rather than providing "faster and broader access," a systematic effort to require studies of off-label uses as a condition of coverage will impede the ability of physicians to develop new uses for existing drugs or devices. CMS states that, in the example of colorectal cancer drugs, contractors continue to have discretion to cover the off-label uses for patients who are not in clinical trials. CMS should maintain that flexibility in cases where it is using the CED approach to cover off-label uses for patients in clinical studies of those uses.
- We are concerned about the additional costs that will be incurred in the CED process and who will bear these costs. If the manufacturer is expected to bear these costs, and the CED process is widely applied, it may pose a substantial additional financial burden on the manufacturer that may stifle innovation, especially by smaller companies.

III. Factors Considered in Applying CED

CMS Approach

CMS states that it will consider requiring CED when additional information is needed to determine if an item or service is "reasonable and necessary." The guidance states that the agency will work "consultatively and iteratively with external experts and stakeholders in developing the criteria and process for determining when to apply CED." It then goes on to list a number of circumstances where CED might be valuable and poses a number of questions for comment.

J&J Position

- CMS does not list high volume or high cost as factors. We recommend that CMS explicitly state that those will not be factors in selecting items or services for CED, to underscore the fact that CED will not be used as a cost containment mechanism.
- One circumstance mentioned is "there may remain questions about the comparative effectiveness of new items and services compared to existing alternatives or to usual care." This circumstance is sweeping, in that many, if not most, new therapies will lack comparative effectiveness studies. If new studies are required as a condition of coverage, the requirement will be a barrier to new therapies and will favor existing treatments. This circumstance doesn't square with CMS's stated objective that CED can enable important new therapies to be available sooner.
- If CMS requires comparative studies, the agency must itself provide the baseline data on the value of the existing treatments or the burden will fall to developers of new treatments to collect data on both new and existing treatments. Again, in addition to the cost, this provides a potential barrier to entry for new treatments. In addition, many times there is not a single comparative treatment that has been established as the standard of care and the standard of care can change before the study has even been completed, making it obsolete.
- CMS should not require CED for all off-label uses of approved drugs or devices. If it plans to require CED, there should be clear and compelling justification for doing so, for example, because it has some evidence that serious safety issues that can be detected only in real world use.
- CMS should clarify how CED will be applied to clinical or diagnostic tests, given the high cost and time required to link them to clinical outcomes.
- As discussed above, "value of information" analysis should not be used until such time as the methods have received more extensive stakeholder input and debate.
- The focus should be on new technologies and CMS-specific populations. CMS should clarify that it does accept clinical trials, used as a basis for FDA approval, to establish the safety and effectiveness of drugs and medical devices. In general, Medicare coverage should be at least as broad or narrow as the approved label, unless CMS believes more evidence is needed to gather more information about use in the Medicare population.
- There should be a process for requesting CED that includes a standardized application with justification and review by an expert panel, if requested. The proposal should be kept confidential until the agency decides it will proceed, for proprietary and competitive reasons. However, once the agency has decided to proceed with CED, the study requirements and coverage conditions should be made public.
- CMS should not define clinical significance, as this is an interpretive issue best left to treating clinicians in meeting individual patient needs.

IV. Process for Deciding When and How to Apply CED

CMS Approach

CMS states it will use CED when it has greatest benefit for Medicare beneficiaries and the Medicare program and lists stakeholders. It asks a number of questions about the process.

J&J Comments

- CMS should establish an open and transparent process for requesting national coverage decisions with evidence development. Requests should be prioritized by giving highest priority to areas of unmet medical need or treatments that may significantly improve treatment but where CMS may hesitate to provide coverage without any additional requirements for post-coverage data.

V. Evidence Development Methods

CMS Approach

CMS describes a number of methods for evidence development.

J&J Comments

- CMS needs to clarify when it will ask for registries, observational studies, or other kinds of clinical studies in relation to a coverage decision. For example, what kind of evidence would CMS request if it were allowing CED for off-label uses of approved drugs? for treatments where long term safety data are not available? We urge CMS to provide concrete examples of when different types of evidence might be requested. CMS should strive to pursue the least intensive and costly methods to obtain the desired level of additional evidence.

- Longitudinal or cohort studies. These should include a retrospective component for comparative analyses.
- Prospective comparative studies: refers to their value in evaluating quality of life, cost effectiveness, and monitoring safety and benefit. These should also include consideration of patient compliance-related outcomes.
- These should include a retrospective component, when appropriate.

VI. Process for Study Design and Implementation

CMS Approach

CMS describes the importance of proper oversight of the data collection and efficient operations systems. The agency raises important questions about patient safety and monitoring, data security, provider training, and patient confidentiality.

J&J Position

- A major question is who will be responsible for overseeing patient safety and monitoring. If CMS is the principal recipient of claims data and registry data that may go along with it, CMS will need to exercise oversight over the data. Physicians will continue to report data to manufacturers and the FDA, but individual physicians will not be able to detect patterns or safety issues that may be evident only when seen over large populations.
- In addition, CMS should work with FDA to determine how Medicare data may be useful to FDA in reviewing requests for modifications of marketing claims or to

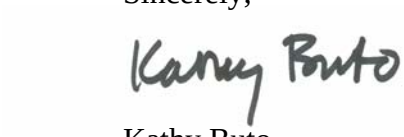
provide additional support for labeling changes. Sponsors of research will have a greater incentive to support CED if the data can support both regulatory (FDA) and reimbursement/coverage (CMS) objectives.

- CMS should develop standards for acceptable study designs and data collection methods to be used to initiate new studies. Without explicit "rules of evidence," interpretation will be subjected to multiple biases and prejudices, which could lead to a "battle of interpretation" among different parties and could waste resources in studies that lack credibility.
- CMS should be consultative and explicit in its anticipated quality weighting of available evidence. One model is the U.S. Preventive Services Task Force that uses a "grading of evidence" approach to developing prevention guidelines.

Conclusion

We appreciate the opportunity to comment on this important guidance and look forward to CMS proceeding in a step-wise manner to implement it, in order to assure that the promise of better patient care and information about new treatments is fulfilled.

Sincerely,



Kathy Buto
Vice President, Health Policy

Organization: Kidney Cancer Association

(Comment on next page)

Kidney Cancer Association

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May 31, 2005

Centers for Medicare & Medicaid Services
7500 Security Boulevard, Baltimore MD 21244-1850

Gentlemen:

The Medicare Modernization Act (MMA) requires the Centers for Medicare and Medicaid Services (CMS) to develop guidance documents on the National Coverage Determination (NCD) process. NCDs outline national coverage policies for procedures, devices, and drugs provided under Medicare Part B. CMS has statutory authority to develop these policies under the "reasonable and necessary" provision, and has gradually used this authority to make these determinations based on applying strict principles of "evidence-based medicine (EBM)."

On April 6, 2005, CMS released a draft guidance document outlining a new policy, "Coverage with Evidence Development (CED)" under which CMS would require the collection of additional data as a condition of coverage. In this guidance, CMS specifically outlines their intention to collect additional information on specific products in cases where they believe that that the existing evidence is not sufficient for coverage, including instances where they determine that data required for Food and Drug Administration (FDA) approval is not adequate. CMS outlines four main reasons for pursuing this policy:

1. It may improve health outcomes of beneficiaries by providing additional information on risks/benefits
2. It may demonstrate the value of treatments in "real-world settings"
3. It may lead to better determinations of maximum value for the lowest cost

It may lead to expansion or revision of policies by identifying certain beneficiaries who may or may not benefit from a certain service

- The Kidney Cancer Association and our members support EBM principles. We are engaged in a variety of evidence development activities that support the production of useful information for physicians and patients.
- Medicare's current policies and the local coverage process maintain both patient access and physician choice of appropriate therapies and should be maintained at all costs.
- CED is not the appropriate venue to define research priorities for the Medicare population.
- CED should only be applied in circumstances of national non-coverage so that coverage can be expanded and beneficiary access improved, particularly in instances where limited treatment options exist for serious conditions.
- Maintaining an open and transparent NCD process is essential to the successful implementation of any CED requirements.

- CMS should evaluate the usefulness of requiring data collection relative to the administrative and financial burdens on stakeholders, inappropriate interference in the physician-patient relationship, and restrictions on beneficiary access to life-saving products.

Detailed Comments by Topic

A. CMS' Process for Obtaining Public Input On CED

Issue: The draft guidance does not specify whether or how CMS will provide opportunities for public input on the purpose of applying CED, the methods chosen, or the implementation of the data collection requirements.

- The draft guidance does not specifically address opportunities for working with practicing physicians, the public, NCD requestors, or those directly affected by the NCD on the goal of conducting CED, chosen methods, and implementation.
- CMS should develop an explicit and accountable process to implement CED requirements that takes into account the significant experience that physicians have in deciding the best course of treatment for each beneficiary, based on existing evidence, clinical experience, and patient preference.
- Each step of the process should have an open comment period. Steps would include:
    - CMS' decision to apply a CED requirement
    - Identification of the CED research questions
    - Selection of a data collection system (or defining the criteria to select an appropriate method to collect evidence)
    - Implementation (stakeholder analysis of the impact, financial responsibility, and data sharing)
    - Use of data collected under CED

B. Circumstances Appropriate for the Application of CED

Issue: The draft guidance offers broad opportunities for the application of CED and no predictability for when this policy may be applied.

- The application of CED should be rare, especially for drugs and biologics, which are already tested for safety and efficacy by the FDA through its rigorous approval process. CMS is not the appropriate agency to consider issues of primary clinical efficacy and safety, nor should it be responsible for post-market evaluations of products.

- The draft guidance suggests CED might be applied in a broad array of circumstances. This is troubling because CED is not the best method to provide evidence that can be used by physicians and beneficiaries to make better decisions about treatments, particularly decisions related to treating cancer.
- Medicare covers uses of drugs and biologics that are within the FDA-labeled indication as well as uses that are recognized within select compendia. Local Medicare Carriers make decisions on coverage outside of these circumstances, often with the advice of local practicing physicians who treat patients on a daily basis. Medicare's existing policies and the local coverage process maintain both patient access and physician choice of appropriate therapies. It is important that this flexibility be maintained.
- Imposing CED requirements to answer CMS' questions on the off-label use of drugs is not appropriate because it would limit physician and patient choice. CMS should expand coverage for uses of FDA-approved products by recognizing and supporting an expanded list of medical Compendia. This may provide a more efficient and flexible way to disseminate information about accepted uses of products to physicians and would retain physician discretion and beneficiary choice in treatment decisions.
- Kidney Cancer Association members are already engaged in a wide range of activities to develop quality evidence, and we urge CMS to work closely with us to better disseminate information about changes in product labeling, recently published peer-reviewed literature, and other information related to the advancement of care in the field.
- Only if a reconsideration of a standing non-coverage decision yields a lack of compelling evidence or if the local coverage process has failed to cover a new technology might CED be an appropriate strategy to expand coverage.

C. Study Designs Appropriate for Developing Evidence Under CED

Issue: The draft guidance defines four evidence development methods that CMS believes may be appropriate under CED:

- Databases or registries
- Longitudinal or cohort studies
- Prospective comparative studies (practical clinical trials)
- Randomized clinical trials

- CMS should consider the potential impact that CED requirements may have on beneficiaries, physicians, other health professionals, and manufacturers.

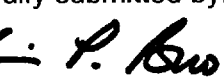
- Mechanisms must be put in place to assure that the data collected will truly lead to expanded coverage. Prior to imposing any CED requirements, CMS should convene an impartial panel of experts in the field to make recommendations to the Agency on what types of studies, endpoints and outcomes are most appropriate to answer their questions. Furthermore, CMS should be specific in outlining the timeframes associated with these data collection efforts.
- CMS must develop a mechanism whereby the information collected is used and disseminated appropriately; following all statutory provisions related to human research endeavors and privacy rights of beneficiaries. The Agency must assure that beneficiaries are never "forced" into participating in trials or receiving therapies that either they or their treating physicians do not think are clinically appropriate.

D. Oversight and Implementation of CED Requirements

Issue: CMS has not provided specific details on the administrative requirements and financial responsibilities associated with CED policy implementation or how the data collected as part of CED will be used by CMS or any other stakeholder.

- CMS should not duplicate efforts that already exist to provide high-quality evidence to physicians and patients.
- CMS should provide further information on the appropriate funding mechanism for CED. CED may add an additional and undue burden on patients and physicians and add to a manufacturer's R&D costs, ultimately increasing the cost of health technologies.
- CMS should establish a mechanism to evaluate the effectiveness of CED in providing additional evidence to bolster physician and patient decision making.
- CMS should consider contracting with an independent entity to review CED policies on an on-going basis. Topics reviewed should include the process for developing CED requirements, their implementation, and their effects on reaching the goal of increasing access to technologies and improving beneficiary and physician healthcare decision making.

Respectfully submitted by:



Chief Executive Officer

Organization: MD Anderson Cancer Center

MD Anderson Cancer Center (MDACC) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS) draft guidance document regarding factors CMS considers in making a determination of Coverage with Evidence Development (CED).

MDACC applauds your leadership for the steps taken to recognize the importance of cutting edge technology across all markets and services, and specifically for those institutions and physicians engaged in the use of anti-cancer treatments. The next decade will witness the proliferation of transformations in oncology treatment and the increased utilization of anti-cancer therapies. The FDA, CMS and other insurers will play a critical role in the evaluation, coverage and reimbursement of these therapies. Our goal at the University of Texas MD Anderson Cancer Center is to reduce death from cancer, improve morbidity, to reduce metastases and to treat and translate effective therapies to appropriate disease sites. Medicare policy for the coverage of off-label anti-cancer indications has generated much interest and concern among payers, oncologists, beneficiaries and patient advocates. MDACC appreciates the opportunity to address the CED draft and would like to offer our expertise regarding: 1) off-label uses of anti-cancer indications and treatment guidelines; 2) considerations for drugs combating rare cancers; and 3) assurance that the informed input from objective and authoritative sources is part of the evaluation and decision-making process utilized by CMS. Whatever that decision-making process is, the collective expertise of an alliance of cancer experts should be utilized in the development of guidance documents for the standard of clinical policy in oncology.

I. Scope and Intent of Coverage with Evidence

MDACC believes that CMS policies can be effective, consistent, sensible and understandable only if there is flexibility, with accountability in both national and regional drug coverage policies. MDACC agrees with CMS that a structured mechanism should be in place that:

- Evaluates and documents drug benefits with accountability, as uses evolve (i.e. indications); and
- Provides efficiency and effectiveness of the health care evaluation process and the tools utilized in its measurement.

MDACC has some concerns regarding the use and intent of the CED and seeks clarification. The objective of the proposed document as stated on page two, is on one hand, “to improve the health of beneficiaries by enhancing access and health outcomes”. The very next sentence indicates that CMS does not “anticipate a substantial number of new coverage decisions that apply the data collection requirements.” CMS must clearly state the reasons for using CEDs. There must be additional input from CMS regarding circumstances where CMS believes there will be ”limited application of CED”. This

statement appears to be in direct conflict to a sentence on Page 7 of the draft guidance document which states, "The general circumstance (of use of the CED) is when a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests that the intervention may provide an important benefit." This statement appears to be in conflict with the statement regarding 'limited application'. MDACC urges CMS to clarify and further define the scope of CEDs, since there appears to be some discrepancies between what was discussed in the May 9, 2005 Open Door Forum and what is stated in the CED draft guidance document.

II. Evidenced- Based Medicine Model: Treatment Options and Outcomes

It is our understanding that by developing the most appropriate data collection techniques based on the "Evidence-Based Medicine" (EBM) model; we will bring treatment options and successful outcomes to the forefront more quickly than the current approval processes. This is particularly important where 'rare cancers' are involved and the treatment thereof. As the largest NCI designated cancer center in the country, MD Anderson conducts research and care every day across a broad spectrum of cancer therapies.

We believe that a request for CED should be used at a **national level to expand coverage** and override local medical decisions where access to the "best treatment" has been denied when there is a hierarchy of evidence-based medicine presented that supports treatment. MD Anderson has had poor experiences with its Fiscal Intermediary in securing the off-label uses of anti-cancer therapies based on supporting evidence other than that contained in the compendia. Furthermore, as CMS is aware, many Medicare beneficiaries are ineligible for clinical trials due to age, comorbidities or complications. It is our understanding that the use of CEDs will be **in addition to** clinical trials. Expanding access by use of CEDs during evaluation, will provide coverage and payment for broader drug indications and allow patients who potentially do not qualify for clinical trials to participate in protocols, registries etc. to receive appropriate therapies.

III. Reasonable and Necessary Guidelines

CMS indicates that the **interpretation of "reasonable and necessary"** will be discussed in the context of coverage determinations in future guidance documents. However, the term "reasonable and necessary" is the core of how treatment is evaluated and utilized by experts in oncology management. Evidenced based medicine includes efficient literature-review and the application of the formal rules of evidence along with the expertise of being able to evaluate, utilize and transfer the treatment of one type of cancer to another. Reasonable and necessary includes not only the review of dozens of journals for appropriate treatment guidelines and input, but also the pragmatic process of utilizing the literature to benefit individual patients while simultaneously expanding clinicians' treatment expertise.

MDACC hopes and believes that utilization of a CED will expand access rather than reduce access to innovative drugs and biologicals, by providing coverage and reimbursement for conditions and diseases where it is either rare and/or is a proliferation or manifestation of a more common cancer.

IV. Expert and Objective Stakeholders

Further, MDACC believes that **expert objective stakeholders** such as The National Comprehensive Cancer Network (NCCN), an alliance of 19 of the world's leading cancer centers, **should participate in the establishment of cancer therapy guidelines.** NCCN should work in concert with other cancer network physicians and cancer centers (i.e. the Alliance of Dedicated Cancer Centers) in defining the questions/hypotheses that will be used for deciding when/if a CED is warranted and how to apply CEDs. NCCN should also be involved in the development, critical appraisal and establishment of treatment guidelines that emphasize the quality, effectiveness and the efficiency of oncology practice to derive the best treatment outcome for Medicare beneficiaries. Other evaluative bodies that should be utilized and included is the National Institute for Health (NIH), Health Office of Medical Applications of Research and the Rare Diseases Clinical Research Network (RDCRN) located in the Extramural Research Program at NIH. RDCRN develops state-of-the-science consensus statements across all types of treatment modalities, particularly those that may be controversial. CMS should look to RDCRN to provide guidelines on when a CED might be initiated. RDCRN can assist and provide uniformity in the decision analysis and implementation of research findings.

V. Data Collection Process, Study Designs and Collection of Information

MDACC believes that one of the most important aspects and concerns has to do with the study designs and the data collection process. There are many study designs and data collection tools currently utilized. These vary within a single hospital and from hospital to hospital. Who defines what is the most appropriate tool and in what circumstances? Clinical pathways vary and must be responsive not only to national evaluations but to those that occur locally. Also if/when a CED project is initiated at the local level and it is determined (at some point) that national input is warranted, how will CMS share the data and what securities will be implemented?

Although the collection of good quality evidence is a must and benchmarking needs to occur, what type evaluation and decision occurs when **a single cancer center** such as MDACC **sees more "rare/orphan" cancers** than any other cancer hospital in the country? One purpose and function of the RDCRN includes clinical data management that incorporates novel approaches and technologies for data management, data mining and data sharing across rare diseases, data types and platforms. CMS should consider using RDCRN to facilitate data methodology strategies, to provide input on how to minimize the data collection burden, and to provide oversight.

Additionally, in order for MDACC to effectively participate and design the most appropriate data bases, collection methods and tools, and process methodologies, CMS should attempt to **clarify the type and amount of evidence** that may be required in order to initiate a CED, and what steps must first be initiated to launch the CED process. How will determination made regarding how long the data collection process should continue to be able to objectively quantify results and render a decision? Since the level of evidence is potentially "less" than in a FDA clinical trial or in peer-reviewed literature, what assessments will determine the 'endpoint', CMS'?

MDACC looks forward to working with CMS to provide further access to Medicare beneficiaries the draft guidance **Coverage with Evidence** document is an important watershed moment. MDACC hopes that our input and that of others will increase CMS' perspective and insight into all the issues we are faced with and the considerations that must be evaluated before implementation occurs. Thank you for your willingness to listen and consider our views.

Organization: Medical Device Manufacturers Association

(Comment on next page)

MDMA

MEDICAL DEVICE MANUFACTURERS ASSOCIATION
Innovation Today For Better Health Care Tomorrow™

June 6, 2005

Dr. Mark McClellan
Administrator
Centers for Medicare & Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

Re: Draft Guidance Documents on Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. McClellan:

On behalf of the Medical Device Manufacturers Association (MDMA), a national trade association representing the innovative sector of the medical device market, I am submitting these comments in response to the draft guidance document on factors CMS considers in making a determination of coverage with evidence development (commonly referred to now as CED).[1] The mission of MDMA is to ensure that patients have access to the latest advancements in medical technology, most of which are developed by small, research-driven medical device companies.

As you know, medical devices are an increasingly important part of the health care system. We appreciate CMS's desire to provide more transparency and predictability in the national coverage process and to set forth the circumstances under which the agency will require the development of further evidence as a condition of granting coverage. We also support CMS's goal of getting physicians the most up-to-date information upon which to base clinical decisions for patients. Nevertheless, MDMA has a number of concerns with the draft guidance, and recommends that CMS:

- Provide more clarity in the guidance about when the agency will apply CED, particularly in light of conflicting public statements about the scope of CED made by CMS officials after the release of the draft statement;

- Refrain from applying CED in cases where a technology has already been demonstrated to improve health outcomes in a broad population of patients;

- Apply CED only in narrow circumstances, where there is clearly insufficient evidence to demonstrate efficacy in the Medicare population but for which the technology's or service's payer mix suggests that Medicare represents equal or greater than the national average Medicare payer mix;

[1] Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development, April 7, 2005 (hereinafter, "Draft Guidance").

- Recognize a stronger role for the local coverage process as tool for gathering further evidence of clinical benefit prior to adoption of the technology on a nationwide basis;

- Work carefully with industry to define the clinical questions that need to be answered and to determine the additional data collection that will be necessary, so efforts are not duplicated and manufacturers have some certainty about the duration and scope of the effort required to secure Medicare coverage (a particular concern for small companies);

- Ensure that decisions about whether or not to apply CED in a particular circumstance are made in an open and transparent way, with opportunity for public comment; and

- Provide further opportunity for public comment before this guidance is finalized.

Thank you for the opportunity to submit these comments. Each of these issues is explained in more detail below.

Recommendation: CMS should provide more clarity about when CMS will apply CED.

At the open door forum hosted by CMS on May 9, 2005, officials from CMS stated clearly that CED would be used very rarely, and only when CMS is engaged in the national coverage determination (NCD) and the coverage determination would otherwise be national noncoverage. These statements are consistent with language in the document in the draft guidance which provides that the agency "[does] not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirement."[2] These statements also are consistent with CMS's parallel efforts to provide more clarity on the circumstances under which the agency will open a national coverage determination. MDMA supports limiting CED to situations where there are legitimate questions about whether a particular technology improves health outcomes in the Medicare population, which the agency would otherwise be prepared to issue a national noncoverage decision absent the opportunity to use coverage as an opportunity to further develop evidence of clinical efficacy.

But these statements conflict with others in the guidance that indicate that at least some officials at CMS are contemplating a more expansive use of CED. For example, CMS states in the guidance that the agency is "aiming to identify a small group of high priority pilot efforts on topics for which there is substantial agreement that better evidence would be valuable in expanding access to specific technologies and services…", and the agency commits to working with a broad range of stakeholders to help identify these priorities.[3] Although MDMA is pleased that CMS has pledged to work with a broad range of stakeholders in identifying these priorities, we nevertheless are deeply concerned by this statement, which suggests that the agency is

[2] Draft Guidance, at pg. 2.
[3] Draft Guidance, at pg. 9.

planning to affirmatively seek out topics or technologies to subject to the CED process. Such a proactive application from CED is quite different from using CED as a mechanism to expand coverage to beneficiaries in specific cases where a particular technology that might be of benefit to patients would otherwise not be deemed covered under Medicare.

CMS also states in the guidance that the agency does not anticipate making any additional national coverage decisions that do not involve some type of conditions.[4] Unless CMS intends to engage the NCD process only when the intervention in question would otherwise not be covered at all or only under specific and limited circumstances, this statement strongly suggests that CMS intends a far broader use of CED, which could limit beneficiary access to potentially beneficial treatments. MDMA urges CMS to endorse the public statements made at the Open Door Forum and include clear provisions in the guidance stating that CED will only be triggered as a possible response to a national coverage determination request, and only in circumstances when the NCD process would otherwise have resulted in a national non-coverage decision.

Recommendation: CMS should refrain from applying CED in cases where a technology has already been demonstrated to improve health outcomes in a broad population of patients.

In subsection C of the guidance, CMS states that its statutory authority for linking coverage decisions to the collection of additional information is derived from Section 1862(a)(1)(A) of the Social Security Act, which provides that Medicare may not pay for items or services provided to beneficiaries unless they are "reasonable and necessary" for the treatment of illness or injury. CMS further defines two general circumstances where clinical care would be considered by the agency to be "reasonable and necessary" only in the context of protocol-driven data collection. Of particular concern to MDMA is the statement that certain medical interventions that have been demonstrated to improve health outcomes in a broad population of patients would nevertheless not be covered unless specific data is collected through CED and reviewed by the provider at the time the service is delivered.[5]

This statement raises more questions than it answers. For example, what criteria will CMS apply to determine when a technology that has been approved by the FDA and has been demonstrated to improve health outcomes will nevertheless need additional data collection in order to be considered to be reasonable and necessary for the patient? If a particular technology is FDA-approved and available to non-Medicare patients, how will CMS justify imposing additional access requirements on Medicare beneficiaries and the physicians who treat them? What does the agency mean by improving outcomes in a "broad" population of patients, and how does the agency intend to distinguish Medicare beneficiaries from this population and thereby justify imposing additional data collection requirements as a condition of coverage? We believe CMS should reconsider applying CED in this circumstance to avoid imposing barriers to care that is available to non-Medicare patients.

[4] Draft Guidance, at pgs. 3-4.
[5] Draft Guidance, at pg. 6.

In subsection C, CMS also identifies a second circumstance where clinical care would only be considered "reasonable and necessary" if the care is provided pursuant to CED, and that is "when a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit."[6] MDMA agrees with CMS that this circumstance may present an appropriate situation for applying CED. But we believe that in most of these cases, local coverage might provide the better option for diffusing the technology more gradually to beneficiaries (and gathering evidence of efficacy during that process). The guidance includes encouraging statements about preserving local coverage[7] -- but aside from these statements, the guidance does not include enough discussion about the role of local coverage in providing a tool for further evidence development and for diffusing innovative technologies more slowly among the beneficiary community. As a result, MDMA is concerned that if CMS sets this second circumstance as a definitive criteria for the application of CED, the availability of local coverage options will diminish or disappear altogether. CMS needs to include more in the guidance about the importance of the role of local coverage and how that role will be preserved and distinguished from national decisions that employ CED. (Further comments on the importance of preserving the local coverage process are set forth below.)

Recommendation: CMS should apply CED only in narrow circumstances, where there is clearly insufficient evidence to demonstrate efficacy in the Medicare population but for which the technology's or service's payer mix suggests that Medicare represents equal or greater than the national average Medicare payer mix.

In section III of the draft guidance, CMS sets forth an initial list of circumstances in which coverage with data collection might be valuable (and this list appears to be in addition to the two circumstances discussed in our comments above and identified in the section of the draft guidance dealing with CMS' legal authority to impose CED). While MDMA believes that some of these circumstances merit the potential application of CED, depending on the particular technology in question, we have concerns with a number of the circumstances presented in this section, as expressed in more detail below.

- CMS Circumstance: The item or service is likely to provide benefit, but there are substantial safety concerns or potential side effects that are inadequately described in the available clinical literature.

  MDMA Comment: MDMA believes concerns about safety are within the jurisdiction of the Food and Drug Administration (FDA), and not CMS. Although we share the agency's concern about ensuring that devices on the market are safe for Medicare beneficiaries, CMS should defer to the FDA's authority and significant clinical expertise on, and staff resources dedicated to, safety issues. No device is eligible for Medicare coverage unless it has been approved by the FDA, or has Category B IDE status. CMS should confine its coverage

[6] Draft Guidance, at pg. 7.
[7] For example, see page 6 ("It is not the intent of this approach to reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program.")

reviews to whether the device is "reasonable and necessary" for the Medicare population – in other words, whether it improves health outcomes for beneficiaries.

- CMS Circumstance: The risks and benefits for off-label uses of an item or service have not been adequately addressed in the available clinical literature.

  MDMA Comment: This provision in the guidance should be clarified so that well-established off-label uses, or off-label uses covered under the Medicare statute, are not inadvertently swept into this category.

- CMS Circumstance: Assessment of important outcomes have not been evaluated in the available clinical studies. These outcomes may include, but are not restricted to, long-term risks and benefits, quality of life, costs, and other real-world outcomes.

  MDMA Comment: We believe it is inappropriate for CMS to apply CED on the basis of cost concerns. Assessment of a technology's economic impact reaches beyond CMS's reasonable and necessary authority, which is designed to consider whether a technology improves health outcomes. The issue of whether CMS should be performing cost/benefit calculations as part of national coverage reviews is not a new one, and further consideration of that issue should be the subject of substantial public debate and not merely as just one component of a related policy question. Collecting data on the other outcomes identified in this example – long-term risks and benefits, quality of life, and "other real world outcomes" – could be very informative, but MDMA believes such data collection should not be a condition of Medicare coverage.

- CMS Circumstance: Risks and benefits of surgical procedures may not be extensively evaluated because limited information about benefits and risks has been developed for many categories of Medicare beneficiaries. (CMS then provides an example of non-invasive FDA-approved devices.)

  MDMA Comment: In the experience of the member companies of MDMA, off-label use of devices in surgical procedures is not uncommon and occurs in the context of surgeons making a clinical judgment about what is best for the patient. If CMS intends to pursue CED on this basis, we recommend the agency consult with the relevant specialty society for additional guidance.

- CMS Circumstance: Comprehensive evidence of effectiveness of treatments for rare diseases is not always available or feasible to development in a pre-market setting. It may be beneficial to evaluate interventions for rare conditions such as use of orphan drugs and humanitarian use devices.

  MDMA Comment: CMS should clarify in the guidance what the agency considers to be a "rare disease." For example, does the agency intend to rely on the definitions associated with orphan drugs and humanitarian use devices? CMS should also take particular care in specifying the scope of data collection for a CED applied in this context. Because

humanitarian use devices are used by a very small number of patients, manufacturers are prohibited from making a profit on them even though they are often essential to preserving and enhancing the health and well-being of the patients for whom they are designed. If CMS imposes extensive and costly data collection requirements through CED, the manufacturer may no longer be able to make the device available to the patients who need them. Because of the small number of beneficiaries impacted, the local coverage process should be sufficient for a majority of humanitarian use devices, although CED may be appropriate in those limited circumstance where a national non-coverage decision is already in effect.

- CMS Circumstance: There may remain questions about the comparative effectiveness of new items and services compared to existing alternatives or to usual care.

  MDMA Comment: We recommend that CMS provide further clarification in the guidance about how the agency plans to evaluate the comparative efficacy of two technologies. On what basis will CMS determine that two different technologies are similar enough to be subjected to a comparative analysis? What methodology will the agency use, and how will comparative efficacy be measured? How does CMS plan to use the results? We recognize that the answers to these questions will vary based on the technology at issue, but we ask CMS to provide some examples in the guidance to provide further clarification to stakeholders on how CED might be applied in this context.

- CMS Circumstance: The evidence to date shows statistically significant benefits but the clinical significance of the outcomes may not be well understood.

  MDMA Comment: There may be instances where CED would be helpful to understanding whether a particular technology provides a clinical benefit to the target patient population. But as with other circumstances where applying CED makes sense in theory, MDMA urges CMS to first consider whether clinical significance would be best established by allowing the technology to disseminate through the local coverage process.

As a final note, Medicare should not be requiring CED in cases where the technology has limited impact on a Medicare patient audience. If a technology is being used in only a minority of Medicare patients, directing resources and further evidence development toward Medicare beneficiaries is not likely to produce information that can be relied upon in making coverage determinations. As a result, the information is not helpful for Medicare and could have a negative impact on non-Medicare patient coverage in the private sector. MDMA recommends that CMS only subject a technology to CED if the Medicare payer mix for the particular technology is equal to or greater than the national average Medicare payer mix.

Recommendation: CMS should recognize a stronger role for the local coverage process as a tool for gathering further evidence of clinical benefit prior to adoption of the technology on a nationwide basis.

As noted above, MDMA agrees that there will be circumstances where CED is an appropriate tool for providing coverage for a particular technology while the agency gathers additional data on whether the device actually improves health outcomes for beneficiaries. In

addition to the example identified above, we agree that in circumstances where the available clinical studies have not adequately described the risks and benefits of a particular technology in specific patient subgroups, or when current evidence is not generalizable to the Medicare population based on available data, it may be appropriate for CMS to apply CED.

But MDMA believes that CMS should first consider whether developing further evidence of clinical benefit might be best accomplished by allowing the technology to disseminate gradually through the local coverage process. We are concerned that the guidance does not go far enough in establishing the local coverage process as the primary mechanism for gathering data about impact of a technology on Medicare beneficiaries. For example, the guidance provides that CED is justified when the agency needs to understand which types of patients benefit from a particular technology, questions that are "best addressed in actual medical practice, where actual conditions of use and patient characteristics may differ significantly from those in a pre-market formal clinical trial."[8] In our judgment, this statement argues strongly for deferring to the local coverage process rather than engaging the technology in national coverage review and applying CED. A statement such as this in the guidance contributes to the perception that CED may become a vehicle that eventually trumps the local coverage process.

CMS could do more in the guidance to establish and ratify the primary role of local coverage in getting innovative technologies to Medicare beneficiaries. As we stated in our May 6, 2005 comments on the factors that CMS considers in opening an NCD, the agency has long acknowledged the importance of the local coverage process and allowing new technologies to disseminate through coverage at the local level before consideration for coverage at the national level. MDMA is pleased to see a few provisions in the guidance indicating that CMS does not intend to diminish the importance of the local coverage process.[9] The focus of this guidance is understandably on applying CED as part of a national coverage process – but merely stating the agency's "intent" to preserve the local coverage process is not enough. Consistent with our previous comments, MDMA believes that the national coverage process – and consequently CED – should be triggered only in rare circumstances. Based on recent public statements from CMS officials, we understand that the agency shares this view. To provide more clarity to stakeholders, the guidance needs to do more to elevate the importance of the local coverage process and more clearly convey the viewpoint about the more limited role of national coverage process (and CED).

Recommendation: CMS should work carefully with industry in determining the additional data collection that will be required.

In circumstances where CED will be applied, CMS should work carefully with industry in determining the additional data that will be required, so efforts are not duplicated and manufacturers have some certainty about the duration and scope of the effort required to secure Medicare coverage. This is a particular concern for small companies, who, after expending significant resources to get a technology through the FDA approval process, typically have little

[8] Draft Guidance, at pg. 4.
[9] Draft Guidance, at pg. 6 ("It is not the intent of this approach to reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program.")

left to spend collecting additional data. To the extent possible, CMS should rely on studies that are already funded and being conducted, such as any post-marketing studies being conducted pursuant to FDA requirements. CMS should encourage local contractors to expediently review and cover Category B and Category A IDE trials according to the appropriate coverage guidelines. The coverage group should also encourage the CMS payment groups to create a vehicle to adequately reimburse these trials to ensure that this important existing vehicle to collect pre-approval data is being accessed to support coverage by Medicare in the post-approval environment and to inform any necessary CED requirements without duplication of data collection that happened in pre-approval trials.

CMS should not impose data collection requirements merely for the sake of having additional information, and we are encouraged by statements in the guidance stating that "data collection should only continue as long as important questions remain and it is determined that the effort and resources required to collect this data are justified by the potential value of the information that will be generated."[10] We recognize that it is not possible to set forth in guidance the specific data collection requirements that will be imposed through CED, as this will vary by technology. But CMS should commit in the guidance that for each CED, the agency will engage industry and other relevant stakeholders in an open and productive dialogue to determine the scope of the additional evidence needed to support Medicare coverage; how best to collect this information; how additional data collection will be funded; when data collection will end; the process CMS will use to analyze the results of data collection; and when stakeholders can expect a final decision on Medicare coverage.

Recommendation: CMS should ensure that decisions about whether or not to apply CED in a particular circumstance are made in an open and transparent way, with opportunity for public comment.

In addition to engaging in an open dialogue with stakeholders to establish data collection requirements within a particular CED, MDMA believes that the decision to even apply CED should be made in an open and transparent way, with opportunity for public comment. As we recommended in our previous comments on the guidance concerning the factors the agency should consider in determining whether or not to engage in national coverage review of a particular technology, CMS should publicize when it is considering engaging in national coverage review and provide for a brief period (30 days) of public comment on whether the agency should move forward. Because CED is engaged as part of the national coverage process, we believe that comment is relevant to this guidance as well. If CMS publishes that it is considering possibly engaging in national coverage review with CED for a particular technology, arguably the agency has not formally launched an NCD, and thus, the timelines associated with completion of the NCD process do not apply. If after this public comment period CMS determines that the NCD process should move forward, the agency can then make a more definitive announcement of national coverage review of a particular technology, and the process will move forward under the statutory timeframes. MDMA recommends that this guidance also include a process for public input into whether or not CMS should engage in CED for a particular technology.

[10] Draft Guidance, at pg. 5.

MDMA

Recommendation: CMS should provide further opportunity for public comment before this guidance is finalized.

We appreciate the hard work that CMS has put into this draft guidance, and in trying to provide more clarity for stakeholders regarding when CED will be applied and the scope of the additional data collection that may be required. But given the importance of this initiative, and the number of important issues that need to be resolved before CED can be implemented, we recommend that CMS provide an opportunity for further public comment on a revised draft before the guidance is issued in final form.

Conclusion

In summary, we recommend that CMS:

- Provide more clarity in the guidance about when the agency will apply CED, particularly in light of conflicting public statements about the scope of CED made by CMS officials after the release of the draft statement;

- Refrain from applying CED in cases where a technology has already been demonstrated to improve health outcomes in a broad population of patients;

- Apply CED only in narrow circumstances, where there is clearly insufficient evidence to demonstrate efficacy in the Medicare population but for which the technology's or service's payer mix suggests that Medicare represents equal or greater than the national average Medicare payer mix;

- Recognize a stronger role for the local coverage process as tool for gathering further evidence of clinical benefit prior to adoption of the technology on a nationwide basis;

- Work carefully with industry in determining the additional data collection that will be required, so efforts are not duplicated and manufacturers have some certainty about the duration and scope of the effort required to secure Medicare coverage (a particular concern for small companies);

- Ensure that decisions about whether or not to apply CED in a particular circumstance are made in an open and transparent way, with opportunity for public comment; and

- Provide further opportunity for public comment before this guidance is finalized.

In conclusion, MDMA believes that it is important that stakeholders and CMS work together in determining the appropriate circumstances for applying CED. Further clarity from the all of the guidance documents will ultimately enhance the coverage decision-making process and benefit all stakeholders, particularly beneficiaries.

MDMA looks forward to working with CMS on the further development of draft guidance documents related to the national coverage determination process. If you have any questions or would like to discuss these recommendations further, please contact me at 202-349-7171 or mleahey@medicaldevices.org.

Sincerely,

Mark Leahey
Executive Director
Medical Device Manufacturers Association

cc: Barry Straube
Steve Phurrough

Organization: MedicAlert Foundation International

(Comment on next page)

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February 13, 2005

Mr. Herb Kuhn, Director
Center for Medicare Management
Chairperson, Council on Technology and Innovation (CTI)
Coverage and Analysis Group
DH&HS Centers for Medicare & Medicaid Services
7500 Security Boulevard MS C1-12-28
Baltimore MD 21244

Dear Mr. Kuhn and Members of the
CMS Council on Technology and Innovation:

MedicAlert Foundation International is pleased to provide comments on the development of the CMS draft "Guidance Document on Medicare Coverage Decisions Associated with Data Collection Requirements" for consideration by the CMS Council on Technology and Innovation.

Executive Summary

The mission of MedicAlert Foundation International is to protect and save lives. Advances in medical and information technologies provide opportunities to improve health status and prevent premature mortality among medically at-risk individuals. There are significant benefits to be gained from processes which expedite clinical trials, regulatory review and coverage determinations that bring life-saving technologies to market sooner. However, patient safety over the short, intermediate, or long-term must not be compromised as a result of these expedited processes.

Life-saving technologies can be both costly and cost-saving, and decisions regarding efficacy of interventions and allocation of scarce resources require data regarding outcome effectiveness. The need for and benefits of obtaining quality data must also be weighed against potential burdens and feasibility of data collection. Potential burdens and conflicts of interest associated with linking coverage decisions to data collection can be mitigated if all stakeholders trust and participate in a structured program in which confidentiality, patient safety, and access to life-saving technologies are guiding principles.

MedicAlert® respectfully suggests that the following elements be considered in drafting the CMS "Guidance Document on Coverage Decisions Associated with Data Collection Requirements."

- Patient-centric orientation
- Overarching goals to ensure patient confidentiality, safety and access to life-saving technologies
- Mechanisms and protocols to ensure patient safety and prevent serious adverse medical events at the point of care, 24 hours per day/365 days per year, regardless of health care setting, provider, or payor source
- Establish independent medical device and implants registry/registries, funded by both public and private resources, to ensure availability and integrity of data for continuous quality improvement and outcomes effectiveness evaluation research
- Consumer and provider incentives to participate in registry and data collection efforts
- Partnerships and system of checks and balances between government, medical device manufacturers, professional medical and hospital associations, researchers and research institutions, non-profit consumer organizations (such as MedicAlert Foundation), and patients/consumers
- Efficient and effective use of resources consistent with respective missions of organizational partners

We believe this to be the least burdensome and most equitable, effective approach to Medicare coverage and data collection considerations.

MedicAlert Background

Established in 1956, MedicAlert Foundation International is a 501(c)(3) nonprofit charitable organization whose mission is to protect and save lives. MedicAlert® has more than 4 million members worldwide. Twenty-six different national/international health organizations have endorsed the services of MedicAlert® Foundation.

MedicAlert Foundation is perhaps best known for our trademarked MedicAlert® emblem, our engraved bracelets and neck pendants and our 24/7 Emergency Response Call Center. MedicAlert® has also expanded into new information and communication technologies to better meet the needs of consumers and professionals. Through MedicAlert's® Personal Electronic Health Records[1] (PEHR), vital patient information is accessible via the Internet, through the MedicAlert® USB Personal Health Record software, or by calling the MedicAlert®

[1] MedicAlert Foundation's Personal Electronic Health Records system is a sophisticated coding and classification system that is compatible with health care industry standards.

Contact Center. Regardless of the particular type of health communication vehicle, MedicAlert® remains the *only* non-profit, consumer-directed comprehensive health database and Emergency Call Center/medical information service of its kind in the world.

MedicAlert® has taken a very public and uncompromising stance on the issue of privacy of personal medical and non-medical information: All our procedures, information systems, and business relationships must honor individuals' right to privacy, confidentiality, and control over their personal information. Our processes and information systems meet HIIPA privacy and confidentiality standards.

MedicAlert provides a wide range of services to ensure patient/member safety, avoid or minimize preventable medical errors and serious adverse events, and improve continuity and coordination of care. Our services include:

24/7 Emergency Call Center and Engraved MedicAlert® Identifier[2] to ensure patients' vital medical information is readily accessible at the point of care, regardless of health care setting, provider, or payor

Family Notification Program to ensure that a member's personal or family contacts are automatically notified during emergencies, and given the name of a contact person and the facility where the member has been transferred

Sponsored Memberships for low-income, medically at-risk children, adults, and seniors

Professional Education Program and Accredited Educational Materials[3] to ensure that emergency responders look for the MedicAlert® emblem, read its engraved list of conditions during patient assessment, and contact the MedicAlert® 24-hour Emergency Response Center for all the member's key medical facts

Personal Electronic Health Records (PEHR) for tracking patients' comprehensive medical information, immediately accessible via the Internet, through the MedicAlert® USB Personal Health Record software, or by calling the MedicAlert® Contact Center

[2] MedicAlert® members receive an annual membership card and an identifier personally engraved with medical information such as known allergies, medications, specific medical conditions, medical devices/implants, advance directive status and other vital medical information.

[3] MedicAlert® Emergency Medical Information Service Training Program is recognized for continuing education credits by the Continuing Education Coordinating Board for Emergency Medical Services.

Medical Documents Repository Services for written advance directives, out-of-hospital Do-Not-Resuscitate orders (DNR)[4], organ/tissue/whole body donation directives, the EMS-C Emergency Information Form and care plans for medically complex special needs children, and other medical documents vital to provision of timely and appropriate care

Clinical Trials Subject Safety Program to ensure trial participants' safety is protected 27/7 and serious adverse events are documented and monitored for intensity, severity, action and resolution, to reduce research risks and ensure regulatory compliance

Federal Drug Administration Approved Medical Device/Implants Registry for patient location, notification, and tracking vital information regarding patients who have received medical devices and implants

Our fourteen-year experience in providing registry services to heart valve recipients may serve as a useful model in the development of the CMS draft "Guidance Document on Medicare Coverage Decisions Associated with Data Collection Requirements."

MedicAlert® Heart Valve Recipient Registry

Approved by the U.S. Federal Drug Administration (FDA) in 1991, MedicAlert® Foundation serves as the U.S. repository for an estimated 35,000 patients who received the *Bjork-Shiley 60˚ and 70˚ Convexo-Concave* heart valves manufactured by the former Shiley Company, which was later purchased by Pfizer, Inc. MedicAlert® also offers Multi-National Registry Services for recipients of this same model Shiley heart valve living in 30 countries.

Approximately 1% of the 86,000 Bjork-Shiley Convexo-Concave (BSCC) heart valves manufactured experience a "strut fracture," of which approximately two-thirds of these failures are fatal to the heart valve recipient. BSCC heart valves that experience strut fracture require rapid surgical replacement of the valve. The BSCC heart valves were voluntarily recalled from the market by the manufacturer in 1986. Thereafter, the manufacturer worked with the FDA and MedicAlert Foundation to develop a patient identification, notification, and registry program. This was the first retrospective identification of medical implant patients ever attempted, yet MedicAlert® located over 90% of the estimated 35,000 patients who received these heart valve implants.

MedicAlert® contacted over 19,000 physicians, cardiologists and cardiac surgeons, 450 hospital CEOs, deployed alerts in medical journals and through medical associations, and publicized and established a separate toll-free telephone number to serve as a central contact and patient referral for individuals

[4] MedicAlert® Foundation is the legislated provider of out-of-hospital DNR emblems and repository services to residents in 10 states.

concerned about these defective implants. Health care associations cooperating with the search for at-risk BJCC heart valve recipients included the American Medical Association, the American Hospital Association, the American College of Cardiology, the Society of Thoracic Surgeons, the American College of Healthcare Executives, and the American Medical Records Association. Once located, MedicAlert provided valve recipients with information about the recall, the risk and symptoms of strut failure, and referral sources for follow-up information and care. Most (but not all) of the heart valve recipients opted for a free lifetime MedicAlert® membership incentive for the added protection it provides during medical emergencies.

MedicAlert® maintains a separate database and designated staff, telephone number and other resources for the Heart Valve Registry. Patient information is "cleaned" of personal identifiers, aggregated and reported monthly and quarterly to the FDA and Pfizer. In conjunction with the FDA and researchers at Stanford and Beaumont Universities, MedicAlert® has also provided data for evaluation and mortality follow-up studies. The Registry was initially funded in part by the FDA, Pfizer, and the Kellogg Foundation.[5] Today, financial support is provided primarily by Pfizer, with continued oversight provided by the FDA.

The MedicAlert Foundation Heart Valve Registry has a number of unique elements that have contributed to its unprecedented success:

- Patient-centric orientation
- Overarching goals to ensure patient confidentiality, safety and access to life-saving technologies
- Mechanism and protocols to ensure patient safety and prevent serious adverse medical events at the point of care, 24 hours per day/365 days per year, regardless of health care setting, provider, or payor source
- Independent medical device and implant registry, funded by both public and private resources, to ensure availability and integrity of data for continuous quality improvement and outcomes effectiveness evaluation research
- Consumer and provider incentives to participate in registry and data collection efforts
- Partnerships and system of checks and balances between government (FDA), medical device manufacturer, professional medical and hospital associations, researchers and research institutions, non-profit consumer organization (MedicAlert Foundation), and patients/consumers
- Efficient and effective use of resources consistent with respective missions of organizational partners

[5] MedicAlert Foundation International is a non-profit organization funded primarily through membership fees, grants and charitable contributions.

MedicAlert Foundation's pivotal role as an internationally recognized independent, consumer-directed organization with 48-year history of working in partnership with health/medical professionals on behalf of medically at-risk patients has contributed to the success of the heart valve registry.

Summary

The mission of MedicAlert Foundation International is to protect and save lives. Advances in medical and information technologies provide opportunities to improve health status and prevent premature mortality among medically at-risk individuals. There are significant benefits to be gained from processes which expedite clinical trials, regulatory review and coverage determinations that bring life-saving technologies to market sooner. However, patient safety over the short, intermediate, or long-term must not be compromised as a result of these expedited processes.

Life-saving technologies can be both costly and cost-saving, and decisions regarding efficacy of interventions and allocation of scarce resources require data regarding outcome effectiveness. The need for and benefits of obtaining quality data must also be weighed against the potential burden and feasibility of data collection. Potential burdens and conflicts of interest associated with linking coverage decisions to data collection can be mitigated if all stakeholders (e.g., patients, manufacturers, providers, funders, and regulatory organizations) trust and participant in a structured program in which patient safety, confidentiality, and access to life-saving technologies are guiding principles.

Thank you for this opportunity to comment on the development of the "Guidance Document on Medicare Coverage Decisions Associated with Data Collection Requirements". Please consider MedicAlert Foundation International an active partner and resource throughout this process. We look forward to continued dialogue with the CMS, the CMS Council on Technology and Innovation, and other stakeholders regarding this very important issue.

Sincerely,

Paul L. Kortschak
President and Chief Executive Officer

For further information please contact: Cherie M. Davis at (209) 669-2461 or cdavis@medicalert.org

Organization: Medtronic, Inc.

(Comment on next page)

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June 6, 2005

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Re: Request for Comments to Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Straube:

Medtronic, Inc. welcomes the opportunity to respond to the Centers for Medicare & Medicaid Services' (CMS') request for public comment on the *Factors CMS Considers in Making a Determination of Coverage with Evidence Development* (CED) draft guidance.[1]

Medtronic is the world's leading medical technology company, providing lifelong solutions for individuals with chronic diseases and enhancing the lives of Medicare beneficiaries. Our comments below reflect our long history in working directly with CMS on numerous national coverage determinations (NCDs) involving many of our products. Medtronic has worked collaboratively with the Agency most recently on the NCD for implantable cardioverter defibrillators (ICDs), which CMS has used to illustrate existing examples of their CED initiative.

While Medtronic has been supportive of the final NCD on ICDs as it reflected an appropriate and significant expansion in the clinical indications covered by Medicare, we have concerns about the implementation of the registry requirement, the accuracy and value of the data being collected, and CMS' attempt to create a policy framework using the unique example of the ICD decision. We described many of the unique factors around the ICD decision in our previous comments at an Open Door Forum in February, 2005 (attached). Many of these factors are not broadly applicable and cannot be replicated as a matter of policy at this time (for example, use of QNET as a data collection tool). We explain our specific concerns with the implementation of the CED requirement on ICDs in detail throughout the letter. We hope that our suggestions will aid CMS in developing a practical and valuable CED component to the Medicare NCD process.

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[1] Centers for Medicare & Medicaid Services. Draft Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development. Issued April 7, 2005.

Medtronic supports CMS' overarching goal to ensure that Medicare beneficiaries receive appropriate, high-quality health care, including access to life-saving and life-enhancing medical advancements. Medtronic also supports CMS' goal to improve physician and patient decision-making. In that regard, it is up to all of us as the stewards of limited clinical research dollars to ensure that the data generated through the CED approach would create meaningful, actionable clinical evidence and would not duplicate existing efforts outside the agency. It is also important that CED be conducted in a manner that is cost-effective and considers the financial and administrative burdens placed on all parties impacted.

Manufacturers engage in a wide range of activities to refine the use of their products, better define appropriate indications, and enhance the understanding of their value. We urge CMS to acknowledge this longstanding expertise and take into account initiatives such as ongoing private sector and Food and Drug Administration (FDA)-mandated post-market studies when considering the need for an additional government-mandated data collection as a condition for Medicare coverage. As Medtronic has suggested in earlier comments on the NCD process, the CMS pathway (the criteria for NCDs) and requirements should be predictable in order to allow requesters to develop studies that meet the needs of all stakeholders without the burden of multiple studies.

Manufacturers such as Medtronic increasingly appreciate the value of evidence-based approaches – including registries and the development of real world data -- and the need to invest in robust clinical and economic evidence to drive appropriate adoption of their therapies by patients, providers and payers. We hope that CMS will implement CED in a manner that encourages the move toward evidence-based medicine. Government incentives to encourage the private sector to design and fund rigorous clinical studies to support new therapies will work to speed a movement that is already taking hold. In general, well-designed studies that demonstrate improvements in health outcomes should be rewarded with timely Medicare coverage decisions that include the populations studied but leave decision-making to physicians and patients.

In reviewing the draft guidance, Medtronic was pleased to see adherence to many of the underlying principles of evidence-based medicine that integrate the clinical considerations of individual patients with the highest-quality research evidence. We also support CMS' acknowledgement of the importance of the local coverage determination (LCD) process, as it affirms individualized clinical decision-making in the context of the physician-patient relationship. The local coverage process allows for flexible evidence-based decision-making and enables contractors to use mechanisms that many private payers use to allow appropriate access to new technologies without granting unrestricted coverage. The LCD process has also consistently allowed for the appropriate diffusion of new technologies to Medicare beneficiaries. As CMS has acknowledged, CED should be used to increase beneficiary access to new technologies and support physician choice of appropriate therapies. CMS' application of CED should not be implemented in a way that reduces coverage available under the existing local process or restricts or impedes physician/patient decision-making.

Prior to our discussion of specific recommendations for this guidance, Medtronic encourages CMS to continue to work with stakeholders to define and develop CMS' interest in requiring data in exchange for Medicare coverage. CMS includes many opportunities for public comment on specific methodological points in the proposed CED draft guidance. However, we believe that there continues to be a considerable need for further dialogue between CMS and critical

stakeholders on the overall policy framework and specific goals for the CED initiative. For example, since the release of the draft guidance, CMS has publicly presented interpretations of the CED initiative that are narrower in scope than CMS' intentions as they are presented in the draft guidance. We appreciate these opportunities for exchange and believe that continued discussions of the value of the CED initiative are essential to ensuring the provision of useful information to beneficiaries and providers.

The next iteration of the draft guidance should more closely reflect CMS' recent public statements that CED will be used only in a limited way and only in circumstances where the alternative would have been national non-coverage. The written draft guidance is vague and wide-ranging in scope. It should be revised and clarified to reflect CMS' most recent comments. Medtronic looks forward to additional opportunities to review and comment on subsequent versions of the CED draft guidance document.

Recommendations for Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Medtronic is pleased to provide CMS the following suggestions on the ways in which the CED initiative can be implemented in the least burdensome manner for providers and beneficiaries while minimizing the financial and administrative costs associated with any potential additional data requirements.

Need for an Evaluation of Existing CED Requirements and Consideration of Alternatives to CED

Because CED represents a significant departure from previous NCD policies, we urge CMS to treat NCDs which incorporate CED requirements as ongoing pilots. If CMS decides to include CED as a requirement in an NCD, CMS should show leadership throughout the CED process – including spearheading its successful implementation (i.e. education of providers, specific plans for data analysis and timeframes for data collection). Medtronic recommends that CMS formally evaluate the lessons learned from recent applications of CED and use them to refine the overall effort and prove the value of collecting additional information. The additional data collection requirements imposed by CMS are not without cost and we elaborate further in this letter. The Agency should monitor and evaluate beneficiary access to care after the implementation of the NCDs for anticancer chemotherapy for colorectal cancer, ICDs, carotid stents, LVADs, and PET scans to verify that these decisions have expanded access to these therapies and that the data collection efforts have minimized the burden and have resulted in useful and actionable data. Lessons learned should be reported to all stakeholders and the overall policy framework for CED should be revised to incorporate these lessons.

Because of the legal issues, patient access concerns, and costs of tying evidence collection to coverage for Medicare beneficiaries, we urge CMS to consider other broad alternatives for improving the evidence available for physician/patient decision-making. Many stakeholders support CMS' goal but the means to achieve this goal has created concern. We are aware of many circumstances in which the highest quality evidence exists but physician patient decision-making is still less than optimal.[2] CMS should consider whether new information needs to be

[2] McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, Kerr EA. The Quality of Health Care Delivered to Adults in the United States. *New England Journal of Medicine* 348(26):2635-45. June 26, 2003.

generated to improve decision-making (and, if so, is the coverage process the most efficient way to generate that data) or whether information exists – or current studies are underway -- but may need to be expanded or disseminated more effectively.

As an alternative to requiring additional data through the coverage process, Medtronic would be willing to work with CMS to develop approaches that might encourage private sector investment and better leverage private sector initiatives. One example might be a new voluntary program to encourage the conduct and funding of real world clinical trials on Medicare beneficiaries in priority disease categories where limited evidence is available. By separating the program from coverage, it could focus more specifically on the scientific questions to be addressed and establish appropriate study methodologies for appropriate questions – without any of the constraints that data collection as a requirement for Medicare coverage causes.

General Circumstances for Coverage with Evidence Development

In the draft guidance, CMS broadly defines two types of general circumstances under which the CED initiative may be applied. For the purpose of this document, we refer to them as Type I and Type II CED.

Type I. "(A) particular medical intervention that may have been demonstrated to improve health outcomes in a broad population of patients, but the evidence would only be adequate, and the service therefore reasonable and necessary for the individual patient, when specific data is collected and reviewed at the time that the service is delivered."[3]

Type II. "(A) particular intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit. In this case, CMS may determine that the adequacy of the evidence demonstrating improved health outcomes can only be assured if additional data is collected, reviewed, and submitted at the time of service."[4]

As stated above, Medtronic believes that CMS should focus its initial efforts on implementing the NCDs that already incorporate CED requirements, using these as pilot cases to refine the approach. To the extent that new NCDs with CED requirements need to be developed, we believe that they should be limited to the Type II category above where the evidence of an intervention's effectiveness is inconclusive. Doing so allows the value of the CED initiative to be clearly established where the link between coverage and data collection can be most clearly supported. CMS should specifically identify the data lacking in the existing body of evidence and how CED will remedy the gap in evidence needed for positive coverage. CMS and other stakeholders should evaluate the true benefit of requiring additional evidence relative to the costs of collecting and analyzing the data in this framework.

[3] Centers for Medicare & Medicaid Services. Draft Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development. Issued April 7, 2005. Page 6.

[4] Centers for Medicare & Medicaid Services. Draft Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development. Issued April 7, 2005. Page 7.

The ICD decision illustrates the tenuous link created by making data collection a requirement for coverage for Type I therapies which have been demonstrated to improve net health outcomes in a broad population of patients. Although CMS positions the ICD CED requirement as only applying to the "expanded" populations that might have otherwise received a non-coverage decision (patients with LVEF between 31 and 35 percent and with Class IV heart failure), that is not, in fact, what happened in reality.

As part of the ICD NCD, CMS reviewed evidence from two major high quality randomized trials as well as a rigorous cost-effectiveness analysis for the entire population studied. After the draft NCD, which included a CED requirement, was issued, manufacturers attempted to work with CMS to try to limit any additional data collection efforts to these "expanded" populations defined above (for which the benefit as CMS states was "less conclusively demonstrated"). CMS rejected this approach and instead chose to apply the data collection requirement to the entire population that had been rigorously studied (in addition to some patients that had been previously covered with no additional data collection requirement). Throughout the process, it has been difficult to understand why the additional collection of data through a registry would result in either circumstances or evidence that CMS would recognize as reasonable and necessary when the statistically significant mortality benefit and cost-effectiveness of ICDs has been demonstrated in two high quality randomized outcome trials.

Factors Considered in Applying CED

Medtronic believes that the CED draft guidance is too broad and provides little predictability in understanding how CED would be applied in the evaluation of valuable health technologies. CMS has publicly stated that CED will be applied rarely, but in the draft guidance document provides a broad list of circumstances in which they believe CED to be appropriate, including when CMS has questions regarding the safety and efficacy of a particular technology - the current mission of the FDA.

CMS should clarify its role relative to the FDA and Agency for Healthcare Research and Quality (AHRQ). The FDA promotes and protects the health of the public by ensuring the safety and effectiveness of medical devices. The FDA is authorized to require post-marketing studies. Often, with the input of expert advisory panels, FDA will require post market studies as a condition of a Pre-Market Approval (PMA), or, less frequently, for a device cleared through the Pre-Market Notification, 510(k), process. The FDA is currently giving a great deal of attention to post-approval studies, and has shifted primary responsibility for study planning from the Office of Device Evaluation to the Office of Surveillance and Biometrics. The FDA is also in communication with industry groups in efforts to focus and improve the post-approval study process. The FDA and industry have both stated that post-approval studies should be required when there is a specific question that was not answered in any studies conducted in the pre-approval period. Medtronic believes that, given these FDA requirements for post-marketing studies, CMS should articulate specifically why the FDA studies or other existing data collection means are insufficient for capturing such safety data before requiring CED for such data. Similarly, AHRQ with its mission to "improve the quality, safety, efficiency, and effectiveness of health care for all Americans", sponsors and conducts research to develop evidence-based data on healthcare services. CMS should clarify how its role in CED will complement AHRQ activities without duplicating functions.

Medtronic requests that CMS develop and communicate a framework for the application of CED. This framework should clearly articulate specific factors that will trigger CMS' decision to apply CED (as opposed to a national non-coverage decision) based on the specific types of questions that remain after CMS has reviewed a body of evidence as part of the NCD process. We also encourage CMS to clearly link the type of study design options that are most relevant for answering the type of outstanding clinical question.

For example, CMS initially stated that the ICD registry would be established in order to better understand which patients benefit from ICD therapy. In this specific case, a baseline registry without controls will not adequately establish comparative effectiveness among patients receiving ICD therapy. As CMS is aware, Medtronic and other companies continue to invest in multiple randomized controlled clinical trials to better understand which patients benefit from ICD therapy. As recently as the Heart Rhythm Society (HRS) meeting in May, CMS revised the purpose of the ICD registry to state that it will be used to generate hypotheses about which patients benefit – hypotheses which would then need to be tested in future studies. We agree that registries can be useful for hypothesis generation, but CMS should further explain in what circumstances data collected to generate hypotheses for future studies would be considered a requirement for the reasonable and necessary test for a particular patient.

Evidence Development Methods

CMS states that an optimal CED initiative is based on data collection requirements that are not burdensome to beneficiaries, providers and other stakeholders. Medtronic supports this position and believes that agreement is needed between all stakeholders prior to the implementation of any CED requirement. CMS should conduct formal analyses to analyze the costs and trade-offs of requiring additional evidence and its burden to stakeholders.

Further, Medtronic believes that, in general, data collection requirements should not be established by CMS for a particular therapy without:

1. Agreeing upon a protocol with well-defined research questions, timeframes for the duration of data collection, and periodic monitoring to ensure quality and responsiveness to research questions;

2. Limiting the sample size to the minimum necessary as defined by the agreed upon protocol. In other words, CMS should, prior to the implementation of a CED requirement, define the needed number of study participants necessary to answer its research question. When the targeted number of patients have been enrolled, CMS should evaluate the data and based on the findings, revise the NCD to eliminate the data collection requirement as appropriate; and

3. Reviewing all existing and planned private and public research efforts in a consistent and comprehensive manner to ensure that these mechanisms are leveraged in an efficient manner and that CMS data collection efforts are complimentary to existing research.

It is worth noting that in the case of ICDs, none of the above elements were in place when the NCD was implemented with a CED requirement. Many of these elements are still not in place almost six months later. For example, there is still no specific timeframe for duration of the data collection.

Process for Study Design and Implementation

Medtronic realizes that undertaking any new initiative presents numerous administrative and implementation barriers, but CMS does not provide clarity on how the information collected under CED will be used by CMS, who will pay for CED initiatives, or who should have access to the data and in what form. CMS should not move forward without further clarification of these points in the next revision of the CED guidance. Failure to articulate these issues in any NCD with a CED requirement will put an undue burden on beneficiaries, providers, and other stakeholders and, ultimately, decrease the potential for any meaningful data collection to lead to improved decision-making.

In the case of ICDs, many stakeholders have devoted significant resources and countless hours correcting coding and definitional errors in the CMS-designed registry, including sorting out confusion about which diagnosis codes need to be included in the registry and which do not. Medtronic has personally assisted CMS to facilitate use of the CMS registry – including the development of materials and extensive education of providers. Even so, according to an April teleconference conducted by the Heart Rhythm Society (HRS), 33% of providers were still not aware of the registry requirement. There was also significant confusion about the definitions used in the CMS-required data form. Without a clear understanding of the definitions, data quality will be questionable. Medtronic has also participated in designing draft protocols for the industry-sponsored registry; determining the feasibility of requiring participation in a private registry as a condition for coverage; and reviewing legal issues related to the required registry.

At this time, close to six months have passed from the implementation date of the NCD on ICD; yet, significant issues remain, such as clarification of definitions and coding terms, determining specific funding arrangements, and planning for the analysis and dissemination of the data. The stakeholders involved in the ICD decision include large manufacturers, well-established specialty societies, and hospital associations. This scenario is the exception not the rule for medical device technologies, which are frequently developed by small companies and for small markets. CMS should not underestimate the extent of these tasks or the costs imposed on manufacturers and the physicians and hospitals, required to submit data to the registry as a condition of Medicare coverage. It is also important for CMS to recognize that the establishment of a CMS-mandated registry could undermine ICD registries the private sector already has planned for all patients – not just Medicare beneficiaries – due to the resistance of providers to enroll patients in multiple registries. For example, if the CMS registry is less robust but participation is mandated to obtain reimbursement, it could eclipse other broad, sample-based registries likely to be deeper and deliver more useful data. A census-based approach, which is required by making participation a requirement for broad coverage, could trade-off important quality and depth of data collection considerations. To the extent possible, CMS should be willing to integrate any additional data requirements into ongoing private sector activities in order to avoid the burden of multiple studies.

Medtronic believes the promise of health information technology (HIT) will significantly enhance the ability to collect patient information at the point of service. Any CED initiative should support and provide incentives for the adoption of HIT, as it is the least burdensome mechanism possible for data collection and is consistent with national goals supporting the adoption of HIT. CMS already supports similar efforts. For example, the Medicare Doctors' Office Quality Information Technology (DOQ IT) demonstration project aims to evaluate the quality of physician care by collecting additional information and providing incentives for physicians to adopt HIT and improve the quality of care for beneficiaries.

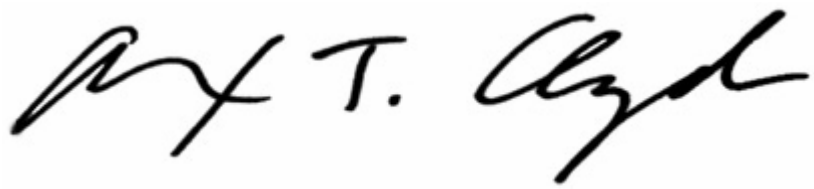
Medtronic suggests that CMS should explicitly develop, working with all stakeholders, the funding arrangements for the data collection and analysis effort required under any NCD with CED requirements. In each potential NCD with CED requirements, CMS should provide reimbursement mechanisms for physicians and other health care professionals participating in CED data collection, including implementing special coding for reimbursement directly to providers for the additional efforts required to collect meaningful and relevant data.

Finally, Medtronic believes that CMS should explain how it will determine when enough evidence has been collected through CED and how that evidence will be disseminated to the public. Ensuring that evidence generated by the CED initiative is being interpreted responsibly and acted upon appropriately must be the foremost goal of CMS moving forward.

Conclusion

Medtronic commends CMS in its effort to foster a more transparent and predictable national coverage process, including the development of any CED efforts. We appreciate the opportunity to provide specific recommendations to CMS on the *Factors CMS Considers in Making a Determination of Coverage with Evidence Development* draft guidance document and we look forward to continuing to work with CMS on this important initiative. Please feel free to contact me directly at (763) 505-2660 with any questions, or if you need additional information on our above comments.

Sincerely,



Alexandra T. Clyde
Vice President, Health Policy and Payment
Medtronic, Inc.

cc: Herb Kuhn, Director, Center for Medicare Management
Steve Phurrough, MD, MPA, Director, Coverage and Analysis Group

Organization: Memorial Sloan-Kettering Cancer Center

I read with interest and concern CMS's proposal to provide coverage for certain services linked to evidence development. Many new and emerging drugs and technologies in oncology show great promise; many of these innovations are also very expensive. All organizations and individuals providing cancer care face difficult decisions every day about whether there is sufficient data to offer these services to desperately ill patients. Accordingly, I appreciate the difficult decisions CMS faces in making coverage decisions for these services. In view of the increasing rapidity with which new drugs, devices, and imaging modalities will reach the market in the coming months and years, there is every reason to anticipate that the demand for off-label application of new products will become much more complex and insistent.

My comments below refer only to the application of this proposal to clinical oncology. I recognize that applying the process to the full spectrum of medicine multiplies the complexities many-fold.

The thrust of the comments below focus on a two essential points. How will the process actually operate to provide useful information in making evidence-based decisions about reimbursement? And will it operate in rapidly enough in real time to be useful to physicians who must help patients make treatment decisions under conditions of some uncertainty every day?

I agree with CMS that the decision to reimburse uses of medical products – particularly expensive ones – should be based on evidence. However, I am very concerned that CMS does not fully appreciate the effort and resources it will require to make CED operationally successful. The draft guidance provided very little information on CMS's thinking about how this proposal will be operationalized. It is not at all clear how any prior CMS evaluative process could be regarded as a reasonable precedent for what will be required here. In principle it is possible to imagine a group of consultants from outside CMS that would advise the agency on reimbursement decisions for particular drug/disease combinations – much the way FDA's advisory committees work for drug approvals. Because of the rapid rate at which new clinical evidence emerges on drug efficacy outside the approved labeling indications, however, it is very difficult to see how such an advisory group (or groups) would work in practice. Perhaps a willingness to meet three to four times a year, assisted by videoconferencing or other telecommunications technologies, would make this possible, but the people selected for this role would have to be very committed to its success and willing to work hard.

In the absence of clear and timely decision-making by Medicare, institutions and their physicians have to choose daily between two bad options: (1) administering very expensive medications and getting stuck with a very big deficit later as a result of a negative CMS decision; or (2) withholding a medication that the physician considers medically justified (and that the patient badly wants) and thereby not giving a patient state of the art care. The point here is simply that a decision-making process by CMS that

is both evidence-based and timely is badly needed and needed now, whether or not Medicare goes on to implement the proposed CED program.

The CED draft proposal itself is silent on the crucial question of who would decide which trials and registries that could lead to more information would be set up. Who would decide what areas to focus on for more information gathering? How can the process operate quickly enough to set up whatever is deemed to be needed, so that the information gathered would actually aid in coverage decisions, once the information was procured? I surmise that this process would have to be coordinated centrally, presumably by CMS. As CMS has never done anything like this before, and as the federal agencies which coordinate and support studies (notably the NIH) have a very substantial infrastructure devoted to this activity, I don't see how it would work without a very significant commitment of resources to CMS. Note also that, despite its substantial infrastructure, the NIH moves quite slowly when it coordinates clinical studies extramurally. That may be acceptable (if suboptimal) for the NIH's various clinical trials programs, but when coverage of sick patients who have limited time remains in the balance, slowness is categorically unacceptable.

Our physicians do a very good job with the daunting task of keeping up-to-date on the latest information about drug-disease combinations. Collecting data to measure outcomes, toxicities and efficacy – whether the studies are prospective clinical trials or observational registries - is costly and requires carefully trained staff. The CMS proposal does not comment on where the resources to enable participation in a CED process would come from. Since I doubt that CMS is contemplating funding multiple sites around the country to do this, I can only assume that institutions themselves would have to support the costs. This is probably unfeasible for most institutions, and increasingly unfeasible as the data-gathering burden becomes heavier. While I appreciate that CMS is proposing to pay for services that would otherwise not be covered, the cost of CED, especially at institutions like ours that are likely to provide more services affected by it, will be very substantial indeed.

Clinical trials are carefully designed to answer specific questions and measure well-defined endpoints; quality control and validation of data is a standard practice in trials. Data collected through observational registries will be of more limited use, but I agree that for certain purposes, such as getting a better fix on toxicity frequencies, registries can be useful. Please note, however, that what is of greatest importance in medicine is a balanced evaluation of both therapeutic benefit and the toxic cost associated with this benefit. It is not obvious how such information will emerge from the usual kind of registry. I very much doubt that simple information on toxicity frequencies will help CMS much with coverage and reimbursement decisions for most applications in oncology. I do appreciate that very detailed and comprehensive registries (such as the Duke Cardiovascular Database) can sometimes produce useful information on efficacy, but these databases are very expensive to set up and curate and require care and feeding over substantial periods of time. There is no indication that the CMS proposal involves anything of this sort. All of which leads to the question: by what process will the proposed registries be designed? How does CMS propose to analyze the data and

determine when data collection relating to any particular drug should cease? I am not aware that CMS currently has this kind of expertise in-house; the proposal does not outline how CMS proposes to secure it.

In summary, I believe that the proposal, as written, will not achieve the laudable goals that CMS wishes to be part of its health-care reimbursement program. I believe that CMS currently lacks the staff and the internal expertise to implement the CED proposal, at least for oncology services, and run it in the timely, efficient manner that would be required to ask and answer the pertinent questions in therapy that would assist coverage decisions. One possibility would be for the agency to contract out this function to an outside group that is both expert and unconflicted, but CMS should recognize that this process would likely be very expensive and challenging in substance.

The idea of focusing post-marketing studies on questions that are unresolved at the time of marketing and that will help in reimbursement decisions does have merit, however. CMS should talk to staff at the NCI's Cancer Therapy Evaluation Program and discuss with them whether the NCI's Clinical Trials Support Unit (intended to be an interface for clinical trials participation with physicians and groups not affiliated with the NCI cooperative group program) might serve a useful role in operationalizing aspects of what CMS has in mind. These discussions could also lead to others about a potential role for CTEP staff in assisting CMS with other features of the CED.

In addition, CMS should seek to better use the formalized, and often high quality, data that already exists by improving its review and comment processes to expedite the promulgation of coverage decisions. Specifically, I recommend the following:

1. The requirement that trial results be published in two papers is no longer practical. Modern information communication techniques, including SEC requirements for immediate reporting of clinically relevant trial results, make the results of clinical trials widely available in the public domain as much as a year before a manuscript can realistically be published. When coupled with the review process, 18 to 24 months can pass between the time when doctors, patients, and investors learn about a study's results and the time when CMS and other third party payors provide coverage for them. This differential is the cause of much of the angst and confusion that physicians and patients are now experiencing.

2. For this reason, CMS should modernize its standards in terms of which data it would consider appropriate. Once a major study showing either a survival benefit in a randomized trial or major antitumor activity in a refractory setting is presented at a major meeting (to be defined), CMS should provide public comment on whether the results of the trial meet the standards of "medical necessity" and "inherent reasonableness" needed for Medicare coverage. This would assume that the data are correct. Obviously, if the initial data turn out to be inaccurate when the final manuscript comes out (a very rare situation indeed), CMS would reserve the right to withdraw coverage for the indication.

3. CMS should define the standards which would be necessary for change in care. These would not necessarily be the minimum required, but would be the standards by which everyone could assume that, if reached, coverage would be warranted. For example, adequately powered, randomized clinical studies showing statistically significant survival advantage, perhaps with a minimum difference (e.g., six weeks survival advantage but subject to discussion) could be the criteria under which CMS would cover the drug.

4. Finally, I would point to the fact that bevacizumab and cetuximab (Erbitux) have been on the market for over 15 months with no Local Coverage Determination from Empire Medicare Services, our local contractor, as to what uses are or are not considered medically appropriate and reimbursable as an example of the type of delay that must be remedied.

I appreciate the efforts CMS is making to expand coverage for experimental drugs and technologies, and hope that the agency is able to address the concerns I have described above.

Organization: Merck

(Comment on next page)

June 6, 2005

Steven Phurrough, MD, MPA,
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
Mailstop C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

Re: Draft Guidance on Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

Merck & Co., Inc. appreciates the opportunity to comment on the April 7, 2005 draft *Guidance on Factors CMS Considers in Making a Determination of Coverage with Evidence Development.* We also listened with interest to the Open Door Forum on this topic held on May 9, 2005 and applaud your willingness to listen to all stakeholders regarding the issues inherent in the proposed process, and to seek to understand the concerns raised by the overall direction of CMS coverage policy and the methodological issues raised by this particular draft *Guidance on Coverage with Evidence Development* (CED).

Merck & Co., Inc. supports the use of evidence-based decision making in U.S. health care policy. We believe the diverse purchasers in the U.S. health care arena deserve the best value for their customers/clients/patients. We strongly believe that evidence-based decision making that is focused on quality and outcomes can lead us to a health care system that, overall, is more efficient and cost-effective. Further, Merck believes that the use of evidence-based medicine among the multiple payers and providers in the U.S. system offers the best balance of diversity, experimentation, methodological development and refinement of approach to, and use of, clinical evidence for treatment and coverage policy.

Creating Value and Assuring Access

It is clear from the variety of draft coverage *Guidance* documents CMS has issued in the last several months, as well as from public comments of CMS officials, that the Centers are attempting to improve the value proposition for the Medicare program by assuring that beneficiaries have access to high quality medical interventions and providers have access to information about the application of those interventions to the Medicare population in particular. Merck supports those goals.

We understand and appreciate that CMS will use various types of evidence to inform its efforts. In the area of coverage policy, all stakeholders and policy makers need to clearly understand that the evidence we have available today, and the evidence CMS is proposing to generate, is population-based. The evidence is aggregated across large populations to produce meaningful inferences about the effectiveness of an intervention for the majority of the population. To the extent that evidence is used for coverage policy, CMS needs to acknowledge that a coverage process based on scientific evidence also must recognize, as a matter of policy, the limitations of the evidence: that there will be patients for whom a medical treatment is necessary even when it is not generally necessary for the majority of the population. As such, coverage policy based on evidence must allow access to services when medically necessary for an individual. To move to a more refined, science-driven policy means that coverage cannot be arbitrary – a service is or is not covered simply because it is less effective than some other treatment for the majority of the population. Beneficiaries need to know that they will have access if their provider can demonstrate that it is medically necessary for the particular patient – regardless of coverage policy based on normative results that will drive the bulk of utilization.

As CMS seeks ways to align resources with science based policy making, it needs to set a goal of moving utilization to higher quality, more effective interventions over time while assuring patients that science will not be used to arbitrarily deny services needed by those whose conditions or profiles are different from those on which the policy is predicated.

CMS also needs to publicly acknowledge the limits of current evidence-based policy making for some services, such as rare disorders and genomic-based technologies. The evidence base for most medical interventions in these areas does not have a large population from which to produce high quality epidemiologic evidence. Ultimately, these issues will need to be discussed and thought through, but CMS could assure patients and other stakeholders that it is aware of the limits of current evidence in these areas, that the Centers are not going to apply existing methodologies to these areas, and that the Centers will treat these issues fairly and substantively in the future but that these issues will not be affected by current policies.

Our specific comments below generally are organized by the headings in the draft *Guidance* document.

National Coverage Determination Process, Coverage Decision Types

We read the *Guidance* to stipulate that CMS intends in the future to have only two mutually exclusive types of coverage decisions: non-coverage or coverage with conditions. To our knowledge, this is the first time CMS has laid out its thinking about the changes in the *types* of coverage determinations it will be making, so in fact, these really are key policy pronouncements not simply "background" for the casual reader. As such, all the assumptions and suppositions embedded in the Background Section of this draft *Guidance* must be subject to debate and comment.

It is possible to interpret this policy of conditional coverage to mean that CMS would no longer make a coverage decision that simply tracks FDA approval/label/indications for instance. Similarly, for an intervention not subject to FDA approval (such as a surgical procedure), it would not be unconditionally approved for coverage even if the evidence supports improved health outcomes.

The intervention would be covered conditionally *if* evidence exists to show greater effectiveness in comparison to alternatives in some relatively undefined subgroup – Medicare patients in contrast to the larger population, or Medicare patients with a condition at a particular stage of disease progression, for instance. A number of proposed criteria for conditional coverage are very broad, others are quite amorphous and subject to a high degree of interpretation. Still other criteria or evidence, such as effectiveness in the Medicare population specifically, are not routinely available today for currently approved or tested interventions. Under this interpretation, it seems quite probable that the conditional coverage category would, in fact, lead to a significant proportion of decisions requiring further evidence development – something CMS officials have repeatedly stated is not the goal. We do not see how coverage with evidence development would remain infrequent under the existing draft *Guidance*, unless CMS refines its criteria.

In addition to clarifying *why* unconditional coverage, where effectiveness of an intervention can be proven (e.g. the recently released NCD for tobacco cessation), would no longer be available, CMS needs to present its vision for national coverage decisions – the process and the policy – as a whole. CMS needs to explain its vision of when it would internally generate a request for an NCD, and how it believes most of the NCDs would qualify for conditional coverage while not requiring further evidence development. The Centers need to explain whether or not it views more interventions moving up to the NCD process from the LCD process relative to current practice. This vision will affect how stakeholders view the NCD categories and CED process. The overall vision of the agency simply is not clear through this or previous draft *Guidance*, which makes it very difficult to offer practical comments to the questions posed by CMS.

If there are more CEDs as a result of evolving CMS policy, how does the stated desire to prioritize evidence collection fit in? For example, if it is determined that a particular intervention is not a priority for CED, but further evidence is required to produce a positive coverage decision, what does it mean that the alternative to CED is simply non-coverage (as CMS has stated repeatedly)? Is it tenable for CMS to deny coverage to something that would have received unconditional coverage because evidence about effectiveness for a subpopulation is lacking and the queue for CED is already full for other interventions? We believe the interactions and ramifications of the new policies need to be fully thought through using a variety of scenarios that lead to different outcomes.

Definitions

The liberal use of new and undefined terminology in this document is problematic. The definitional issues arise generally in the Background section of the draft *Guidance* in describing the NCD process.

Of particular interest, and key to understanding the whole CMS approach to coverage in the future, is the term "net health outcomes." Merck believes that this term should be defined, and that the definition should be as broad and flexible as possible to allow advantages for specific health outcomes which can be important at the individual level. It needs to be broad so that the effect on an intervention on medical condition, overall health status, and functional and cognitive ability is taken into account. The document speaks about "improvement in net health outcomes" and also about "improved health outcomes," and "significant net benefits." CMS needs to clarify if there is a definitional or contextual distinction in these terms.

In the first paragraph of Section II C, CMS has tied the concept of "reasonable and necessary" to the improvement in health outcomes. (Note that "net" health outcomes are not discussed here.) There are many situations in which treatment is reasonable and necessary to *maintain* health status or to slow deterioration. An example here would be physical therapy. Typically under current coverage policy, PT is terminated if the patient is no longer improving; the fact that PT maintains function and prevents decline is not a factor. Others have proposed to the Centers in years past that this is an insufficient and cost-ineffective standard since the termination of PT that maintains functional status is often accompanied by a rapid physical decline, an acute event such as a fall that causes a new hospitalization and a renewed cycle of acute and post-acute intervention. In a medical world increasingly geared to treatment of life-long chronic conditions, the use of the "improved health outcomes" and similar phrases needs to be considered very carefully. Definitively linking "reasonable and necessary" with improved health outcomes in a *Guidance* about coverage policy where a discussion of "reasonable and necessary" is expressly deferred to a future document seems premature.

The terms "particular clinical condition," "specific clinical situation," also need clarification. CMS intends to **no longer cover interventions that are demonstrated to improve the net health outcomes for all *patients with a particular clinical condition***. (Emphasis added.) However, CMS **will conditionally cover an intervention that demonstrates improved net health outcomes for patients with a specific clinical or demographic characteristic…limited to *patients with certain diseases, severity levels, age, or other factors*.** (Emphasis added.**)** How these terms interact, and what they mean, are critical elements but are quite inscrutable in this draft *Guidance*. We recommend greater clarity and precision that is then subject to public comment and discussion.

Linking Coverage with Required Data Collection

Distilling the thinking in Section IIB of the draft *Guidance*, CMS lays out an argument for using the coverage process for developing clinical treatment guidelines. Developing clinical treatment guidelines and refining the best available evidence is an important goal. However, there are aspects of this that are not fully reflected in the *Guidance* document. How and when will CMS involve practitioners and medical societies in reviewing and

interpreting the 'evidence?' Who will pay for the collection of the evidence if it is something more than use of a registry to identify claims for analysis? (We also note that the term registry is one that can mean different things to different audiences beyond analysis of databases. This needs to be clarified.) Will the intervention be covered according to FDA approval or the protocol of clinical trials during the CED phase? An item could be covered, and evidence development undertaken apart from coverage, unless the intent of CMS is to restrict access to all new interventions that are not clinically defined for a very narrow band of potential patients.

We also note a bit of disconnect in the rationale contained in this section. Evidence-based medicine is applied in different ways when used at the individual and population levels. Population-based policies (e.g. guidelines, coverage decisions) are based on methodologic techniques derived from evidence-based medicine. The evidence used for these policies is based on identifying normative effects/responses. The evidence is not individualized. However, CMS in this section speaks to the use of their CED process as helping "…doctors and patients get the most benefits…in our increasingly complex and individualized health care system." CMS also speaks in the *Guidance* to CED "…developing better, more individualized evidence about new medical technologies and services." However, it does not speak to how this would be accomplished. CMS needs to elaborate on how it sees developing and interpreting the evidence to arrive at these newer concepts of evidence-based medicine.

As mentioned earlier, we note that consumers and providers have expressed concern about evidence-based medicine used for broad coverage policy precisely because the evidence is normative in nature and patients and their presenting conditions can be highly individualized and non-normative. The concern is that evidence-based coverage policy will be definitive – an intervention is either covered or not because it does or does not prove effective (as opposed to efficacious) for a majority of patients. As such, CMS should assure that medically necessary treatments will be available to those for whom it is necessary even if coverage policy denies coverage of a treatment for the majority as not reasonable and necessary. Science and evidence need to be the basis all the way through – from population based coverage policy to individual treatment decisions. Arguably, only then can the process and the science have credibility.

Legal Authority for CED

In Section IIC concerning the legal authority for CED, the rationale for CED is neither entirely clear nor consistent, and the tie to the reasonable and necessary statutory requirement is indirect. CMS stipulates that a service may be reasonable and necessary *only* when a provider collects *and reviews* data *at the time the service is delivered*. This is arguably the very protocol of good, standard, medical practice.

Instead, CED is needed to make good, future, coverage decisions. Evidence for this purpose is not primarily for the care of an individual patient – beyond what is required for good clinical practice. Therefore, what is "reasonable and necessary" for CMS to determine coverage is not equivalent to what is required for clinical decision making at the bedside. Evidence of real world effectiveness is different than what the FDA needs to

determine safety and efficacy, which for drugs and devices occurs separate and apart from a CMS national coverage decision. Clarity in these distinctions may lead to greater clarity in other aspects of the draft *Guidance*, such as the distinction between evidence to refine clinical knowledge with respect to the Medicare population, and when evidence of an intervention's general effectiveness for the Medicare population is clearly lacking. We would suggest that CMS consider evidence development as a component of coverage when effectiveness is not known, and could consider evidence development for a covered intervention when there is a sense that the there are Medicare subpopulations for whom the intervention might be *more* effective.

Factors Considered in Applying CED

In Section III, the language concerning local contractors is potentially confusing. CMS indicates that local coverage policies will be guided to apply CED if it is needed to determine if an item or service is reasonable and necessary. This indication seems inconsistent with a discussion earlier in the *Guidance* that CMS did not envision that CED would produce a net reduction in coverage available under existing local coverage policies. Between this *Guidance* and earlier *Guidance* on the NCD process, it is no longer clear if local coverage policy and process will be changing; CMS seems on one hand to indicate that local coverage policies will not change – neither policies nor process. However, on the other hand, Section III of this current *Guidance* calls that into question. CMS should be very clear about its intent and needs to identify the ramifications of changing local policies, processes and criteria. For example, if local contractors cannot provide "unconditional coverage," they would need to institute CEDs to determine coverage. What effect would this have on the system in terms of beneficiary access to new interventions? Would there be multiple (and conceivably different) evidence development activities for the same intervention? Creating simultaneous change in the local process, as implied here, really necessitates CMS clearly articulating its vision for how it sees the NCD and LCD systems fitting together as a coherent, efficient whole that affords patients access to new interventions. The public needs to understand this in order to comment effectively. If this is not the CMS intent, the language should be clarified.

In this Section also, CMS articulates its view that it will generate a series of NCD/CED processes. The first CEDs will be initiated internally – calling into question earlier *Guidance* about the NCD process and the extent to which CMS would take it upon itself to initiate national coverage decisions. Earlier *Guidance* stated that CMS might initiate an NCD on its own when an intervention was determined to have a "large programmatic impact" on Medicare or related programs. Here, the standard for internal initiation is wholly different: items where better evidence would expand access while learning more about the risks and benefits of those items. Clearly, these are two entirely different bases for internal generation of an NCD. Again, we stress CMS needs to put forth a coherent, systematic vision and strategy for the whole of the NCD/LCD process and allow public comment on that overall strategy. Commenting on different small aspects is potentially without value since the individual components presented may not even represent the whole that CMS is considering.

In its May 9th Open Door Forum on CED and in other public forums, CMS has specified that CED will be rare. However, the list of factors to be considered in applying a CED seem to argue that CMS will have a proclivity to apply CED; the reasons to pursue CED are overly broad and can be applied to many long term interventions that treat chronic conditions – effectiveness for certain Medicare beneficiaries, long term risk and benefits, "real-world" outcomes, for example. It is important for CMS to develop solid, discrete criteria and to establish a methodology for when and how those criteria would be applied.

It also seems that using only a conditional coverage category will restrict coverage relative to former unconditional effective coverage determination option. Therefore, it is only in this restricted coverage determination process that CED will increase access to coverage. Is CMS expressing a presumption that it does envision more restrictive access to new interventions that can only be abated by CED? If so, it should say so and this should be actively debated.

In general, CMS has laid out a very broad data gathering agenda that is not easily reconciled with its statements that CED will be used only infrequently. CMS needs to prioritize its data gathering efforts into a few key groupings. CMS also needs to consider what evidence development is undertaken or likely to be undertaken by different stakeholders in regard to a specific intervention; CMS should not duplicate or closely replicate other research efforts. It seems that the focus of CMS evidence creation activities should be comparative effectiveness of specific interventions – this is a very broad rubric in which to operate, but narrower than what CMS has proposed. Data development on risks and benefits may be undertaken by other researchers.

CMS poses the question about whether there are evidence development efforts that are not effective when linked to coverage decisions. Arguably, evidence development is not inherent or inextricable to the coverage process in most cases. In fact, we would suggest that it is preferable in most situations to de-link the two processes and provide coverage while gathering refining evidence for further coverage evaluations.

When and How to Apply CED

CMS intends to apply CED to issues with the greatest potential benefit for Medicare beneficiaries and the Medicare program. CMS also has publicly stated that the alternative to CED is non-coverage. Priority setting against a backdrop of non-coverage is not mentioned in this Section, but is obviously crucial relative to all other factors. How important is coverage of the item relative to CED and non-coverage? How can priority setting for CED be established against the alternative of non-coverage?

Here again, the process for CED is not clearly stated but several possibilities are intimated throughout this *Guidance* document. For a CED, priority setting in the context of an externally requested NCD would be one situation requiring criteria. Priority setting for an internally generated NCD where CMS knows in advance that evidence development is required is another matter altogether in the context of priority setting and basic implications.

Further, earlier CMS *Guidance* about the NCD process stipulated that the agency will internally generate an NCD for items or services that have substantial programmatic impact on Medicare or related programs; CMS has also said that CED (a subset of NCD) will be applied to issues with the greatest potential benefit for Medicare beneficiaries. How are these two criteria to be reconciled – and further reconciled knowing that the alternative to NCD is non-coverage?

In terms of stakeholders, we applaud CMS for expressing a desire to be inclusive. We do believe, however, that it may be useful for CMS to identify core Medicare stakeholders as one group distinct from general health system stakeholders.

Conclusion

Merck & Co., Inc. believes that evidence-based medicine and evidence-based health policy are very important to the future U.S. health care system. We believe there is great promise in developing methodologies for improving the quality of care provided in the U.S., thereby improving the overall efficiency of the system. How CMS addresses these issues will have a significant impact on the future success of these initiatives and how the public views them. We respectfully suggest that CMS needs greater clarity in expressing its intent for the Medicare program and that only then can there be a robust public dialogue about the direction the Centers should take.

It would appear that CMS should initiate another round of policy development that better integrates all the proposed policies: the overall NCD processes, the NCD coverage types, the role of LCDs in the NCD process, and the role of CED in the NCD process. It is really only possible to comment thoroughly on developing an evidence-based coverage process when the entire proposal is apparent.

We at Merck have given a great deal of thought to issues of evidence-based medicine and the different venues in which it is used: demonstrating safety and efficacy through clinical trials, physician/patient treatment decisions and clinical best practice guidelines; coverage policy using comparative effectiveness analysis. We would welcome the opportunity to work with CMS as you develop your coverage process and protocols to lend our expertise.

Sincerely,

s:/William Keane
Vice President, Medical and Scientific Affairs
US Human Health

Organization: Muse Associates

As additional legal authority for CED (Section C on page 6 of your draft), have you considered Section 1833(e) of the Social Security Act for Medicare Part B; and Sections 205(d) and (e) and 1872 of the Social Security Act generally?

Organization: National Electrical Manufacturers Association

NEMA is the largest U.S. trade association representing the U.S. electroindustry. The Diagnostic Imaging and Therapy Systems Division of NEMA represents over 95% of the market for x-ray imaging equipment, (including mammography), CT, radiation therapy, magnetic resonance, diagnostic ultrasound, nuclear medicine imaging and medical imaging informatics equipment.

We recognize that use of CED, as set forth in this draft guidance, represents a significant, alternative direction in the national coverage determination process. NEMA appreciates the opportunity to share its views and concerns with you on the development of this draft guidance document. We understand that submission of these comments represents only the first step in an iterative process. NEMA is eager to be an active participant with CMS and other stakeholders as the development of CMS coverage guidance documents proceeds.

General Comments

At the outset, NEMA wishes to commend CMS for introducing coverage with evidence development into the national Medicare coverage process. By linking coverage of promising technologies with collection of data on their real – world performance, CED represents an important tool that helps achieve the needs of patients, innovators, and Medicare. We also welcome CED because it recognizes the realities of device innovation, in particular that the ultimate value of many medical technologies does not become apparent until they are used in everyday clinical settings by practicing clinicians. By providing coverage during this important period, CED sends a signal to innovators and investors that CMS is serious about truly understanding the clinical value of new technologies. We look forward to working with Medicare in making CED successful and understand that submission of these comments represents only the first step in a continuing and iterative process.

In its draft guidance, CMS has posed a wide range of questions regarding the process of making CED determinations, identification of appropriate participants in the process and how the process should function. We will address a number of these questions in our specific comments set forth below, and also provide comments on various portions of the draft guidance. Specific questions raised in the draft guidance are in *italics*.

Process for Deciding When and How to Apply CED

In the draft guidance document, CMS identifies two circumstances where coverage with evidence development may be appropriate. One of these circumstances is where "a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit." The draft guidance goes on to say, on

page 7, that "CMS may determine that the adequacy of the evidence demonstrating improved health outcomes [emphasis added] can only be assured if additional data is collected, reviewed and submitted at the time of the service." The recent national coverage determination for FDG PET was cited as an example of this circumstance (draft guidance, pages 8-9).

NEMA agrees with CMS that coverage with evidence development is appropriate in circumstances where existing information on a technology's benefit is promising, but not conclusive. We think that the recent FDG PET coverage determination, linking coverage to data collection, was a sound approach that may prove to be a useful model for other imaging technologies.

However, we want to raise a cautionary flag that the data gathered will typically not connect the technology in a causal way to health outcomes. Generating evidence linking diagnostic technologies to health outcomes, while desirable, is typically not practical. Efforts to do so are extremely costly, and they pose special methodological problems—notably, accounting for multiple intervening steps between accurate diagnostic findings and improved health outcomes. To determine the impact of a diagnostic test on improved health outcomes means taking into account confounding factors (for example, multiple treatment options). We note that the discussion of the FDG PET determination on page 8 of the draft guidance references data collection as having the "potential to improve health outcomes by influencing patient management" and "helping physicians appropriately evaluate the PET scan results…" This discussion of the purpose of data collection requirements associated with the FDG PET determination appears to be reasonable. For this reason, we suggest that CMS revise the draft guidance document to reflect this fact, stating that the goal of data collection in this circumstance will be tailored to endpoints appropriate to the technology. In the case of diagnostic imaging
technologies, the appropriate endpoints may involve changes in patient management, rather than demonstrated direct relationship to improvements in health outcomes.

It is important that CMS permit requests for coverage with evidence development to be generated by stakeholders for public review. While it is understood that CMS will have the final decision on whether a particular request for CED is accepted, stakeholders should be permitted to not only submit their own requests for CED, but also should be allowed to comment on other requests which have been submitted. CMS states in the *Purpose of this Guidance Document* that one of its goals in issuing this draft guidance is to seek public comment to ensure transparency and the most effective use of this kind of coverage decision. NEMA believes that the right of public comment should begin at the earliest stages of the process, when the request for CED is initially made either by CMS or by stakeholders.

NEMA recommends that CMS also permit input from various types of stakeholders, such as those set forth in Section IV of the draft guidance, with respect to the potential benefit of any item or service to the Medicare program. In the case of diagnostic imaging technologies, it is essential that diagnostic imaging equipment

manufacturers be afforded the opportunity to provide CMS with their views on the potential benefit which may be derived from these technologies. Determination of which item or service will provide the greatest potential benefit is an extremely complicated question, which is affected by many variables. Allowing input from various stakeholders will provide the opportunity for CMS to gain an understanding from many different perspectives on the potential benefit which may be gained from any particular item or service. We believe this will improve the quality of the Medicare coverage decision-making process.

We would like to emphasize that NEMA strongly supports continued local decision-making for new imaging technologies and indications under the local coverage process. Local coverage plays a very valuable role in the diffusion of new technologies. In those instances in which there is insufficient evidence to make a national coverage determination, stakeholders should be able to utilize the local coverage process. In addition, where such national non-coverage situations exist, CMS should be open to CED initiatives by stakeholders.

-Should the focus of these activities be only on new technology and services, or the entire spectrum of technologies and services?

NEMA believes that the focus of CMS activities should be on new technologies and services. The rate by which such items and services are entering the healthcare marketplace is increasing rapidly, thus creating a difficult challenge for CMS to keep pace with product innovation. By concentrating on these new technologies and services CMS can play a vital role in enhancing patient access to them, without diluting its efforts on technologies already in use in clinical practice.

-Should there be a process for requesting national coverage decisions with evidence development, and how should such requests be prioritized?

NEMA recommends that a formal process for national coverage decisions with evidence development be established jointly by stakeholders and CMS. Such a process should be clear, understandable and efficient, and should be developed only after ample opportunity has been provided for stakeholder input. Both CMS and outside parties should be permitted to request a national coverage decision with evidence development.

When such a request for CED is made, whether internally or externally generated, it should be promptly posted on the CMS website for public review. Stakeholders should be given an opportunity to provide comments to CMS on the prioritization of such requests, with CMS making the final decision. We believe that CMS would miss an information gathering opportunity if, for example, patient advocates and consumer groups were not allowed to weigh in with their views on how a particular item or service would affect them as Medicare beneficiaries, since the impact of a potential coverage decision may fall most heavily on them. Likewise, medical equipment manufacturers possess the most knowledge and expertise about their equipment. Thus, the process for a request for coverage with CED, which affects

medical devices, should have the benefit of manufacturers' views. Prioritization of requests will be better informed if input from a wide variety of stakeholders is permitted, since each constituency has its own perspective on the potential benefits of various items and services.

Collection of data

CMS declares in its draft guidance that,

> "The potential value of information generated through coverage linked to evidence development must be carefully considered in the context of the burden associated with the collection of this data…. Data collection should only continue as long as important questions remain and it is determined that the effort and resources required to collect this data are justified by the potential value of the information that will be generated. "

CMS further emphasizes that no unnecessary costs should be imposed and only the minimum data necessary to answer specific questions should be collected. The agency states that acquiring the data should use " the least-resource intensive mechanisms available."

NEMA commends CMS for its intent to collect data in an efficient, non-duplicative manner. We appreciate CMS' recognition that collected data from "administrative sources" can enhance the efficiency in the process of evaluation of items and services for coverage.

CMS has acknowledged that it will make use of existing databases and data collection mechanisms where appropriate. This is an essential principle because imposing an unnecessarily burdensome data collection requirement on requestors will impede, rather than enhance, access to new medical technologies for Medicare patients.

To effectuate its intent, it is vital that CMS recognize and utilize where possible available sources of information. Duplication of collection efforts regarding data, which has already been produced for the purposes of FDA product clearance, for example through the 510(K) or PMA process, must be avoided. Data contained in 510(k)s and PMAs should be carefully considered and used by CMS to meet data requirements for a request for CED wherever appropriate. Data, which exists in the medical literature or from other sources, should also be carefully scrutinized to determine its value with respect to any particular coverage request.

-What approaches to study design and implementation would be least costly and most

efficient?

It is important to recognize that each item or service is unique, and accordingly data collection requirements and study design should be evaluated on a case-by-case basis. There is no one type of evidence development method, e.g. longitudinal study, randomized controlled clinical trial, which will be appropriate for all items and services. As CMS has correctly stated, "To minimize the financial and other resources required, careful attention must be paid to collecting the minimum data necessary to answer specific questions. Collecting that data should use the least resource-intensive mechanisms possible."

The selection of the data collection method and study design should be a joint decision by the parties conducting the study and CMS, with CMS having final approval authority. These decisions should be reached through periodic meetings, as necessary, and ongoing communications between CMS and the parties conducting the study.

Process for Study Design and Implementation

The details of study design should be determined by the party conducting the study, subject to CMS approval. Study design could cover details such as:

-Study hypothesis
-Sample size
-Site selection
-Patient safety and monitoring
-Training for providers and others
-Patient confidentiality
-Data security and quality assurance
-Data collection instruments and methodology
-Clinical endpoints

-*Who should participate in study oversight and implementation?*

CMS provides in Section VI. of the draft guidance that it must be assured there is appropriate oversight of any data collection method. NEMA recommends that the party conducting the study should have principal responsibility for study design with consultation and approval by CMS. Trial sites should be under the supervision of the party conducting the study. However, CMS should be kept fully informed on a regular basis through study reports on the operation and results produced from the study to ensure that study objectives are achieved.

-How should CMS determine the qualifications of investigators involved with coverage evidence development?

The party conducting the study should determine the qualifications of investigators involved with coverage evidence development, subject to the approval of CMS. CMS should be informed of and approve the members of any clinical advisory board or a biostatistician.

-Who should have access to the data and in what form?
-How will evidence collected through CED be disseminated?

The questions of access to the data, the form of the data and its dissemination should be determined through agreement of the parties. In any event, CMS will need access to the data in order to monitor and evaluate the results of the study. Patient privacy regulations will need to be observed. Final results of the study should be made available to the public, and should be accessible on the CMS website.

-How should the costs of study design, data collection, analysis and other activities associated with these programs be fairly allocated to various stakeholders?

Allocation of costs of study design, data collection, analysis and other programs pertaining to the study should be determined on a case-by-case basis. NEMA believes that CMS should be prepared to reimburse providers for certain costs they incur in these data collection efforts, even though reaching a formula prospectively may be elusive. Agreements regarding allocation of these costs should be reached between participating stakeholders, and should not be determined solely by CMS. It is hoped that such studies would encourage the financial participation of industry, academic and research institutions, professional societies, patient advocacy groups and others in funding the study.

Conclusion

Instituting a process linking coverage with evidence development will best succeed if CMS takes into account all of the perspectives of affected stakeholders. Proceeding with an iterative process which evaluates the broad array of interests will ensure that Medicare beneficiaries have more rapid access to lifesaving medical technologies.

NEMA eagerly anticipates working with you on this worthwhile goal and playing a vital role in this process.

Organization: National Organization for Rare Disorders

(Comment on next page)

National Organization for Rare Disorders, Inc.®

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June 3, 2005

Steve Phurrough, M.D.
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mail Stop: C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

Re: Draft Guidance: Factors CMS Considers in Making A Determination of Coverage with Evidence Development, April 7 2005

Dear Dr. Phurrough:

We have reviewed the proposed guidance on "coverage with evidence development (CED)" and have two concerns. One deals with the overall guidance and the other with issues specific to orphan drugs.

Viewed from a distance, it is hard to understand why CMS wants to oversee clinical trials, their implementation, and their initial evaluation. There are a number of federal agencies with much greater experience and depth of knowledge in these functions, notably NIH, FDA, AHRQ, and VA.

Also, at least for drugs and devices, it is FDA that has the responsibility for requesting and monitoring post-approval trials. They have a significant number of staff members who are:

- trained to differentiate good and bad study designs,
- knowledgeable about IRB and other ethical requirements, and
- capable of determining whether study results are satisfactory, flawed, generalizable, etc.

If there is some problem with the FDA's exercise of this responsibility, then we should fix it at FDA, rather than create parallel authority at CMS.

With specific regard to orphan drugs, the draft guidance states:

> An initial list of circumstances in which coverage with data collection might be valuable includes....comprehensive evidence of effectiveness of treatments for rare diseases is not always available or feasible to develop in a pre-market setting. It may be beneficial to evaluate interventions for rare conditions such as use of orphan drugs and humanitarian use devices.

By this statement, CMS presumes that FDA approves orphan drugs without demanding adequate proof of safety and efficacy. This is not the case. The Orphan Drug Act does not provide for a different standard for the approval of orphan drugs. To the contrary, advocates made it very clear during negotiations that orphan drugs must comply with the same standards of safety and efficacy as other pharmaceuticals and biologicals.

Some clinical trials of orphan drugs for very rare conditions may result in studies that are statistically underpowered. FDA accounts for this in both their analysis of the data and the stringent post-marketing requirements. In these cases, we do not know what increment of knowledge would be of such benefit to CMS that it would justify duplicate information gathering during the post-market period, especially given the very small populations involved in many of the trials.

In sum, we urge CMS to consider alternatives to CED. We would favor approaches that keep CMS out of the clinical trial business.

If CED is implemented, then we would ask for the deletion of all references to orphan drugs and humanitarian devices as examples of therapies that might undergo the CED process. In addition, if CED is implemented, its use should be limited solely to circumstances where another research-related agency, such as NCI, makes a formal request to CMS for coverage of investigational drugs or devices in a trial in order to facilitate enrollment.

Thank you for your consideration of these comments. If you have any questions about our views, please contact Diane Dorman, NORD's VP for Public Affairs.

Sincerely,

Abbey S. Meyers
President

Cc: Dr. Mark B. McClellan, Administrator, CMS
Diane E. Dorman, Vice President, Public Policy

Organization: National Patient Advocate Foundation
Name:

(Comment on next page)

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May 31, 2005

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Re: Draft Guidance: Factors CMS Considers in Making a Determination of Coverage with Evidence Development

To Whom It May Concern:

The National Patient Advocate Foundation (NPAF) is a non-profit organization dedicated to improving access to health care services through policy reform. The advocacy activities of NPAF are informed and influenced by the experience of patients who receive counseling and case management services from our companion organization, the Patient Advocate Foundation (PAF), which specializes in mediation for access to care, job retention, and relief from debt crisis resulting from diagnosis with a chronic, debilitating or life-threatening disease. From July 1, 2003 to June 30, 2004, PAF received 3.2 million requests for information and/or direct professional intervention in the resolution of access disputes. The majority of our cases deal with the diagnosis of cancer.

The NPAF Scientific Board[1] has reviewed the Draft Guidance on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development" published on April 7, 2005 and appreciates the opportunity to provide written comments. We understand that the Centers for Medicare and Medicaid Services (CMS) intends to work with all affected stakeholders to ensure that its approach will lead to improving the health of beneficiaries by enhancing access to medical technologies and services that improve health outcomes. However, the draft guidance, while very comprehensive, left quite a few unanswered questions and concerns for providers.

Our primary topic of concern regarding the proposed Coverage with Evidence Development (CED) proposal is patient access to medical technologies and services.

[1] Otis W. Brawley, MD, Professor, Emory School of Medicine, Emory University; F. Marc Stewart, MD, Medical Director, SCCA, Professor of Medicine, University of Washington, Fred Hutchinson Cancer Research Center; and Richard L. Theriault, DO, MBA, Professor of Medicine, MD Anderson Cancer Center were not present at this meeting.

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Any change in the incentives for health care delivery, including how resources are allocated, will have a major financial impact on the health care marketplace and will likely affect access to care.

In an attempt to delineate our concerns, our comments follow the draft guidance, section by section and address the following major topics of the draft:

Purpose of Linking Coverage with a Requirement for Data Collection

NPAF supports the need for quality data collection in relation to evolving therapies and treatments; however, any process that seeks to stall or add additional clinical and data requirements to a process that is already considered quite rigorous, could serve only to slow down Medicare beneficiaries' access to much-needed therapies.

NPAF is concerned about how CMS will collect data as part of the CED initiative. Of particular concern is how data will be collected, and whether a new infrastructure would be required to accommodate this new decision-making process. The answer to this question would have significant implications for providers and their patients. Within the oncology community, any new data collection requirements would be another paperwork requirement being piled onto practices reeling from reimbursement cuts flowing from the Medicare Prescription Drug, Improvement And Modernization Act of 2003 (MMA). Any additional data requirements would require additional staff resources, not available in most community practice settings, and could take physicians away from their primary mission of treating patients.

In addition to the strain on staff resources for physicians in community settings, we also wonder who will pay for the data collection and whether providers will be reimbursed for their data collection efforts. We anticipate providers could be required to hire an additional person that would be an expert in data collection and wonder whether federal funding would be provided. If funding is not provided, NPAF is concerned that this would be seen as an unfunded mandate.

We wonder who will make the determination that the data for a particular CED meets the appropriate quality standards. In terms of tracking patient care, we would be interested in knowing what CMS anticipates in terms of how many patients will likely be needed to make final determinations, and what the average accrual length of time will be to complete the data collection process.

We are also concerned that CMS is building another process that duplicates what organizations that are already expert in collecting data, such as the National Cancer Institute (NCI), the National Institutes of Health (NIH), the Cancer and Leukemia Group B (CALGB), the Coalition of National Cancer Cooperative Groups, Inc., are doing. NPAF recommends that CMS harvest data through the Food and Drug Administration (FDA) in the post-marketing reporting process by manufacturers as is required for expedited and fast track FDA approval, where it might accomplish

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more. FDA's data collection system is already statutorily established and would provide an immediate vehicle for implementation, as well as an additional level of scrutiny through the agency's internal office of safety. This process allows the immediate overlay of off-label experience in drug utilization with the initial drug approved information that may be extremely expeditious.

It is critical that CMS assure that the data collection process will be open for review by the public, as is done at the FDA, and is encouraged as part of its clinical trial system. Likewise, the public should have access to the data results as they are announced.

Since CMS will begin data collection under Part D with a requirement that CMS collect 36 elements of electronic data for each drug purchase under Part D, NPAF suggests that CMS integrate this system of data collection rather than setting up an entirely new process. In the absence of completed CED data, determination of medical necessity should be decided between physicians and patients.

Factors Considered in Applying CED

The draft was quite comprehensive in delineating concerns that most stakeholders would have in terms of how the CED would be applied. One of our primary concerns, which is unclear from the document, is whether the agency will require the CED process for off-label usage.

NPAF strongly recommends that CMS continue to reimburse for off label uses of approved cancer drugs. CMS must recognize, however, that the listing of acceptable compendia applicable to Part B in Section 1861(t) (2) of the Social Security Act is outdated. Of the three named compendia, only one, the United States Pharmacopoeia – Drug Information is currently maintained and the update process utilized by that publication is generally regarded by the oncology community as being less than timely. The timeliness problem, along with accompanying beneficiary access problems that come with it, is only further compounded by the months that it frequently takes before carriers pick up new additions to the compendium and begin paying claims for what is by then a not-so-new medically accepted off-label use.[2]

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[2] The rights to the U.S.P - Drug Information have recently been purchased by Thompson Publishing and it is conceivable that the name of the compendium will be changed, leaving CMS with no operational compendium reference expressly listed in the statutes governing Part B. It also appears that the update process being contemplated by the new publisher will further slow down the process for updates. In NPAF's view, the current situation poses a significant barrier to patient access that could be easily overcome if the Secretary would exercise his authority under Section 1861(t)(2)(B)(ii)(I) to use "other authoritative compendia" to identify anticancer drugs that are eligible for automatic coverage under Part B and, therefore, ineligible for application of the CED.

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Process for Deciding When and How to Apply CED

Other Stakeholder Groups that should be Included/Appropriate Forum

CMS was quite comprehensive in their discussion of outreach to stakeholders. NPAF recommends that CMS include oncology nurses, office practice managers, and oncology social workers in any future discussions with stakeholder groups. We also recommend that CMS post questions on the NCI *Listen and Learn* website (http://ncilistens.cancer.gov/) that is targeted to receive responses from 121 patient advocacy organizations. Other forums might include http://clinicaltrials.gov/ and forums hosted by the Coalition of National Cancer Cooperative Groups, Inc., at: http://www.cancertrialshelp.org/patientsCaregivers/patientsCaregivers.jsp.

Discussion of Study Designs

NPAF does not advocate for one particular study design, however we would suggest the type of study depends on the set of questions to be examined and what information is being sought from the data being collected. NPAF believes that data should provide information on the demographic nature of the beneficiaries to determine the characteristics of patients being selected to receive certain therapies. We also support data collection that includes information about patient care, including information about whether patients receiving a particular therapy require hospitalization, emergency room visits, and/or extra clinic visits; the length of survival and/or disease-free survival with this therapy; and in certain cases, the cause of death for these patients.

Longitudinal or cohort studies could best address questions about any side effects and toxicities a beneficiary is experiencing over time, and can lead to better information about the quality of life of patients while they are receiving therapy as well as post-therapy, as well as the costs associated with different therapies.

Prospective comparative studies could best answer questions related to the response rate of beneficiaries receiving a particular therapy compared to patients receiving some other therapy or no therapy. Questions relating to side effects and toxicities, quality of life issues, and costs are also relevant questions to use under this model.

Randomized clinical trials could best address questions regarding the effectiveness of new therapies, though effectiveness would have to be defined, in terms of treating the disease in this patient population, as opposed to a more standard treatment. We would also suggest that comparisons could be made about the toxicities of new treatments versus current standard therapy, as well as quality of life issues. These studies are listed in ascending order as to burden, cost associated with administering the studies, and difficulty in maintaining quality, as well as in the quality of the evidence they produce. The first three design models are probably most appropriate for what CMS is proposing to do. While CMS has covered most

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of the waterfront on study design, creative combinations of designs can be used to answer specific questions.

The portion of the trial dealing with the least expensive and burdensome data collection should be made available to all beneficiaries. A second, more expensive and burdensome portion of the trial should be available only to providers who are willing to assume the additional burden and who could demonstrate the ability to collect and report the data required in a quality manner. NPAF believes this process would also give the most beneficiaries access to much-needed therapies. A portion of the trial would be structured to answer more complex questions and would require fewer subjects.

One example of an institution that might serve as a model for how this could work, because they collect and monitor similar data, is the Center for Blood and Marrow Transplant Research (CIBMTR - the old IBMTR/ABMTR). CIBMTR has been doing minimally reimbursed, voluntary data collection from multiple treatment centers for years and has learned a lot of lessons about how to do it. They also could give a perspective on the quality of data that can be collected in this manner, as well as some of the costs that would be associated with such an undertaking. CIBMTR does primarily database and longitudinal and cohort studies, and the results of their studies are published quite extensively.

Process for Study Design and Implementation

The Draft CED Guidance states, "Each evidence development enterprise should appoint an individual with appropriate clinical, scientific, and technical expertise to oversee all aspects of data collection." NPAF hopes CMS will provide more information in the next CED draft about how this oversight will be maintained. There are a number of specific questions relating to qualifications of an oversight authority, how that person(s) will be compensated, whether it will be necessary to have such a person at every practice site, among others.

NPAF strongly encourages CMS to define specific, systematically congruent responsibilities for these representatives so that data collection is universally consistent. We believe it is important to identify concrete reporting processes that an oversight authority must adhere to as it relates to point of contacts within CMS. All reporting deadlines and published dates for public reporting of the CED findings should be widely circulated. We also encourage CMS to identify universally used software programs already in place in the oncology practice setting to enhance CED program participation and consistency of data collection, which will reduce costs to the provider community.

NPAF would like to thank CMS for the opportunity to offer comments on CED draft guidance and looks forward to being a part of continuing discussions on these

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issues. If you require additional information, please don't hesitate to call me at (202) 347-8009.

Respectfully submitted:

Nancy Davenport-Ennis
CEO
National Patient Advocate Foundation

Organization: National Venture Capital Association

(Comment on next page)

June 6, 2005

Administrator Mark McClellan, M.D. Ph.D.
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: Draft Guidance for Coverage with Evidence Development

Dear Dr. McClellan:

The National Venture Capital Association (NVCA) appreciates this opportunity to comment on the draft guidance describing the factors considered by CMS when making a determination of Coverage with Evidence Development (CED) issued by the Centers for Medicare and Medicaid Services (CMS) on April 7, 2005.

NVCA applauds your commitment to innovation and your efforts to bring new medical technologies to market as rapidly as possible. We strongly support the concept of expanded and earlier Medicare coverage for new medical devices, drugs, and biological products. We are also committed to an evidence-based approach to medicine that provides meaningful and relevant data to best inform physicians and patients about new and clinically important products. NVCA would like to offer its perspective on the draft guidance, given our members' experience working closely with many of the companies developing these new technologies. Our comments are also based in part on your remarks during the NVCA Annual Meeting held in New York on May 11, 2005. In addition to offering our perspective on this issue, NVCA would like to continue working with CMS on any future issues related to emerging technologies, including innovative new medical devices, drugs, and biological products.

Background on the National Venture Capital Association

The National Venture Capital Association is the trade association that represents the U.S. venture capital industry. NVCA's mission is to foster greater understanding of the importance of venture capital to the U.S. economy and support entrepreneurial activity and innovation. The NVCA represents the public interests of the venture capital community, strives to maintain high

professional standards, provides reliable information and data regarding our industry, sponsors professional development, and facilitates interaction among its members.

The life sciences industry (biotechnology and medical devices) has traditionally been one of the largest areas of investment for venture capitalists, representing $5.6 billion in 2004, approximately 27% of all venture capital dollars invested. It is estimated that more than 100 million Americans have benefited from innovations developed by life sciences companies originally financed with venture capital. These innovations have revolutionized the practice of medicine in several fields by helping physicians detect diseases earlier, treat chronic diseases, and prevent some of the leading causes of death. For example, MRI and diagnostic imaging, which have eliminated the need for "exploratory surgery", were both pioneered by venture-backed life science companies. Drugs such as EPOGEN, Rituxan, and Enbrel have improved the lives of millions of patients living with end-stage renal disease, cancer, and rheumatoid arthritis, respectively. And innovations in treating heart disease, the leading cause of death in the U.S., such as angioplasty, minimally invasive by-pass, and implantable defibrillators were all originally pioneered by venture-backed companies.

Venture capital plays a critical role in the field of life sciences, even relative to other industries. Life sciences companies tend to require a larger amount of investment than startup companies in other industries because of the high costs of clinical trials required to meet the safety standards of the FDA. In most cases, these costs must be incurred before the company starts generating revenue. In addition, the high degree of risk and lengthy timeframe before a return on investment can be realized makes investments by individuals insufficient and investments from banks and public capital markets unlikely. Venture capital is usually the only viable source of funding to support the development of the majority of life sciences innovations.

Recommendations

The NVCA supports the broad policy goals of the draft CED guidance and wishes to share specific recommendations related to emerging technologies. NVCA is concerned that the CED process if not used selectively could become a barrier to market entry for new innovative products. CMS will have an increasingly critical role in the development of the new innovative therapies and products for patients through its coverage, reimbursement and data collection policies. As noted above, NVCA looks forward to working in a collaborative fashion with CMS on these issues.

I. Circumstances Appropriate For CED

NVCA believes that CED should only be applied when the alternate decision would have been a national non-coverage decision. CED should not be used as a method to limit coverage of existing products that are presently covered under either a national or local coverage policy. Additionally, CED should not be used for on-label use of medical devices, drugs, or biologics. CED should be limited to use in rare instances with products that CMS would like to cover, but where there is limited data available.

It is critical that the manufacturer have a pivotal role in the decision of whether CED is applied to its therapy, diagnostic or other technology, as the CED process will rely upon the clinical and product expertise, as well as the financial resources, of these manufacturers. The CED process could be modeled after the process in which medical technology sponsors may affirmatively request that the FDA re-classify a device subject to premarket approval (PMA) either as a novel class III device, or upon a 'not substantially equivalent' determination, from class III to class I or II. This policy allows FDA and sponsors to respond to innovation and the lack of technological predicates or precedents with great flexibility. Another example would be the fast track designation and approval process used by the Food and Drug Administration (FDA) in evaluating new drugs, in that it is the sponsor - and not the FDA - who determines whether to submit a request for fast track designation. The sponsor also defines the scope and timing of the resulting fast track drug development program including sponsor-agency meetings, rolling submission of the application, and even application of accelerated approval or expanded access.

II. Additional Factors Appropriate for Consideration

When applying CED, CMS should consider the financial resources of the underlying companies, particularly the disproportionate burden placed on small companies in collecting data. In the medical device industry for example, the cost of collecting data, will frequently exceed the gross margin dollars generated by the product, making data collection an untenable solution for companies that are not generating cash flow from other established product lines. NVCA remains open-minded to any potential solutions to this problem, but would suggest a few options: i) temporarily pay a premium over the normal level of reimbursement for the product, ii) require CED only in certain regions while allowing full reimbursement in others without CED, or iii) create some sort of premium reimbursement payment for data collection that would only be available to smaller companies.

We appreciate CMS's flexibility in not stipulating the use of one particular methodology or study design for CED. For some products a data collection registry may be more appropriate than a clinical trial. Although placebo controlled randomized clinical trials are considered the best form of evidence in an ideal world, they are not the only acceptable form of evidence. In fact, in certain fields, such as the medical device industry, it is generally unrealistic to conduct a placebo controlled randomized clinical trial because of the practical and ethical issues associated with implanting a non-functioning device. Thus, other advanced statistical techniques, including some combination of trials and expert opinion, possibly including Bayesian expert consensus evaluation techniques, are frequently used to demonstrate efficacy.

CMS should also consider adjusting required evidence levels in relation to the likely risk-benefit of a particular product or procedure. Allowing coverage of procedures which are demonstrably safe, but for which evidence of efficacy is weaker than desired, allows the market time to evaluate such products or procedures itself and also allows for technological improvements and more data collection. Conversely, CMS might require products or procedures which have high morbidity or complications to produce stronger evidence of efficacy sooner.

Finally, CMS should revise the draft CED guidance to better acknowledge and address the differences in development strategy, product life cycle and technology between medical devices

and new drugs or biological products. It should also reflect the differences in clinical evidence available from products undergoing premarket review and approval under New Drug Applications (NDA) or Premarket Approval (PMA) Applications or 510(k) clearances with clinical data, compared to classes of products which do not undergo any premarket clearance or approval by FDA, such as certain human cell, tissues and cellular and tissue-based products (HCT/P). In particular, CMS should presume that clinical data provided to the FDA in support of granted Approvals or Clearances, is strong "evidence" of efficacy under the CED standards.

Ongoing Involvement of NVCA With CMS

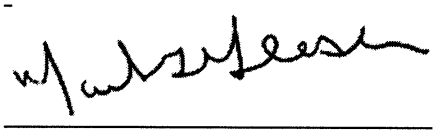
Given NVCA's expertise in understanding the issues unique to emerging companies, NVCA would like to work more closely with CMS to refine how CED can most safely and efficiently provide innovative new treatments to all Medicare beneficiaries. We would also like to participate in the activities of the Council for Technology and Innovation as a stakeholder in the life sciences industry.

We understand that CMS is presently working on a memorandum of understanding with FDA on data sharing between the two agencies. NVCA would like to work with CMS and FDA on the development of this proposal to help inform them on its potential impact on emerging companies and their development programs.

We look forward to working with you and CMS to help develop the next generation of medical breakthroughs. The twenty-first century will be the life sciences century, and the venture capital and private equity community will play critical roles in shaping and fueling that growth. We would like to meet with you at your convenience to outline an agenda and work plan to discuss how the NVCA can best serve as a resource to CMS.

Thank you for your attention to this matter.

Very truly yours,



Mark G. Heesen
President, NVCA

cc: Steve Phurrough, M.D.
Director, Coverage and Analysis Group

Organization: Novartis

(Comment on next page)

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June 6, 2005

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Re: Comments on *Factors CMS Considers in Making a Determination of Coverage with Evidence Development* Draft Guidance

Dear Dr. Straube:

On behalf of Novartis Pharmaceuticals Corporation ("Novartis"), we are pleased to submit these comments on the *Factors CMS Considers in Making a Determination of Coverage with Evidence Development* (CED) draft guidance document issued by the Centers for Medicare and Medicaid Services (CMS) on April 7, 2005.[1]

Novartis Pharmaceuticals Corporation is part of Novartis AG, a world leader in health care with core businesses in pharmaceuticals, consumer health, generics, eye-care, and animal health. Novartis shares CMS' interest in providing strong evidence to support the appropriate use of our products and give physicians and patients the information needed to make the most appropriate health care decisions. While we continue to have significant concerns regarding the lack of specificity provided in the initial draft guidance, we are pleased to be able to work with you collaboratively to achieve our common goal of improving the health status of Medicare beneficiaries. It is critical to more clearly identify when CED would be used by CMS, in order to ensure that it will not be a barrier to patient access to needed medications.

[1] Centers for Medicare & Medicaid Services. Draft Guidance for the Public, Industry and CMS staff: the Factors CMS Considers in Making a Determination of Coverage with Evidence Development. Issued April 7, 2005.

Given the concerns we discuss below, we encourage you to increase opportunities for public discussions with all stakeholders who have a vested interest in this issue, most importantly Medicare beneficiaries and the dedicated providers who furnish health care services to this vulnerable population. As part of this effort, we believe that CMS should hold additional open public meetings to discuss initial comments received and publish a second draft guidance document with further detail that would be open to additional comment. We also recommend that you extend any additional comment periods to at least 90 days to provide interested parties with ample opportunity to provide helpful comments.

With the rapid increase in medical technology and the complexity of treatment options, we strongly support the use of better evidence to help physicians and patients make treatment decisions and welcome this opportunity to provide recommendations to CMS on its initial draft guidance document. As requested by the agency, we have focused our comments on the four key areas raised in CMS' draft guidance document: 1) CMS' process for applying, developing, and implementing CED; 2) factors considered in applying CED; 3) evidence development methods; and 4) issues with implementation.

CMS' Process for Applying, Developing, and Implementing CED

Novartis believes that the application, development, and implementation of data collection requirements would be most effective if done through a process that includes input from independent clinical and research experts as well as stakeholders most affected by CED requirements, such as patients, providers, and manufacturers. The development of an independent and accountable process for defining individual CED initiatives as part of any national coverage review is crucial for giving CMS the breadth of information it needs to make appropriate decisions regarding CED. In addition, ensuring openness and transparency in the application of CED is in keeping with the broader Congressional mandate requiring CMS to provide a process for public comment and defined timeframes for the national coverage determination (NCD) process.[2]

Specifically, Novartis recommends that CMS develop a process for defining the appropriate application of CED in the NCD process when outstanding questions regarding the evidence evaluated would otherwise lead the agency to issue a broad noncoverage policy. Such steps might include:

- Rationale explaining the decision to apply CED for a specific NCD;
- Development of research questions that would be answered by the evidence required;
- Selection of an appropriate study design; and
- Implementation process, including financial responsibility for collecting the evidence, the criteria that will be used to judge when the data collection may end, and how the data collected under CED will be used and shared.

[2]Section 731 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Pub.L. 108–173, enacted on December 8, 2003)

As part of the public comment process, we recommend that CMS convene an independent committee whose role would be to advise the agency on when and how to apply CED requirements. The committee could review the appropriateness of each case in which CMS has proposed, as part of a draft NCD, to apply CED requirements and review the questions CMS seeks to answer through the required data collection. In the event that the committee recommends that the CED requirements are appropriate for answering CMS' outstanding questions, the committee could also recommend the most effective and efficient methods of collecting and analyzing the required data.

The membership of this committee should include clinicians, researchers, patient advocates and industry members to obtain the full range of perspectives needed to best assist CMS in its CED initiatives. In addition, committee meetings should be open to the public so that a wide range of perspectives could be heard before the committee submits its final recommendations to CMS.

Novartis recognizes the difficulty that CMS may have in developing an additional advisory committee, such as the potential regulatory burdens of establishing a committee compliant with the Federal Advisory Committee Act (FACA). Therefore, we suggest that CMS work within the existing structure of the Medicare Coverage Advisory Committee (MCAC) to form a CED subcommittee that would have the role and function described above.

Finally, we also note that the CED process may have the potential to involve other agencies, including the Food and Drug Administration (FDA). In keeping with the spirit of openness and transparency, we stress that the CED process must not lead to a decline in the collaborative relationships manufacturers have developed with FDA within the product approval framework. Rather, to ensure that the regulatory process serves the public most efficiently, we request that CMS include manufacturers in any discussions that may occur with FDA under the CED process. Not doing so could undermine the positive effects of open communication between manufacturers and the FDA and could set CMS and manufacturers on the wrong path moving forward.

Factors Considered in Applying CED

Clearly defining the circumstances under which CMS may consider applying CED is of critical importance to stakeholders most affected by CED requirements. CMS has made public statements suggesting that the application of CED will be "rare." We believe that this would only be the case in limited circumstances related to off-label uses of certain pharmaceuticals. We would like CMS to more explicitly specify in the revised draft guidance the areas it expects to apply CED moving forward. In addition, we would like CMs to clarify that NCD or CED will not apply to drugs covered under Medicare Part D. Below, we suggest specific circumstances we believe would be appropriate.

The draft guidance outlines a broad set of circumstances in which the agency might consider requiring additional data collection. We recommend that CMS limit the application of CED requirements to cases where a standing national non-coverage policy exists or where the agency would otherwise issue a national non-coverage determination, particularly for off-label uses of pharmaceuticals.. We believe that safety assessments should be the province of the FDA and that CED should not replace or duplicate this FDA role. Within these standing or potential non-coverage determinations, the potential usefulness of CED may be most appropriate in cases where the registration trials for a drug or device excludes patients that match the Medicare population *and* there is a plausible biologic reason for believing that the product may act differently or produce serious adverse reactions in Medicare patients. CED might also be useful as a way to explore the benefits of a product seen in an unplanned subgroup analysis of data in a completed trial or to expand the understanding of a treatment for a rare or orphan disease or condition that is currently non-covered.

We believe these situations represent the only type of NCDs where CED would constitute an expansion of coverage and would ensure that CED's stated goal of "enhancing access to medical technologies and services" is met. This would also allow for the local coverage process to remain as the primary area in which decisions regarding coverage of individual items and services continue unfettered and match the evolving practice of medicine in specific areas of the country, particularly for conditions where few treatment alternatives exist.

Conversely, we strongly believe that CMS should take care to not apply CED in situations that could infringe on the basic practice of medicine or compromise patient access to proven therapies. We note that the draft guidance indicates that CED could be applied as a way to determine the risks and benefits of an off-label use of a drug. Novartis recommends that CMS identify a specific concern raised by a particular off-label use of a product that is subject to a noncoverage determination before proposing a CED requirement, rather than developing CED requirements with the goal of broadly understanding the off-label use of a drug.

Finally, we urge CMS to finalize its criteria for coverage of "non-deemed" clinical trials under the June 2000 NCD (CMS 310.1). Finalizing these guidelines would open the possibility for beneficiaries to particpate in a wide range of clinical trials rather than narrowly selected NIH-sponsored trials.

<u>Evidence Development Methods</u>

As stated, Novartis recommends the development of an open and transparent process for defining CED requirements in order to increase the likelihood of identifying the optimal, least burdensome methods for collecting information. Novartis supports CMS' stated intention of "developing methods for conducting simple, inexpensive clinical studies" in cases where CED may be applied. It is critical that study designs are feasible, well-suited to providing the specific evidence CMS seeks, and create no undue burdens on physicians or patients. Therefore, we recommend that CMS choose the method for collecting the required data that is the most practical, effective and non-burdensome of those recommended by the independent advisory committee. Novartis also believes that these qualities should be part of the criteria for how data collection methods are evaluated by the independent review committee.

CMS should also consider other accepted research methods, including meta-analyses and modeling, for obtaining CED when it is determined that collecting data by other means is not logistically feasible or is overly burdensome. In such circumstances, CMS and stakeholders could work together to identify qualified research experts to determine if such alternative research methods are appropriate and, if so, exactly which methods should be applied.

We also note that the draft guidance suggests that randomized clinical trials (RCTs) may be one of the potential study designs for CED requirements. We are concerned with the potential ethical dilemmas that the use of RCTs in the context of CED could present. For example, requiring patients to be enrolled in an RCT in order for Medicare to provide coverage and payment may, in effect, coerce patients into participation. In addition, these patients may only have a fifty percent chance of receiving the treatment being studied in this context. Therefore, we ask CMS to consider the ethical issues that may be present when considering whether to require RCTs as a potential data collection method for CED.

Issues with Implementation

Novartis believes that the success of CMS' CED initiatives is contingent on the continued collaboration of all key stakeholders in ensuring that CED initiatives are properly implemented. Therefore, we recommend that CMS provide greater clarity in the revised guidance document on who will bear the financial responsibility for collecting the evidence; the criteria that will be used to judge when the data collection may end; and how the data collected under CED will be used and shared. One approach may be for CMS to describe in detail how these issues have been worked out for past NCDs in which CMS has chosen to require additional data collection.

For the revised draft guidance document, we recommend that CMS specify how the costs of collecting data under CED would be allocated across various stakeholders. CMS also notes that "There should be no redundancies in the data collection system." We fully support this objective. Novartis is committed to ongoing research on its products. We emphasize that a critical step in determining whether CED is appropriate will be gaining a complete understanding of the information that already exists or is already being developed about a particular product.

In our commitment to optimizing the breadth and depth of information available about our products to physicians, payers, and patients, Novartis routinely conducts a large number of post-market clinical trials and health economics/outcomes research studies. These studies may investigate new indications, evaluate the product against active comparators, or evaluate the safety, effectiveness, and economic impact of the product in actual practice settings. Therefore, *before* CMS makes an initial determination that CED should be applied, it must tap into existing industry knowledge and resources that describe current evidence and ongoing studies. Before applying a CED requirement, Novartis recommends that CMS contact the manufacturer to determine whether the data CMS seeks is already available or is already being collected. In these discussions, CMS must also protect the confidential nature of any discussions of proprietary research undertaken by manufacturers.

Manufacturers should be integrally involved in any CED evidence collection. This may be in collaboration with outside entities, but relying on outside entities alone, without any manufacturer involvement, would create serious administrative problems.

Finally, we are concerned about the potential costs of CED for providers. We recommend that CMS reimburse providers for data they must collect under CED. This is particularly important in cases where the study design chosen involves collection of data at the point of delivery. Physicians subject to these requirements may be required to implement new systems or capabilities in their clinic or office. Physicians who actively participate in research on a routine basis may have the administrative capabilities already built into their practices, but we believe it is only a minority of providers who fall into this category. We recommend that, as part of the CED planning process, CMS first evaluate the existing infrastructure for providers to collect data and determine the costs and burdens that may be associated with a potential CED requirement, and then consider alternative reimbursement methods which would best foster the collection of the additional data without creating undue hardships.

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Novartis appreciates the opportunity to provide recommendations on this guidance document. Should you have any further questions, please do not hesitate to contact me at (202) 662-4378.

Sincerely,

Bonnie Washington
Vice President
Health Policy
Novartis Pharmaceuticals Corporation

Organization: Pfizer

(Comment on next page)

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June 6, 2005

Pfizer Global Pharmaceuticals

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Re: Request for Comments on the Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED)

Dear Dr. Straube:

Pfizer is pleased to respond to the Centers for Medicare & Medicaid Services' (CMS') request for public comment on the *Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED)* draft guidance document.[1]

Pfizer is a research-based organization with considerable experience in applying objective data to clinical problems. Pfizer recognizes the value of scientific evidence and supports CMS' stated goal of providing Medicare beneficiaries and their physicians with clinical information to help them choose the best course of care. We also support the broader evidence-based medicine movement; we agree with its premise that clinical evidence is most effective when considered in conjunction with clinical judgment and individual patient values and experience.

CED requirements represent a significant departure from previous Medicare coverage policies, and Pfizer encourages CMS to provide multiple opportunities for public input as the agency pursues this new initiative. We recommend that CMS release a subsequent draft version of the CED guidance document, before applying new CED requirements in national coverage determinations (NCDs). The second revised draft guidance should be issued with a 90-day comment period. In addition, we encourage CMS to revisit the CED coverage guidance document each year to allow the public to stay abreast of the agency's current thinking and provide feedback on how new CED requirements impact stakeholders. An incremental approach to the development of the CED initiative may be the most effective way to meet the goals of the agency while minimizing the burden of CED requirements on patients, providers, and manufacturers.

Our comments included in this letter, in part, reflect our recent experience with CMS on the NCD for off-label uses of anticancer drug therapies for colorectal cancer.[2] The resulting NCD policy for colorectal cancer raised a number of concerns, including whether restricting coverage to CMS selected clinical trials constituted a meaningful expansion of coverage and the lack of

[1] Centers for Medicare & Medicaid Services. Draft Guidance for the Public, Industry and CMS staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED). Issued April 7, 2005.
[2] Medicare Coverage Issues Manual. Section 13-3 (Anticancer Chemotherapy for Colorectal Cancer).

public accountability in CMS' process for choosing the specified trials. Pfizer submitted comments on the draft NCD raising these issues and appreciate the efforts of CMS to address these concerns in the draft guidance on CED.

We welcome the opportunity to provide recommendations that will assist CMS in clearly defining the goals of CED and that reflect our shared goal of improving the health of Medicare beneficiaries. We have developed comments around each section of the draft guidance document and would like to emphasize the following overarching positions:

- The application of CED requirements is only appropriate in cases where there is a clear opportunity to expand coverage and the value the information will bring to patients and their physicians outweighs the costs of collecting the additional evidence

- The development and implementation of CED requirements must be done through an open and transparent process that addresses the financial and administrative impact CED requirements may have on manufacturers, providers, and patients, and the potential for data collection requirements to stifle innovation

- CMS' CED initiative should neither impede the agency's current policies to promote local coverage decision-making and cover clinically proven uses of off-label cancer drugs, nor overlap with the Food and Drug Administration's (FDA's) authority regarding questions of safety and efficacy

Recommendations for *Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED)*

Pfizer is pleased to provide CMS with the following suggestions on how CMS can best develop CED requirements for future NCDs. We have organized our comments according to sections of the draft coverage guidance document. We intend for these recommendations to complement comments to the draft guidance document submitted by the Pharmaceutical Research and Manufacturers of America (PhRMA) and by the Biotechnology Industry Organization (BIO), both of which we endorse.

Process for Deciding When and How to Apply CED

It is essential that CMS develop an open and transparent process that incorporates the perspective of and is accountable to beneficiaries and other stakeholders directly impacted by Medicare coverage decisions, such as drug and device manufacturers. As referenced above, Pfizer does not believe the agency's recent NCD on off-label uses of anticancer drugs for colorectal cancer allowed for meaningful public input, particularly in choosing the specific clinical trials in which to limit Medicare coverage. Although this draft guidance document attempts to address these concerns, we believe CMS still does not specifically define opportunities for the public, NCD requestors, or those directly affected by the CED requirements to provide input into the development and implementation of such policies.

Maintaining an open and transparent process is essential to the successful implementation of CED requirements

Pfizer recommends that CMS develop an explicit and accountable process for applying CED to individual NCDs and that this process be described in the suggested revised draft guidance document. This process should begin when CMS releases a draft decision memorandum that proposes CMS' intention to apply a CED requirement. The current NCD process could serve as a model for developing a separate CED process in that it guarantees a level of public involvement, predictability through specified timeframes, and access to expert opinions through the Medicare Coverage Advisory Committee (MCAC).

CMS should establish a similar standardized process for developing CED requirements and provide transparency and timelines around, and the opportunity for public input into: 1) the agency's decision to apply a CED requirement; 2) identification of specific remaining questions, including related endpoints and metrics, of most interest to CMS; 3) selection of a data collection system (or defining the criteria to select an appropriate method to collect evidence); 4) implementation (analysis of the impact, financial responsibility, and data sharing); and 5) use of data collected as part of the CED requirement. We recommend that this process fall outside of the mandated timeframes for the NCD process in order for CMS to develop a system that allows for meaningful input from all interested parties on CED requirements.

In developing and implementing new CED requirements, the independent authorities of FDA and CMS should be maintained; the FDA should continue to be recognized as the sole authority for determining safety and efficacy

Pfizer supports and shares CMS' mission to provide better clinical evidence to patients and physicians to improve the health of Medicare beneficiaries. We consistently demonstrate our commitment to this mission through the development of innovative therapies and continued research into our existing products and their most appropriate and effective uses in a wide range of populations, including Medicare beneficiaries.

Current law establishes the FDA as the sole authority to review clinical evidence for safety and efficacy.[3] Pfizer has a long-standing relationship with the FDA to ensure that the products that we develop and market meet the FDA's safety and efficacy concerns. We recognize that CMS, in turn, retains the authority to establish that an item or service is "reasonable and necessary" for payment in the Medicare program.[4] Pfizer believes that CMS' authority to develop coverage and reimbursement policies for the Medicare program should not overlap with the FDA's authority regarding safety and efficacy.

When appropriate, we have and will continue to engage with CMS and FDA as well as other government agencies; we believe that this type of flexibility and independence to work with each agency is critical to our business. Ensuring that manufacturers are part of any discussions between FDA and CMS is vital to retaining the openness of these relationships. Therefore, prior

[3] The regulatory process for securing FDA approval for new drugs is described in 21 CFR subchapter D part 312 and new devices in 21 CFR subchapter H part 860.
[4] Social Security Act 1862 (a)(1)(A).

to FDA approval, CMS should not consult with the FDA without informing the requestor(s) or subject(s) of an NCD. In the rare instances when both CMS and FDA are concurrently reviewing a technology, CMS should contact the manufacturer in an effort to develop study protocols that are consistent with the requirements of both agencies. The manufacturer should be a part of these discussions, as appropriate. Finally, the authority to establish post-marketing requirements for approved drugs should remain with the FDA and continue to be done in collaboration with manufacturers.

Factors Considered in Applying CED

One of the most important areas in which CMS must provide further clarity is the appropriate circumstance for CMS to apply a CED requirement.

CMS should apply CED requirements rarely in NCDs and only in circumstances when the alternative is non-coverage

Pfizer supports CMS' stated objective to apply CED rarely in NCDs and encourages the agency to clarify this in subsequent revisions of this draft guidance. At this time, the draft guidance articulates a broad range of opportunities for CMS to apply CED and offers no predictability for when this policy may transpire. Therefore, we recommend that CMS limit CED to circumstances where there is an existing non-coverage decision. If CMS is reviewing a technology that does not have an existing NCD, CMS should only apply CED requirements as an alternative to a non-coverage decision, for example when an intervention may pose significant side effects or toxicity, but may provide a clinical benefit when used for a serious disease. CED may also be appropriate when an external party, such as the National Institutes of Health (NIH), requests assistance in payment and enrollment of Medicare beneficiaries in sponsored clinical trials where the intervention is non-covered by CMS. Clinical trial sponsors commonly confront the challenge of low enrollment rates in clinical trials by elderly patients and CMS' CED policy may, in the limited circumstances described above, assist in encouraging such participation.

However, safeguards are necessary to ensure that all Medicare beneficiaries are treated equally. We recommend that if CED requirements include enrollment in a clinical trial, CMS allow local contractors to provide coverage of the item or service to Medicare patients who are unable to participate in the selected clinical trials. This is particularly important to Medicare patients unable to participate in the clinical trial due to either ineligibility based on the study's selection criteria or because of the geographic inaccessibility of trial sites. Forcing patients and physicians to participate in clinical trials in exchange for Medicare coverage without proper safeguards raises significant ethical concerns of equitable access.

The prominence of local coverage decision making should be maintained to ensure patient access to and physician choice of treatment options. Statutorily mandated coverage of off-label uses of anticancer medicines should not be subject to CED requirements

Medicare's existing policies, such as the prominence of the local coverage process, and statutory requirements of covering proven off-label uses of anticancer drugs maintain CMS' stated goal of

ensuring patient access to and physician choice of appropriate therapies.[5] Therefore, Pfizer recommends that CMS assess the potential impact that each new CED requirement may have of eroding the success of the local coverage process and statutorily mandated coverage of off-label uses of anticancer drugs.

In general, CMS should consider the impact on beneficiaries and providers of applying CED requirements when there are remaining questions on the off-label uses of a drug. Particularly in the area of off-label uses of drugs for the treatment of cancer, imposing CED requirements is not appropriate because it would limit physician and patient choice in ways that are incongruent to current medical practice. Oncology relies on off-label uses of anticancer drugs to identify important innovations in effective treatments for patients. In fact, a 1993 policy statement issued by the American Society of Clinical Oncology (ASCO) notes that the National Cancer Institute (NCI) has stated the most beneficial uses of chemotherapy drugs are often discovered after FDA approval for a labeled market indication.[6] Therefore, we encourage CMS to be sensitive to how current policies encourage innovation (and the potential for new CED requirements to stifle innovation), particularly in area of oncology.

CMS should develop sector-specific guidance on the appropriate circumstances for the application of CED and criteria for what constitutes "reasonable and necessary"

Finally, CMS should issue sector specific circumstances for when CMS believes CED requirements would be necessary. Decisions of whether or not to apply CED ideally should be driven by the type of questions that remain after CMS has reviewed a body of evidence to determine whether the item or service is reasonable and necessary. It is well accepted that the feasibility of developing rigorous clinical evidence differs by the type of technology. For example, for both practical and ethical reasons, conducting the type of study that is the gold standard in clinical evidence, a double-blind, randomized controlled trial (RCT) is more difficult for many surgical interventions.[7] Already, drugs have a high evidentiary threshold for FDA approval where approval for marketing is given only after completion of two well-controlled RCTs (or a large multi-center trial) demonstrating the safety and clinical efficacy of the drug.

The draft coverage guidance does not adequately address these differences and makes broad sweeping statements regarding the quality of evidence of a technology that CMS may review as part of the NCD process. For example, as stated earlier, we believe that CMS is neither the appropriate agency, nor has the authority to apply CED requirements when outstanding questions of clinical efficacy and safety exist for drugs. These questions are best answered and fall under the authority of the FDA. Therefore, we recommend that CMS recognize the individual characteristics of specific types of interventions such as drugs, devices, surgical interventions, and diagnostic technologies by developing more specific circumstances for when CED will be

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[5] The Social Security Act (SSA) was amended by Congress to extend uniform Medicare coverage of off-label uses of anticancer drug therapies as part of the Omnibus Budget Reconciliation Act (OBRA) of 1993. The Medicare Carriers Manual, Part 3, Chapter II, 2049 describes the congressionally mandated coverage of anticancer therapies.

[6] ASCO Policy Statement on Coverage of Unlabeled Drug Indications, < http://www.asco.org/ac/1,1003,_12-002334-00_18-0010803-00_19-0010805-00_20-001,00.asp>.
See also: http://www.asco.org/ac/1,1003,_12-002217-00_18-0010345-00_19-00-00_20-001,00.asp.

[7] Piantadosi, Steven. (1997) Clinical Trials: A Methodologic Perspective. New York: Wiley-Interscience.

applied for each. Subsequently, CMS should clarify in future guidance documents the evidentiary standards and factors CMS uses in determining if a health technology or service is "reasonable and necessary" for these various types of technologies.

Evidence Development Methods

We appreciate CMS' acknowledgement of the inherent difficulty in answering questions of clinical effectiveness through data collected outside the context of a RCT, such as through observational studies and registries. We encourage CMS to weigh the type of evidence collected through CED requirements with whether it advances the goal of providing useful information to patients and physicians.

A formal analysis of each CED requirement should be conducted to weigh the value of collecting the additional information relative to the burdens it places on stakeholders and restrictions on beneficiary access

In considering the application of a new CED policy, CMS should analyze the potential impact that the CED requirement may have on beneficiaries, physicians, other health professionals, and manufacturers. Excessive CED requirements could lead to increased costs of health technologies and, ultimately, result in slowing the pace of medical innovation. Pfizer recommends that the implementation of CED be driven by a formal analysis similar to regulatory impact analyses conducted as part of the rule-making process.

This analysis should assist CMS in determining whether the additional information collected as part of a CED requirement represents a worthwhile investment relative to the burdens it places on stakeholders and restrictions imposed on beneficiary access. We strongly encourage the agency to convene a working group of academic researchers, clinicians, manufacturers, and patients to further discuss how CMS may conduct this type of analysis. Another approach would be to conduct a value of information (VOI) analysis, which can assist CMS in determining whether the information and the time involved in collecting additional evidence is worth the cost and time required to obtain it.[8]

An independent third party should provide technical expertise to CMS on the appropriate application of CED and necessary data collection systems

Regardless of the final approach chosen by CMS, the analysis to inform a CED requirement in a NCD should be conducted for CMS by a qualified, independent third party with transparent and explicit opportunities for public comment. This independent third party could assist CMS in defining appropriate circumstances for the application of CED and provide technical expertise in data collection systems and methods that would minimize the burden of CED to all stakeholders. One approach would be to create a standing subgroup of the MCAC to serve in this function. If done appropriately, Pfizer believes that CED may provide additional evidence to enhance physician and patient decision-making. However, if done improperly and without considering all stakeholder perspectives, it could create an undue burden that may ultimately fail to provide useful information in a timely and cost-effective manner.

[8] Claxton, K, J. Cohen, and P. Neumann. "When is Evidence Sufficient?" *Health Affairs*. 24, no. 1 (2005):93-101.

Finally, we acknowledge that CMS has historically not used economic (cost and cost-effectiveness) information in making Medicare coverage determinations. Pfizer supports the agency's current separation of the evaluation of the effectiveness of a technology for the Medicare population from its decision on the level or method of reimbursement of the technology. Cost should remain a factor used by Medicare solely for the purpose of payment and reimbursement.

We recommend that CMS provide ample opportunity for the public to comment in a separate process on the complex issue of incorporating economic information into the agency's reimbursement decisions. One approach would be for CMS to convene a public meeting and task force to discuss how economic information should be standardized and used appropriately by Medicare and other payers. When considering economic data, it is critical that CMS consider the impact that a product or service may have on a beneficiary's *total* Medicare health expenditures (Medicare Parts A, B, and D).

Process for Study Design and Implementation

CMS has not provided specific details on the administrative requirements and financial responsibilities associated with CED implementation or how CMS or others may use the data collected as part of a CED requirement.

CED initiatives should complement other research already being conducted, as identified by manufacturers, professional societies, providers, and researchers

Pfizer is already engaged in a variety of post-marketing and evidence development activities. Because of this, at a minimum, CMS should not duplicate efforts that already exist to provide high-quality evidence to physicians and patients and should work with manufacturers, professional societies, providers, and researchers that currently conduct this type of research.

CMS should clarify who will be financially responsible for collecting additional information required through CED and how the agency will determine when enough evidence has been collected in order to terminate CED requirements

In the revised draft guidance, we ask that CMS provide further information on the range of appropriate funding mechanisms for CED. Although this may differ for individual NCDs, it is important for the public to understand the types of contractual relationships that CMS anticipates developing in order to finance CED requirements. It will also be important for CMS to understand when it may be adding an additional and undue burden to a manufacturer's research and development costs that may, ultimately, increase the cost of health technologies.

Pfizer also asks CMS to clarify in the revised draft guidance how it will determine when enough evidence has been collected through CED; what constitutes a "stopping rule;" and when a reconsideration of coverage is necessary. We recommend that once CED requirements are proposed in a decision memorandum, CMS state how it intends to use the evidence collected. For example, whether CMS intends to develop appropriate dissemination tools (e.g. educational

materials, peer-reviewed journal articles), generate additional research hypotheses, or for future reconsiderations of the NCD.

CMS should evaluate early CED initiatives to determine whether they meet the agency's goal of improving physician and patient decision-making

Our final recommendation is for CMS to establish a mechanism to evaluate the effectiveness of CED in providing additional evidence to bolster physician and patient decision-making. For example, each year in CMS' report to Congress on the NCD process, the agency's Office of Research, Development, and Information (ORDI) could conduct an internal evaluation of CED initiatives. Alternatively, CMS could contract with an independent entity to review CED policies on an on-going basis. The criteria for the evaluation of CED must include the process for developing CED requirements, their implementation, and their success in meeting the goal of improving beneficiary and physician healthcare decision-making. CMS should publish reports evaluating the CED initiative at least every three years.

Conclusion

Pfizer appreciates the opportunity to provide specific recommendations to CMS on the *Factors CMS Considers in Making a Determination of Coverage with Evidence Development (CED)* draft guidance document. Please feel free to contact me directly at 212-733-6973 with any questions, or if you need additional information on our above comments.

Sincerely,

Cathryn M. Clary, MD

cc: Herb Kuhn, Director, Center for Medicare Management
Steve Phurrough, MD, MPA, Director, Coverage and Analysis Group

Organization: PhRMA

(Comment on next page)

PhRMA

Richard I. Smith
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June 6, 2005

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Dear Drs. Straube and Phurrough:

RE: Draft Guidance on Factors CMS Considers in Making a Determination of Coverage with Evidence Development

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit comments on the Draft Guidance on Factors CMS Considers in Making a Determination of Coverage with Evidence Development by the Centers for Medicare and Medicaid Services (CMS). PhRMA is a voluntary, nonprofit organization representing the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives.

We would like to begin by emphasizing the importance of Medicare coverage, and stating our intent to work collaboratively with CMS in developing policy guidances that improve the clarity and predictability of the national Medicare coverage process and that promote improved beneficiary access to innovative and medically appropriate care.

I. Introduction

The policy approach set out in this Draft Guidance document—extending national coverage in the context of protocol-specified prospective data collection—appears to have merit in some instances where Coverage with Evidence Development (CED) genuinely represents an expansion of coverage for Medicare beneficiaries and provides evidence to inform CMS coverage decisions.

In addition, we appreciate several of the steps CMS has taken in this Draft Guidance to assure the public of its commitment to working "intensively and carefully with all affected stakeholders." We applaud this step toward active engagement with stakeholders in coverage policy, and we look forward to interacting with the agency. Further, we are re-assured by the agency's statement in the Draft Guidance that required data collection will be tied closely to the agency's statutory authority for making coverage decisions.

However, the Draft Guidance also raises significant questions and concerns that we hope CMS can address in the next iteration of this document. In some circumstances described in the Draft Guidance, the proposed CED policy appears to unnecessarily condition coverage and restrict beneficiary access (for example, where evidence already demonstrates efficacy), impose substantial new administrative burdens on providers and reduce predictability of national coverage decision-making. The potential impact on the clinical research enterprise is of particular concern in areas like oncology and off-label uses of anticancer therapies, where medical progress often is achieved through a series of advances, each of which is incremental, and the role of new therapies evolves rapidly. In addition, the Draft Guidance has the potential to inadvertently increase current coverage barriers facing Medicare beneficiaries and oncologists in the area of off-label use of anticancer therapies.

II. General Recommendations

Before providing more detailed comments on the Draft Guidance, we are making six basic recommendations to CMS as it works to finalize this CED guidance:

1) Revise and reissue the Draft Guidance reflecting comments received, with an additional public comment period. Given the importance of this matter, extended public input can only serve to improve the guidance and generate support for the eventual product.
2) Maintain and strengthen beneficiary access to cancer drugs by:
    a. removing coverage barriers that appear to be eroding access protections to off-label use of cancer therapies enacted by Congress in 1993;
    b. maintaining coverage without conditions as an option for beneficiaries in these circumstances; and
    c. maintaining local coverage as an option if it is already available.

3) Clarify for stakeholders the statutory basis for coverage with evidence development. We appreciate language in the Draft Guidance describing CED as intended to inform CMS coverage decisions and linking it to statutory authority under Sec. 1862(a)(1)(A) for making determinations of whether items and services are "reasonable and necessary." However, other goals of CED described in the guidance, such as imposing research protocols in order to alter provider behavior, appear to conflict with this. The guidance should focus use of CED on development of evidence needed by CMS to make determinations of whether an item or service is "reasonable and necessary." The data collected in these circumstances must be essential to ensure that the new technology is "reasonable and necessary."
4) Establish a more clearly defined set of circumstances for use of CED in cases where it genuinely expands coverage (e.g., the item or service otherwise is subject to a national non-coverage policy) to gather evidence needed to make coverage determinations. Stakeholders need to know clearly where CED is an avenue to coverage. Consistent with the goals stated in the Draft Guidance, the circumstances for CED use should be limited to such situations.
5) Describe the circumstances in which CED would not be applied. CED should not be applied to proven medical interventions already backed by high levels of evidence. Use of CED in these instances could result in reduced beneficiary access and impose unnecessary burdens on oncologists and other providers.
6) Establish a clear, open process for designing and implementing CED research protocols. This process should include early opportunities for learning about alternative research, defining appropriate research questions, and discussing best approaches to answering these questions.

III. Specific Comments

The Draft Guidance raises a significant number of issues, and it requests the public to comment on over 25 distinct questions following an explanation of CED and the circumstances in which it is intended to be used. We understand CMS' desire for stakeholders to provide specific responses to these questions, and we will endeavor to be as specific as possible in our comments. However, as described below, the Draft Guidance leaves a number of fundamental concepts concerning the application of CED vague, undefined and inconsistent. As a result, it is more difficult to provide responses to the specific questions the Draft Guidance poses. More clearly defining the fundamental approach toward CED in the guidance will not only help stakeholders provide meaningful responses to the questions the Draft Guidance poses, but, more importantly, will provide the predictability that guidance documents are intended to provide.

For this reason, we urge CMS to commit to revising the Draft Guidance in light of public comments and reissuing it as a revised draft.

Our specific comments on the Draft Guidance follow:

A. Beneficiary Access

As indicated by CMS in the Draft Guidance, the proposed CED policy could have a significant application to prescription medicines and other medical interventions used for off-label indications under the current Medicare program. In order to accomplish the goal of "faster and broader, more effective access to new medical technologies" that CMS has specified in the guidance we urge the agency to take several specific steps to: a) address the apparent emergence of barriers to beneficiary access to medically appropriate off-label uses of anticancer medicines, b) expand beneficiary access to medical interventions in clinical trials, and c) protect existing beneficiary access to medically appropriate off-label uses of anticancer medicines and other interventions.

Off-label use of anticancer medicines is an essential aspect of caring for cancer patients.[1] Maintaining local flexibility in coverage of off-label cancer therapies is particularly important for a number of reasons. Because new anticancer medicines must be supported by strong prospective clinical data in order to gain FDA approval, it is appropriate to maintain the ability of treating physicians to apply these medicines in the most medically appropriate ways to meet the needs of individual patients.

Once approved, a cancer drug's role in caring for patients can evolve rapidly for a number of reasons. For example, the cancer stage at which a therapy is provided can change; a medicine's mechanism of action may indicate it may be effective against tumor types other than those for which it is approved; a drug approved based on its effect against one biological target may be found in subsequent research to be effective against additional targets; and a medicine's place in multi-drug chemotherapeutic regimens often evolves.[2] The current, vigorous clinical research enterprise in oncology is continually developing new evidence to inform these changes in medical practice.

In the Omnibus Budget Reconciliation Act of 1993 (OBRA '93), Congress revised the Medicare law to help ensure that beneficiaries do not face barriers to coverage of anticancer medicines prescribed for medically appropriate off-label uses. The statute provides for Medicare coverage of off-label uses of anticancer medicines that are supported by listings in recognized compendia or findings from recognized peer-reviewed journals.[3] Enactment of these changes was prompted by findings by the

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[1] The National Cancer Institute states: "Frequently the standard of care for a particular type or stage of cancer involves the off-label use of one or more drugs." (NCI "Q&A: Off-Label Drugs," accessed at http://www.nci.nih.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5, May 31, 2005). The American Society of Clinical Oncology notes: "The off-label uses of approved drugs have been an important tool for advancing the treatment of cancer." (ASCO, "Off-Label Drug Indications, accessed at http://www.asco.org/ac/1,1003,_12-002275,00.asp, May 31, 2005.

[2] National Cancer Institute, *Ibid.*

[3] *See* GAO, "Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies" (Sept. 1991) (GAO/PEMD-91-14) (report to the Chairman, Sen. Comm. on Labor and Human Resources) ("GAO Report"), at 4. As a result of the GAO findings, Congress amended the Social Security Act as part of the Omnibus Budget Reconciliation Act of 1993 (OBRA '93) to extend uniform Medicare coverage to off-label uses of anticancer drugs and biologicals.

Government Accountability Office that Medicare beneficiaries were facing barriers to medically accepted off-label uses of anticancer therapies.

Address current barriers to beneficiary access:

Medicare beneficiaries appear to encounter barriers to access to anticancer medicines for medically appropriate off-label uses that should be covered under current law. These barriers would remain unaddressed or, potentially, inadvertently increased under the new Draft Guidance.

Preliminary results of an in-depth survey of 40 oncologists and oncology practice managers conducted for PhRMA by the research group Covance indicate that coverage and reimbursement barriers affect access for a significant number of patients, with Medicare beneficiaries facing more significant barriers than cancer patients covered by private insurance. We look forward to discussing these findings with CMS in more detail in the near future when this report is finalized.[4]

Expand beneficiary access to interventions in clinical trials

To further advance CMS' goals of developing clinical evidence and expanding beneficiary access, we recommend that the agency complete implementation of its policy on covering routine patient care costs in clinical trials by issuing final guidelines to guide identification of "non-deemed" trials (those not automatically covered as "deemed" trials, such as trials conducted under an investigational new drug application) that should receive coverage under the policy. Until final guidelines are issued, there is no mechanism to certify that a non-deemed trial satisfies the applicable criteria. Though it is possible that the new policy on "Coverage with Evidence Development" might in some instances expand coverage, Medicare could achieve this same end through implementation of its existing policy on clinical trials coverage.

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[4] While these results are based on a relatively small sample of providers, they nonetheless warrant further research and consideration of steps by CMS to ensure patients under Medicare have full access to appropriate cancer care.

For example, in the Covance survey "fifty-three percent of oncologists [interviewed] report that Medicare non-coverage frequently or very frequently interferes with their clinical decision-making; only 29 percent of oncologists report that private payer policy frequently interferes." This finding echoes findings from the Government Accountability Office (GAO) survey in 1991, which reported: "[t]he third-party payers most frequently cited by oncologists as causing them to alter their preferred treatments were Medicare claims processing contractors."
The findings suggest that Medicare beneficiaries may face coverage barriers even for uses of anticancer medicines backed by compendia listing or recognized peer-reviewed literature. For example, "several oncologists who submit claims for off-label use report that Medicare may deny payment for physician-administered therapies even if the diagnosis is compendia-accepted," and "many oncologists reduce payment denials from their respective local Medicare carrier by using therapies for off-label diagnoses that are accepted by drug compendia."

Protect Current Beneficiary Access Under CED:

The Draft Guidance states that CED is not intended "to reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program" and CMS "do[es] not anticipate circumstances under which CED would represent a net reduction in coverage available under existing local coverage policies."

Local coverage pathways should be maintained for beneficiaries while data collection is ongoing under CED. However, some of the practical effects of this policy could work to undermine this goal and the Draft Guidance should be revised to avoid this result. For example, some patients may be unable or unwilling to participate in clinical trials or registries (e.g., certain patients may be ineligible to participate in a clinical trial due to its exclusion criteria, or they may be unable to travel to trial sites, or reluctant to participate because they would need to change doctors or because they are not assured of receiving in the trial the treatment they seek). Patients might also face access restrictions if their providers are not able to participate in the data collection system due to extra costs not reflected in Medicare's payments.[5]

In discussing the colorectal cancer drug NCD, CMS also states that "[t]he national coverage linked to data collection again represents a net expansion of coverage because it ensures that all contractors would provide coverage for any patient enrolled in the NCI trials, while also leaving in place the current discretion available to contractors in coverage [of] off-label, unlisted uses of anti-cancer drugs in other settings." The practical effect of such an approach may or may not be a net expansion of coverage. While it may lead to some expansion by assuring coverage for patients enrolled in the trial, it is also possible that the existence of the trial could encourage local contractors to deny more claims of these off-label uses outside of the trial, resulting in a net reduction in coverage. CMS should carefully monitor local access outside of CED protocols to ensure that this essential coverage option is not undermined.

To support net expansions in coverage, we urge CMS to maintain coverage without conditions as an option for national decisions, and to clearly state in the guidance that when local coverage is available patients will continue to have this option for receiving anticancer medicines and other therapies.

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5 CMS has stated that data collection instruments should be designed to minimize burdens on providers and patients (p. 14). Nevertheless, the discussion of "Process for Study Design and Implementation" at pp. 13-14 of the Draft Guidance suggests that participating in a data collection system might be a costly undertaking. For example, "[e]ach evidence development enterprise should appoint an individual with appropriate clinical, scientific and technical expertise to oversee all aspects of the data collection," "[p]roviders involved in the evidence development enterprise must be educated about the reasons for the study, receive training about data collection, and be informed of all aspects of the study's purpose and design," and "[t]here should be a data auditing system to ensure data integrity for continuous quality improvement." At the same time, increasing provider payments to account for the costs of participating in the data collection enterprise may also have drawbacks; besides increasing costs to CMS, it would also increase beneficiaries' copayments.

B. Goals for CED

As stated at the outset, we believe the concept of coverage with evidence development may have merit under certain circumstances. However, it remains unclear what CMS' exact goals are and whether this policy is the most appropriate approach for achieving them. neither the specific goals that CED seeks to achieve nor whether this policy is the appropriate vehicle is clear. CMS should reissue the guidance as a revised draft document to more clearly articulate its goals and explain how CED will achieve them.

On the first page of the Draft Guidance, CMS states that "[t]he primary purpose of obtaining additional evidence through CED is for the agency's use in making payment determinations," i.e. that a treatment is reasonable and necessary. PhRMA had recommended such clarification in its pre-guidance input, and, while further clarification is needed as discussed below, we appreciate the initial steps taken in the Draft Guidance.

At the same time, other statements in the Draft Guidance, as well as recent public comments by CMS officials, indicate purposes for the policy other than coverage decision-making. For example, a CMS staffer at the Open Door Forum held by CMS May 9 appeared to contradict the Draft Guidance, stating "In many instances, the data will be used only to inform physicians and patients, and to generate more specific questions that we can then design a trial around."[6]

In addition, the guidance itself describes goals beyond that of making coverage determinations. For a number of reasons discussed below, the national coverage process is not well-suited to achieving these goals. Seeking to achieve them via CED could inadvertently make it more difficult for Medicare beneficiaries to obtain access to medically appropriate interventions in the current Medicare program. In addition, for the broader type of research agenda described by CMS, it is important to establish a priority-setting mechanism that is independent of payment policy decision-making. Additional goals identified by CMS include:

1. CMS states in the Draft Guidance, "This evidence will also assist doctors and patients in better understanding the risks, benefits and costs of alternative diagnostic and treatment options" ; factors such as the difficulty of addressing "practical" questions in a pre-market clinical trial setting "highlight the value of a systematic expansion of practical clinical research efforts to address the information needs of health professionals and patients"; CED will "provide useful information to doctors and patients faced with complicated clinical decisions and the need to personalize those decisions for individual patients." While we fully support development of good information to support patient and physician decision-making, we believe other, more effective mechanisms are available to CMS to achieve that objective. We discuss some of these in more detail below and would be pleased to continue working with CMS in this area. CMS data collection for purposes other than making determinations of reasonableness and necessity

[6] "CMS Plans Limited Use of 'Coverage With Evidence Development' Option," *The Pink Sheet,* Vol. 67, No. 20, May 16, 2005, p. 15.

of items and service – the statutory basis for CMS coverage decision-making – should properly occur outside of coverage policy.

2. The Draft Guidance states that "care provided under these [data collection] protocols generally involves greater attention to appropriate patient evaluation and selection, as well as the appropriate application of the technology" ; certain services may be reasonable and necessary for a patient only "when specific data is collected and reviewed by the provider at the time the service is delivered," which data "would be used to support appropriate treatment decisions for such patients" ; "CMS may decide that the service is reasonable and necessary only in the context of additional data collection, because the additional care in clinical decision-making and monitoring of the patient offers greater assurance that the benefits of receiving the service will exceed the risks." We disagree with the suggestion that care provided by physicians in the absence of CMS-required data collection protocols would not be reasonable and necessary because the data collection requirements are needed to make physicians more careful and attentive.

C. Linking the CED policy to "reasonable and necessary"

We appreciate the statements CMS makes in the Draft Guidance linking CED to its statutory authority under Section 1862(a)(1)(A) to make determinations of whether items or services are reasonable and necessary. At the same time, we believe some of the new interpretations do not fit within the concept of reasonable and necessary.

First, the Draft Guidance seems to confuse the evidence needed to determine reasonableness and necessity with other types of evidence for decision-making by patients and clinicians. The Draft Guidance at certain key points seems to equate or replace the concept of reasonable and necessary with that of "evidence to support decision-making by patients and clinicians." For example, CMS says it expects to apply CED "in specific cases where better evidence to support decision making by patients and clinicians is an essential part of reaching a conclusion that a treatment is reasonable and necessary." As stated in our pre-guidance comments, the evidence needed to define the threshold of reasonableness and necessity for Medicare coverage purposes can be dramatically different from "better evidence" for physician/patient decision-making. Better evidence for physicians and patients is an important goal, but requiring it as a condition of coverage could inadvertently restrict beneficiaries' access to care (if a service is only made available in CMS-approved protocols or if national CED has the practical effect of increasing local coverage denials) and reduce predictability for product researchers. The data relied on by CMS to make coverage decisions is one valuable component of evidence to support individual decision-making. However, when evidence to support individual decision-making goes beyond that needed by CMS to make a coverage decision, it should be pursued through other means such as those discussed below.

In addition, the Draft Guidance mixes the evidence needed to determine whether an item is reasonable and necessary with other reasons for collecting data. On page 9, the Draft Guidance states CMS "will consider requiring data collection as a condition of coverage

when additional information is needed for CMS and its contractors to determine if an item or service is reasonable and necessary." Moreover, the same section of the Draft Guidance states that CED will initially focus on topics "where there is substantial agreement that better evidence would be valuable in expanding access to specific technologies and services while learning more about their risks and benefits to support shared decision-making." The Draft Guidance does not explain how collection of evidence in order *to determine* reasonableness and necessity relates to policy articulated elsewhere in the guidance (and described above) of requiring data collection *to assure* provision of the item and service is reasonable and necessary. We strongly recommend that CMS focus the guidance on describing the evidence it will seek via CED in making determinations of reasonable and necessity and delete or revise discussion of other research activities that are not directly relevant to the coverage decision.

D. Alternative Vehicles for Research

Development of additional evidence for patient and physician decision-making is an important goal and one that PhRMA fully supports. However, use of national Medicare coverage policy as described in the Draft Guidance is not the appropriate mechanism for advancing a federal research agenda that does not bear on national coverage decisions. As described above, we are concerned CED has the potential to inadvertently restrict beneficiary access to medically appropriate care, enter into treating physicians' decisions about the care of individual patients, impose new administrative burdens on oncologists and other caregivers, and reduce the policy predictability that is needed to support medical innovation.

In addition, use of Medicare coverage policy to define a broader research agenda could result in research weighted towards CMS' decision-making needs, while patients and physicians may have different perspectives. Priority setting for research outside of national coverage decisions should be conducted independent from coverage policy.

CMS has policy mechanisms available to it outside of the national coverage process to collect additional evidence that is useful but not directly connected to coverage determinations. We recommend it use these mechanisms to achieve broader research goals and remove those goals from the Draft Guidance itself. For example, CMS could make extra payments to providers that collect certain data without conditioning coverage of the underlying treatment on data collection (as in the current demonstration project paying physicians to collect certain information on the care of cancer patients), or establish other demonstration projects. We believe that these mechanisms are superior for purposes of achieving CMS' objectives because they avoid the concerns about patient access restrictions, minimizes the burden on physicians, and compensates them for the additional administration requirements of the initiative.

Additionally, Section 1013 of the Medicare Modernization Act establishes a research program to improve the quality, effectiveness and efficiency of care provided to patients under Medicare, Medicaid and SCHIP. It also mandates an open public process for setting research priorities. The initial research agenda focuses on priority diseases and

conditions. If appropriately implemented to examine the full range of medical interventions and the broader health care system in which they are used, such research can provide the kind of evidence CMS identifies to support decision-making by patients and physicians and improve health care quality and efficiency.

To the extent that CMS seeks alternative vehicles for such research, we recommend that it employ an open, transparent process for priority-setting similar to that established under Section 1013.

By pursuing its research goals through other means, CMS can advance these goals while reducing the risk of inadvertently restricting Medicare patients' access to promising therapies.

E. Defining Circumstances for Linking Coverage with Data Collection

General approach to defining circumstances for CED:

In the Draft Guidance, CMS identifies two general circumstances for the CED approach. These circumstances are based on the level and quality of clinical evidence that is available prior to coverage decision-making. These circumstances include: (1) situations where an intervention is promising—but has yet to have been demonstrated conclusively as bringing about an improvement in health outcomes; and (2) situations where there is evidence that an intervention has already been demonstrated to improve health outcomes in a broad population of patients.

In the second circumstance, in which an intervention has been proven in a broad population, we believe CMS should not impose CED as a condition of coverage. These items and services have already demonstrated their effectiveness. This does not mean that this information would not be of interest to CMS—only that its collection is not essential to finding these items and services to be "reasonable and necessary." Therefore, data collection in these instances should not be made a condition of coverage.

In the first circumstance, where an intervention appears clinically promising, use of CED may be of value in certain circumstances, but CMS should ensure it uses this approach in ways that do not inadvertently disrupt current coverage options for Medicare beneficiaries or impose burdensome data collection requirements on providers involved in the care of patients.

We support CMS' description of a category of medical interventions that appear promising but are not yet fully proven. Indeed, such a category is implicit in Section 1862(a)(1)(A) in that it directs Medicare not to make payment for items and services that *are not* reasonable and necessary for treatment of an illness or injury. Thus, Medicare is authorized to make payment for items and services that may be reasonable and necessary but clinical evidence is not yet conclusive. Many such items and services are represented in the over ninety percent of Medicare coverage that occurs at the local level (for example, procedures that enter use apart from the FDA approval process), and PhRMA

believes it is important to maintain beneficiary access to and continued evidence development for these items and services through the local coverage process. Removal of the local coverage option and imposition of general non-coverage with access provided more narrowly through coverage with evidence development would represent a significant net reduction in beneficiary access that should be avoided.

Thus, as an important policy principle, if Medicare coverage is already an option for beneficiaries for a particular item or service (for example, via local Medicare carriers or fiscal intermediaries), CED should only be implemented as a supplement to, not a replacement for, the existing local coverage option.

Specific circumstances in which CED may be imposed:

The Draft Guidance states that the CED policy is intended to be used in limited circumstances. We appreciate that, operationally, CMS intends to continue to use the national coverage process for a very small number of coverage decisions. However, the Draft Guidance also posits "the value of a systematic expansion of practical clinical research efforts," and lists nine circumstances in which "coverage with data collection might be valuable." These circumstances are so broad they apply to a very large proportion of medical items and services currently in use, and certainly every coverage review that would be initiated by CMS. As a result, the Draft Guidance does not clarify when CMS believes CED is or is not appropriate and seems out of step with statements elsewhere in the document and by agency officials that CED will only be used in limited circumstances.

CMS should establish a more clearly defined set of circumstances in which coverage with evidence development can help answer coverage-relevant questions related to the reasonableness and necessity of an item or service. These circumstances should focus primarily on use of CED to provide initial coverage of items and services that are currently subject to national non-coverage policy. Where CMS seeks to use CED beyond this primary focus, it should be used as a supplement to existing local coverage options so that beneficiary access is not restricted.

Consistent with the "value of information" approach described in the Draft Guidance, the circumstances described below would be among those where development of additional data would be of higher value to address gaps in evidence and inform CMS coverage policy.

Criteria for application of CED in such circumstances could include:

- Off-label uses of items and services that have been in use for a sufficient period of time to establish their role in patient care, for which medical appropriateness has not already been established through compendia listing or peer-reviewed research, and for which similar research is not already ongoing or planned;

- New items or services not supported by prospective clinical research for any indication, for which development of such data is not likely to be addressed through other means;

- Development of evidence on interventions for rare diseases in instances where similar research is not being pursued or is not feasible in a premarket setting;

- Currently available items and services not subject to FDA regulation for which:

  - Significant controversy has arisen regarding their role in patient care, and this controversy can not be adequately address via local coverage decision-making;

  - Interpretation of credible, new peer-reviewed evidence indicates that changes may be warranted in current policies and local coverage processes are unlikely to resolve or address these concerns; and

  - Basic evidence on effectiveness is insufficient or not available.

Specific circumstances in which CED would be excluded:

We also strongly recommend that CMS establish criteria to define when CED *is not* necessary prior to describing criteria for when CED *is* necessary. Such criteria will be important to ensure local carriers are not discouraged from issuing local coverage determinations.

Specific circumstances for which CED would not be used include:

a) Proven technologies (e.g., medicines approved by FDA based on prospective clinical data demonstrating the product to be safe and efficacious). New medicines typically must be supported by rigorous randomized clinical trials in order to gain FDA approval. FDA's approval standard is among the most stringent in the world and should continue to provide an adequate basis for making a new medicine available as an option for physicians and Medicare beneficiaries;

b) Medically accepted indications for anti-cancer medicines as established under Section 1861(t)(2)(B) of the Social Security Act. Congress has established baseline of reasonable and necessary uses of anticancer medicines to include many "off-label" uses. Particularly in light of the potentially significant access barriers described above, CMS should clarify in the guidance that uses recognized by Congress as reasonable and necessary (i.e., those listed in recognized compendia, supported by research in recognized peer-reviewed journals, and other uses generally accepted as standard of care) are not subject to CED restrictions.

c) Off-label uses of newly introduced medicines. Based on the extensive data required by FDA for approval, the unique aspects of innovation in and off-label use of medicines described above, and the rapid evolution in the role of new medicines in patient care that often occurs, CMS should not apply CED until the role of a new therapy is more clearly established (two to three years after introduction). At such time the appropriate coverage-relevant research questions can be more easily identified. Attempting to do so earlier increases the likelihood that data collection efforts would pursue questions that are not as useful to CMS by the time they are answered.

d) Other items and services for which research already is underway or is planned that would answer the research questions identified by CMS as the rationale for a CED decision.

F. Other Factors Identified by CMS Related to CED

The Draft Guidance identifies certain other issues that lead to tying data collection to coverage. Such issues, while important to consider, are not appropriately addressed via coverage policy and should not be included in the guidance.

1. ***Payment Policy.*** The first paragraph of the Draft Guidance (p. 2) states that additional evidence is needed for "making payment determinations," and that the "document focuses on why we are collecting this data for Medicare payment purposes." We assume that CMS intended to use the term "coverage determinations," in that it defines the term as whether the item or service is reasonable and necessary. We suggest that to improve consistency the guidance use the terms "coverage determinations" and "Medicare coverage decision-making" purposes.

2. ***Safety.*** PhRMA and its member companies are committed to regulatory policies that provide strong assurance of product safety. As stated in our May 6 comments on CMS' Draft Guidance on initiating national coverage decisions, regulatory responsibility for drug safety rests squarely with the Food and Drug Administration. This is a unique, safety-focused regulatory structure not applicable to most health care services. In its September 2003 *Federal Register* notice on the national coverage process, CMS notes that the agency "adopts FDA determinations of safety and effectiveness."[7] Current language in the Draft Guidance could undermine the recognition of FDA's responsibility for assuring the safety of pharmaceuticals and other FDA regulated products. To the extent that CMS would like to explore steps to support FDA in its safety mission, we recommend it do so via formal rulemaking consistent with FDA's statutory authority and through a transparent, collaborative process with FDA and non-governmental stakeholders A change of this magnitude should not be pursued via a guidance document that interprets a Medicare statute.

[7] September 2003 Federal Register Notice, at 55,636.

3. ***Utilization.*** The Draft Guidance — in discussing the purpose of linking coverage with a requirement for data collection (p. 4) — states that: "Care provided under these protocols generally involves greater attention to appropriate patient evaluation and selection, as well as the appropriate application of the technology. These additional data may alter the course of patient treatment...and may lead a physician to reconsider the use of the item or service or otherwise alter a patient's management plan, potentially improving health outcomes."

It is problematic to initiate research with the goal of changing provider treatment choices and, apparently or reducing utilization of a service before results of the research are available. We understand if CMS believes that data gathering is needed to answer specific outstanding questions relating to the covered intervention. However, the research protocol itself should not be used as a means to restrict access to the intervention.

G. Elimination of Coverage without Conditions

CMS states it does not anticipate issuing additional decisions that grant coverage without conditions or restrictions. As stated above, in order to maintain and improve beneficiary access to appropriate items and services, we believe it is important to maintain national coverage without restrictions as an option for patients under Medicare. This is also important from the standpoint of encouraging innovation by improving predictability – innovators need to understand when they have sufficient data for a new product to be made broadly available to Medicare beneficiaries. Under the policy framework described by the Draft Guidance, that threshold of sufficient evidence for broad coverage is unclear at best.

H. Using CED to Answer Coverage-Relevant Research Questions: Evidence Development Methods

Premature or inappropriate interpretation and use of evidence to inform coverage or other policy decisions could result in inadvertent, unwarranted limitations on patient access to medicines or other medical technologies or have an adverse effect on downstream health and economic outcomes. For example, conditioning coverage of off-label uses of cancer chemotherapies during a required period of evidence collection could have significant ramifications for patient access and might create disincentives for physicians and manufacturers to expand the evidence base to inform patient care and coverage policy.

As CMS implements CED, it will be critically important for the agency to identify appropriate methods to answer specific evidence questions and to apply these methods in ways that do not create new restrictions on access to medically appropriate care. CMS in its Draft Guidance identifies four main potential study designs: 1) databases (registries), 2) longitudinal or cohort studies, 3) prospective comparative studies (also called practical clinical trials or PCTs), and 4) randomized clinical trials (RCTs). The circumstances under which any of these types of studies might be appropriate under CED depend on the specific coverage-relevant research question being asked. PhRMA would be pleased to

meet with CMS to provide additional background in this area and answer specific questions posed in the Draft Guidance.

I. Requirements for Coverage Determinations

In addition to introducing new definitions of reasonable and necessary care for purposes of Medicare coverage, the Draft Guidance also employs but does not define several important concepts related to the types of evidence needed to demonstrate that an item or service is reasonable and necessary. In addition, there appears to be some inconsistency in the terms used in the Draft Guidance. The agency states that it intends to "discuss in greater detail the interpretation of 'reasonable and necessary' in the context of coverage determinations in future guidance documents." As CMS works to finalize the April 7 Draft Guidance, we recommend use of a common set of consistently defined terms related to standards of evidence. In addition, we note that use of undefined terms leaves significant unanswered questions about how the policy would work and its impact on beneficiary access and medical innovation. Such terms include: comparative effectiveness; improved health outcomes; improved net health outcomes; "sufficient inference of benefit"; and cost outcomes such as "long-term risks and benefits, quality of life, utilization, costs, and other real-world outcomes." Undefined terms such as these raise particular concern in areas such as cancer therapy where innovation often occurs incrementally but over time adds up to dramatic gains in life expectancy for patients with many types of cancer.

J. Process for implementing coverage with evidence development

PhRMA supports CMS intention to seek broad public input in its application of CED as described in the Draft Guidance's section on process, as well as the agency's request for additional input in this area. We recommend that this section be revised and expanded to ensure a transparent, collaborative process is established.

This section of the Draft Guidance should reference CMS' pending guidance on the agency's process for initiating national coverage decisions and explain how the two guidances would interact.

The Draft Guidance describes some options for seeking public input on one key aspect of the process – priority setting. As stated above, CED should be limited to instances where data collection can help provide evidence needed to demonstrate an item or service to be reasonable and necessary. In this context, priorities for imposition of CED should be guided by the specific factors CMS describes that would lead to a CED decision. Early public input in these instances should focus on how well CMS' proposed uses of CED in individual coverage reviews meet these factors.

To the extent that priority setting relates to a broader CMS research agenda to answer questions not directly related to collection of evidence needed for a determination of reasonableness and necessity, broader public input is critically important. For this type of broader research, we recommend that CMS work with other relevant federal agencies and

public stakeholders to develop options for independent priority setting with broad stakeholder input.

Additional public input on use of CED to answer coverage-relevant questions:

Public input will be important at several additional points beyond priority setting. Some of the concerns that have arisen over the initial CMS uses of CED cited in the guidance for implantable cardioverter defibrillators, colorectal cancer drugs and positron emission tomography scanning (such as lack of clarity over the research questions CMS is seeking to answer, how the required protocol will answer those questions, whether it is redundant to other research, and whether it is the best approach to answering the questions) could potentially be avoided via a clearer, more open process.

PhRMA urges CMS to describe specific mechanisms for public input on:

- The appropriateness of proposed CED decisions (this could be accomplished, for example, by CMS posting draft proposals for coverage with evidence development prior to issuance of a draft decision memo, potentially as part of its list of items for which it is considering initiating national coverage reviews as described in its March 9 guidance on opening national coverage decisions);

- Collaboration with stakeholders on appropriate research questions to be answered and the most appropriate, least burdensome means to answer them. This could potentially be achieved through smaller workshops with relevant stakeholders or input on CMS draft documents.

- Opportunities for private-sector alternatives. CMS should seek broad input on whether there exists ongoing research in the private sector that would make CMS-mandated studies redundant. It also should provide an opportunity for private-sector alternatives to CMS mandated CED.

- Evaluation and reporting of results. A clear, independent mechanism is needed for evaluation and reporting of results, particularly considering the broad range of research methods described by CMS. This should include reporting on how research conducted under the CED improved Medicare beneficiary access to items and services.

K. Limitations on Data Use and Privacy

In connection with its data collection activities, CMS needs to identify how it will comply with laws relating to the confidentiality of health information including, but not limited to, the Health Insurance Portability and Accountability Act (HIPAA). Under HIPAA, CMS is a covered entity as are the providers who deliver treatment and who are tasked with the data collection effort. While providers may disclose protected health information (PHI) for payment purposes, to the extent objectives are unrelated to

payment purposes for the particular provider's patients, and are research related, release and use of such data is much more constrained in its ability to obtain such data and to use such data. In particular, CMS may not condition treatment or payment on the provision of an authorization for research.[8] Research is defined in the privacy rule as "a systematic investigation, including research development, testing, and evaluation, designed to contribute to generalizable knowledge."[9] As stated in the Draft Guidance, there is a value to a systematic expansion of practical clinical research efforts to address the information needs of health professional and patients." (p.4) CMS may not request data from providers for research purposes without a patient authorization, subject to certain other conditions. CMS should identify how it intends to comply with the HIPAA privacy rule requirement.

L. Procedural Issues

Section 731 of the MMA provides that CMS "shall make available to the public the factors considered in making [NCDs] of whether an item or service is reasonable and necessary," by "develop[ing] guidance documents . . . in a manner similar to the development of guidance documents under section 701(h) of the [FDCA]."[10]

Much of the Draft Guidance focuses on data collection activities designed to achieve broader goals not directly connected to determinations of whether an item is reasonable and necessary. In this regard, the Draft Guidance exceeds the policy scope described in Section 731. The broad CED policy envisioned by the Draft Guidance is not an "interpretive" rule exempt from formal rulemaking requirements because the draft goes well beyond "interpreting" the reasonable and necessary language in the Medicare statute. Therefore, we recommend that CMS focus the Draft Guidance on describing the factors it considers in making national coverage decisions of whether an item or service is reasonable and necessary.

In addition, as activities under the Draft Guidance would impose significant paperwork burdens on providers, CMS should solicit comment on this burden consistent with the Paperwork Reduction Act.

M. Conclusion

PhRMA appreciates this opportunity to provide input on CMS Draft Guidance on implementing coverage with evidence development. The document represents an important new initiative that could have a significant impact on Medicare beneficiaries' access to medicines and medical technologies under the current Medicare program.

The proposal for use of CED may be of use in some circumstances, particularly in cases where it allows for limited coverage of an item or service currently subject to national

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8 45 C.F.R. § 164.508(b)(4)

9 45 C.F.R. § 164.501

10 Social Security Act § 1862(l)(1).

non-coverage. At the same time, the Draft Guidance could inadvertently result in new limits on beneficiary access to medically appropriate care and the existing clinical research enterprise.

To help address these concerns, we urge CMS to maintain coverage without conditions as an option, protect local coverage options, and establish a transparent, collaborative process of use of CED.

As CMS works to revise the Draft Guidance, we also ask the agency to clarify its statutory basis for CED; limit its research activities under CED to those within its authority for coverage decision-making under Sec. 1862(a)(1)(A) and examine other mechanisms for achieving research goals outside the scope of coverage policy; establish a more defined set of the circumstances in which CED would and would not be imposed; clarify the basis or rationale for establishing and validating study designs to answer these questions, and explain how the new evidence will be incorporated into revised coverage policy, as appropriate.

We respectfully request that CMS reissue the Draft Guidance as a revised draft that addresses the questions and concerns identified above and by other stakeholders. We look forward to continuing working with CMS to implement policies that can remove existing barriers in access to cancer care and work towards appropriate application of CED as a policy tool to further expand beneficiary access.

Sincerely,

Richard I. Smith

Organization: Reimbursement Principles, Inc.

Our firm, Reimbursement Principles, Inc., works with small medical device innovators. We assist them to develop coding, coverage and payment for new technologies with both Medicare and the commercial health benefit plans.

We believe that the draft guidance regarding coverage with evidence development (CED) is a step in redressing the serious imbalance among all health care policy makers, including but not limited to CMS, between coverage for "old" versus "new" diagnosis and treatment procedures. We strongly believe that CED should be applied to the entire spectrum of technologies and services.

We suggest a method for deciding priorities for the application of CED to existing technologies and services: Medicare's largest expense categories should be the first to be converted to CED status. As a corollary to that, we believe that new technologies below a certain level of expense should be accorded automatic CED status following FDA approval or clearance. There is much appropriate emphasis within CMS policymaking these days on "practical." We think the ultimate in practical is to tie the need for evidentiary scrutiny of a technology or service to its financial impact on the Medicare program. It does not make sense to keep new technologies and services with minimal financial impact off the market while old technologies and services with a much higher financial impact continue to escape any evidence based scrutiny.

The CED guidance document recognizes that Medicare payment for certain technologies and services will be essential in order to develop the evidence necessary for an evidence based coverage decision. It is possible, even likely, that a major expense category will be eliminated for lack of adequate evidence to support coverage, thereby allowing more promising but as yet little used new technologies and services to develop.

Organization: Sage Health Management Solutions, Inc.

I am a member of Medical Alley's Board of Directors and saw the submission for comments on your Draft on Coverage on Evidence Development. As I read through both the Draft document and the comments from Medical Alley/MN Bio, I realized that someone at CMS might be interested in the Internet technology that we have at Sage Health Management Solutions. We have an Internet tool that could be used universally by Providers to order services with Decision Support that conveys whatever Evidence that a Local Review organization uses or the National Coverage standard is for whether or not a specific patient would be eligible for a service. It could also be used for data collection (in advance of knowing the proper standard) in order to determine what might be the proper evidence for a service. Our Decision Support tool is very extensible and scalable and might help in your efforts to "standardize" the service delivery using Evidence-based medicine. The tool is usually paid for by either a payer or large integrated delivery system and made available for free to the end users (physicians and other practitioners).

If you are interested, we could organize a web-demo or even a visit to show you how it works and what it might be able to do to help in your efforts. I know this note is cryptic, but it is hard to know who at CMS would be a good contact. Thanks for your attention.

Organization: sanofi-aventis

(Comment on next page)

Hugh M. O'NEILL
Vice President

June 6, 2005

Dr. Steve Phurrough
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mailstop C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

Re: Draft Guidance on Factors CMS Considers in Making a Determination of Coverage with Evidence Development

Dear Dr. Phurrough:

Sanofi-aventis[1] appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) draft guidance on "Factors that CMS Considers in Making a Determination of Coverage with Evidence Development."[2] As one of the companies with a colorectal cancer therapy that has actually been subject to an early example of "coverage with evidence development" or CED, we believe we have a unique perspective on some of the issues raised by this initiative. We support CMS' efforts to provide more transparency to the CED initiative, and we hope that the final guidance document will strike the right balance between evidence, accountability and reasonableness needed to ensure that beneficiaries' access to important advances in health care is preserved.

Sanofi-aventis supports the concept of evidence-based medicine (EBM) and CMS's goal of using CED *selectively* to facilitate more rapid access to new technology under the Medicare program. In support of this goal, we offer the following recommendations:

[1] These comments are submitted on behalf of Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, which are both part of the sanofi-aventis Group.
[2] Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Making a Determination of Coverage with Evidence Development, April 7, 2005 (hereinafter, "Draft Guidance").

1. The guidance should clearly state (a) that the scope of CED is limited to a very small number of cases that would otherwise result in a non-coverage determination, and (b) the extent of data collection that could be required;

2. The guidance should emphasize the role of the local coverage process as the primary means for beneficiary access to new technology, and to permit local coverage while other areas or specific indications are subject to a CED data collection process;

3. The guidance should focus primarily on providing CMS with a clearer basis for making targeted Medicare coverage decisions, not broader clinical decision-making of physicians;

4. The guidance should be modified to better delineate and acknowledge the unique roles and responsibilities of CMS, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH);

5. The guidance should ensure that every aspect of the CED standards and process requirements are as specific, transparent and predictable for relevant stakeholders, as possible;

6. The guidance should include a process and a timeframe for defining the data collection objectives, analysis and appropriate releasing of the results of each CED project, including the final coverage determination; and

7. CMS should republish the revised guidance, and offer the public further opportunity to comment, before the CED guidance is finalized or any further NCDs requiring evidence development are initiated.

A more detailed explanation of these recommendations, and the concerns underlying them, is set forth below.

1. The guidance should clearly state (a) that the scope of CED is limited to a very small number of cases that would otherwise result in a non-coverage determination, and (b) the extent of data collection that could be required.

(a) When CED will be Applied

Clarification of scope. Sanofi-aventis recommends that CMS clarify in the guidance that CED will be used only if the criteria to open a national coverage determination are met and only when that process would otherwise have resulted in a determination of noncoverage. For example, CMS should make clear that CED will not be used to limit coverage that is provided pursuant to specific provisions in the Medicare statute. Under provisions enacted by Congress in the Omnibus Reconciliation Act (OBRA) '93, anti-cancer drugs are covered for on-label indications as well as for off-label uses, if the use is approved by one of the approved compendia, or if the use is supported by clinical research that appears in one of a list of peer-

reviewed medical journals.[3] At the Open Door Forum on CED (May 9, 2005), CMS officials stated that that CED would not be applicable to services that are not eligible to undergo an NCD, including items or services covered through a specific statutory provision or FDA–approved indications for covered cancer drugs. Sanofi-aventis was pleased to hear that statement, and we recommend that CMS state this explicitly in the next draft of the guidance to ensure that beneficiaries and other stakeholders have accurate information about how CED is likely to impact the coverage of anti-cancer therapies.

Elimination of cost and utilization references. We also recommend that CMS remove provisions in the guidance stating that CMS will use CED in circumstances where a particular technology raises cost or utilization concerns. Specifically, in the guidance CMS states that data collection might be valuable if "assessment of important outcomes has not been evaluated in the available clinical studies," including "long-term risks and benefits, quality of life, utilization, costs, and other real-world outcomes."[4] CMS can already use existing claims processing mechanisms to gather cost and utilization data. Further, CED is not the appropriate vehicle for such an initiative. CED is a tool of the national coverage process, and is triggered only when the outcome would otherwise be noncoverage. CMS should not turn CED and the coverage process into a mechanism for impairing beneficiary access to safe and effective therapies because the agency has questions about cost or utilization.

CMS public statements. During the referenced Open Door Forum, CMS officials affirmed that CED would be used only for technologies for which the criteria to open an NCD are met, and only in cases where the NCD would have resulted in a lack of national coverage under Medicare. Such statements are consistent with language in the draft guidance stating that the agency "[does] not anticipate a substantial number of new coverage decisions in the near future that apply the data collection requirement."[5] Sanofi- aventis is encouraged by these statements, particularly given CMS' ongoing efforts to clarify the factors that the agency will consider in opening an NCD and to preserve a role for the local coverage process.[6]

Conflicts among statements and guidance language. The above statements appear to be in conflict with other provisions in the draft guidance that suggest a more expansive use of CED, and we recommend that CMS resolve these conflicts in favor of the public position described above. For example, CMS states in the guidance that it may use CED in cases "where a particular medical intervention has been demonstrated to improve health outcomes in a broad population of patients," but where the evidence would only be considered "adequate" if specific data is collected and reviewed by the provider at the time the service is delivered.[7] It is unclear from the guidance what types of interventions would fall into this category, or how CMS will monitor its implementation (*i.e.*, whether physicians are actually reviewing the data

[3] Section 1861(t)(2) of the Social Security Act (2005).
[4] Draft Guidance, at 9.
[5] Draft Guidance, at 2.
[6] *See* Draft Guidance for the Public, Industry, and CMS Staff: Factors CMS Considers in Opening a National Coverage Determination, March 9, 2005.
[7] Draft Guidance, at 6.

at the time that the care is provided). We are concerned that the provision suggests that proven interventions could be subject to CED.

Criteria for CED topics. CMS states in the guidance that the agency is "aiming to identify a small group of high priority pilot efforts on topics for which there is substantial agreement that better evidence would be valuable in expanding access to specific technologies and services…", and that the agency commits to working with a broad range of stakeholders to help identify these priorities.[8] Although we are pleased that the agency is pledging to work with stakeholders in identifying criteria for CED, these particular statements suggest that CMS is actively seeking out topics for CED instead of just using CED as part of the NCD process to ensure more rapid beneficiary access to a new technology or service that would otherwise be deemed to be noncovered. We urge CMS to revise the guidance so that it more clearly and consistently communicates to stakeholders that CED will be used only in the context of an NCD that would otherwise have resulted in non-coverage.

(b) The Extent of Data Collection that could be Required Under CED

Clarification of scope of data collection. CMS should clarify the extent of data collection that could be required under CED. Sanofi-aventis is pleased that CMS is seeking to implement CED in a way that imposes "no unnecessary costs" and ensures that data collection continues only as long as "important questions remain, and that it is determined that the effort and resources required to collect this data are justified by the potential value of the information that will be generated."[9] We agree that in some cases, there may be value in collecting additional evidence. However, there should be consensus among the medical community and stakeholders regarding the question to be researched and the appropriate data needed to answer the question.

Parallel research enterprise and resource concerns. We are concerned that CED could be implemented in a way that greatly expands the evidentiary burden associated with ensuring beneficiaries access to the latest treatments. Clinical research is currently supported and monitored by entities such as NIH, the Centers for Disease Control, the Agency for Healthcare Research and Quality (AHRQ), academic institutions, the Department of Defense, and private companies and organizations. We believe it is unnecessary for CMS to create a parallel research infrastructure, which could end up diverting scarce research dollars toward accomplishing potentially more narrow objectives associated with Medicare coverage. If CMS decides that additional data is needed to approve coverage for a particular intervention, CMS should first rely on research that is already being conducted.

Expanded Medicare program support and beneficiary impact. If CMS determines that additional research is needed, the responsibilities for funding the additional studies or data collection should be determined up front, as part of the NCD process. CMS should include in the guidance a policy that the cost to beneficiaries of accessing an intervention through CED

[8] Draft Guidance, at 9.
[9] Draft Guidance, at 5.

cannot be greater than the beneficiary would have paid for that service if it were not subject to additional data collection requirements associated with CED. Further, CMS should be willing to support the cost of data collection from the agency's administrative or research and demonstration budget. We also hope that CMS will consider opportunities to provide coverage for the intervention targeted by CED, as well as for the routine clinical trial costs if the evidence development involves a clinical trial.

2. The guidance should emphasize the role of the local coverage process, the primary means for beneficiary access to new technology, and to permit local coverage while other areas or specific indications are subject to a CED data collection process.

Value of the local coverage process for technology review and dissemination. We are pleased to see provisions in the guidance document that appear to affirm the value of allowing new health interventions to be disseminated through the local coverage process. This is consistent with the recent NCD on Coverage of Colorectal Anti-Cancer Drugs Included in Clinical Trials, in which CMS clearly states that "contractors shall continue to make local coverage determinations for medically accepted uses of off-label indications." We encourage CMS to reiterate that position in the current draft guidance. Additionally, CMS states that many types of practical questions associated with coverage decisions and clinical decisionmaking are difficult to answer in a pre-market setting and are "best addressed in actual medical practice, where actual conditions of use and patient characteristics may differ significantly from those in a pre-market formal clinical trial."[10] CMS also states in the guidance that it is not the intent of CED to "reduce the importance or frequency of local coverage determinations as a pathway by which new technologies are made available in the Medicare program."[11] We agree that the local coverage process can be an important mechanism for gathering further information about the efficacy of a particular treatment. CMS should state more clearly in the guidance that the agency will continue to rely on the local coverage process for diffusion of new technologies, and that CED will be an option only in cases where some type of national coverage determination is appropriate in order to ensure expanded beneficiary access to a therapy.

Continuation of the local coverage process when CED project initiated. When CMS decides to use CED for a particular technology, the agency should, to the extent possible, allow local coverage to continue during the data collection process in areas (or for beneficiaries) not participating in the studies or data collection efforts, or for indications not under consideration through CED. It is common for Medicare contractors to cease providing payment for interventions that are the subject of a pending NCD. Therefore, CMS must provide clear instructions to all stakeholders – particularly to contractors and providers – to ensure that beneficiaries can continue to access needed therapies during the data collection period.

[10] Draft Guidance, at 4.
[11] Draft Guidance, at 6.

Assuring beneficiary access to promising new therapies. CMS should ensure that CED does not have the unintended consequence of reducing access to the latest, cutting edge therapies, particularly in the case of anti-cancer drugs. Under current Medicare policy, local carriers have the discretion to cover medically accepted uses of anti-cancer drugs, including off-label uses that are not covered pursuant to the statutory coverage provisions enacted as part of OBRA '93.[12] If CMS does not preserve this route of local coverage even when a particular use is being further examined at the national level through CED, beneficiaries could be forced to participate in one of the trials included in CED in order to have access to the drug. For many beneficiaries, participation in a CED clinical trial is not a viable option. The presence of multiple co-morbidities and functional limitations are key reasons why the elderly are often denied participation in clinical trials.[13] For those who want to participate in a trial, they may not be physically located near a participating trial site (a particular concern for rural beneficiaries), or their customary provider may not be participating in a covered clinical trial. If CMS is questioning national Medicare coverage for a particular therapy and imposes CED to gather further evidence, the agency should at a minimum continue local coverage while the CED is pending to avoid reducing coverage to beneficiaries not able to participate in the clinical trials included in the CED.

3. The guidance should focus primarily on providing CMS with a clearer basis for making targeted Medicare coverage decisions, not broader decision-making of physicians.

Provider clinical decisionmaking algorithms are *not* the focus of CED. CMS states that one of the primary goals of CED is to facilitate better clinical decision-making by providers. Although we support the concept of evidence-based medicine, we do not agree that CED should be focused on assisting physicians with clinical decisionmaking. Such algorithms are best developed by expert groups who can assess information from multiple studies and sources. Further, many patient-specific and other variables, both clinical and non-clinical, are taken into account by physicians as they decide on an appropriate course of care for a particular patient. Many if not most of these variables are outside of the scope of a CED project. Coverage determinations should not direct or interfere with physicians making appropriate recommendations to patients based on their best clinical judgment. If impacting upon clinical decision-making is a stated goal of CED, the agency risks having the coverage process be viewed as inappropriately influencing or attempting to influence clinical care decisions.

4. **The guidance should be modified to better delineate and acknowledge the unique roles and responsibilities of CMS, FDA, AHRQ and NIH.**

"Safety and efficacy" are not part of CMS's statutory authority. CMS states in the guidance that "substantial safety concerns or potential side effects that are inadequately described in the available clinical literature" provide a potential area where additional data

[12] Medicare Benefit Policy Manual (CMS Pub. 100-2), ch. 15, §§ 50.4.2 and 50.5.
[13] *See* Joy H. Lewis et al., "Participation of Patients 65 Years of Age or Older in Cancer Clinical Trials," *Journal of Clinical Oncology*, Vol. 21, No. 7 (April 1, 2003), pp. 1383-89, 1388.

collection through CED might be valuable. The U.S. Congress has designated the FDA as the agency in charge of ensuring that drugs and devices are not brought to market until they have been proven to be safe and effective (and an assessment of side effects is inherent in making a determination regarding whether or not a drug is safe enough to be marketed to the public). We do not believe that CMS has the resources to duplicate FDA's mission. If a product has been approved by the FDA as safe and effective, CMS should rely on that decision, as the agency has done in the past, and should instead concentrate its resources on ensuring that beneficiaries have the same access to FDA-approved products as do patients not on Medicare.

CMS reliance on other research sources. Similarly, the guidance sets forth provisions concerning when additional data collection requirements will be imposed through CED, and what types of additional studies might need to be conducted. As mentioned above, we already have a comprehensive infrastructure in place to facilitate and oversee the conduct of clinical research in the U.S. CMS should ensure that CED is structured in a way that does not duplicate the research mission of NIH, and the primary role that NIH and other research institutions play in determining the nation's clinical research priorities. To the extent possible, CMS should rely on research that is already being conducted by NIH and through other major research initiatives.

5. The guidance should ensure that every aspect of the CED standards and process requirements are as specific, transparent and predictable for relevant stakeholders, as possible.

Involve a broad range of stakeholders in the decision about whether to apply CED. Sanofi-aventis appreciates the efforts of CMS, through this draft guidance, to provide more clarity to stakeholders about the scope of CED. If CMS is considering a national coverage review that could include CED, the agency should try to involve all potential stakeholders (including nurses, social workers, and case managers, in addition to manufacturers, beneficiaries/beneficiary advocacy groups, providers and clinical researchers) in iterative discussions about the additional types of evidence that are needed to support coverage; how best to collect this information (including from ongoing trials and other existing data collection mechanisms); how additional data collection will be funded; when data collection will end; and when stakeholders can expect a decision on further coverage.

Solicit meaningful input early in the process. Stakeholders should be solicited for input early in the process - if possible, before CMS makes the formal decision to open a NCD and to use CED. This preliminary review should be specified in the announcement of the proposed CED project to ensure that the comment period specified in the law is focused on the very specific elements of a particular CED, i.e. research objectives; study protocol and scope; timelines and expected publication of findings. Including independent research stakeholders early in the process will also ensure that research activities will adhere to industry data standards across all data sources and provide clarity and transparency with respect to database rules and design. This is critical to ensuring that the scientific community has confidence in the information that is gathered through CED.

6. The guidance should include a process and a timeframe for defining the data collection objectives, analysis and appropriate release of the results of each CED project, including the final coverage determination.

Absent in the guidance is information on who will have access to the data, what intermediate information and monitoring will be provided, how the study data will be analyzed and reported, and -- most importantly -- whether a particular CED results in an expansion of coverage for beneficiaries. The recent NCD covering off-label use of colorectal cancer drugs was issued as an expansion of coverage. We understood that local coverage was expected to be continued and the new coverage allowed in the nine NCI trials was provided *in addition* to any coverage provided at the local level. When that NCD was pending, we expressed concerns that the NCD could result in a reduction in benefits and additional co-payment costs. We understand that this was not CMS's intent, and we look forward to hearing positive results at the conclusion of those trials.

Before considering CED in the first place, CMS should specify which beneficiaries are having difficulty accessing the therapy and how the application of CED is expected to increase patient access to it. Then, as part of evaluating the impact of CED as a policy as well as disseminating to the public the results of a particular CED, CMS needs to monitor and report on the impact of CED on patient access. Both of these processes should be set forth clearly in the guidance

7. CMS should republish the revised guidance, and offer the public further opportunity to comment, before the CED guidance is finalized or any further NCDs are made requiring evidence development.

We hope that CED will ultimately become a tool for providing more rapid beneficiary access to innovative therapies. But the issues raised in this draft guidance are numerous, and we believe it will require more than one draft to resolve the concerns of the various stakeholders. We recommend that CMS consider this draft guidance document to be the first draft, and commit to providing the public with at least one more opportunity to comment before the guidance is finalized or any further NCDs requiring evidence development are initiated.

Conclusion

Sanofi-aventis appreciates this opportunity to share our concerns about the draft guidance document on CED. We ask CMS to consider our recommendations to clearly limit the scope and application of CED; reiterate the importance of the local coverage process; focus on providing appropriate data; limit duplication of FDA, NIH, and other research organization's responsibilities; provide transparency, participation, and predictability in the CED process and resulting determinations; and provide a revised guidance document for further public comment. We believe these recommendations will help ensure that CED is implemented to provide more rapid beneficiary access to important therapies. We look

forward to working with CMS on its efforts to clarify and improve the national coverage determination process.

Finally, during our discussions about the NCD for off-label uses of certain colorectal cancer drugs, CMS indicated its interest in exploring ways to increase the participation of the elderly in clinical trials. We would be happy to work with you to explore ways to achieve this important goal.

Please contact me if you have any questions or if we can be of further assistance.

Respectfully submitted,

Hugh O'Neill
Vice President, U.S. Integrated Health Care Markets

cc: Dr. Barry Straube, Chief Medical Officer and
Acting Director, Office of Clinical Standards and Quality

Dr. Louis B. Jacques, Coverage & Analysis Group

Organization: Society for Women's Health Research

On behalf of the Society for Women's Health Research, we are responding to the Centers for Medicare & Medicaid Services (CMS) solicitation of comments on the Draft Guidance for the Public, Industry, and CMS Staff on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development." We appreciate having this opportunity and hope that you will take our comments into consideration.

The Society is the nation's only not-for-profit organization whose mission is to improve the health of all women through research, education and advocacy. We advocate for increased funding for research on women's health; encourage the study of sex differences that may affect the prevention, diagnosis and treatment of disease; promote the inclusion of women in medical research studies; and inform women, providers, policy makers and media about contemporary women's health issues.

As CMS makes decisions about extending national coverage for items and services with coverage linked to a requirement for prospective data collection (or "coverage with evidence development"), we urge the agency to ensure that any such data collection includes the study and examination of biological sex differences between women and men. As noted in the draft guidelines, there are many cases in which the benefit of a technology or service will be evident in a specific patient population, such as women and minorities. In order for members of these groups to benefit accordingly, the appropriate data collection and analysis must be performed to ensure that any important sex differences are understood and can be factored into CMS's reasonable and necessary coverage decisions.

Scientists have long known of the anatomical differences between the sexes, but only within the past decade have they begun to uncover significant biological and physiological differences between the sexes. Sex differences have been found everywhere from the composition of bone matter and the experience of pain to the metabolism of certain drugs and the rate of neurotransmitter synthesis in the brain.

In April 2001, the Institute of Medicine (IOM) of the National Academy of Sciences released a report entitled, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" The report, initiated and supported by the Society and released by the National Academy of Sciences, found that sex differences important to health and human disease occur in the womb and throughout the life span, affecting behavior, perception, and health.

Regardless of the IOM report and efforts by the scientific community to include women in clinical research, it is challenging to get participants to enroll in clinical trials. For fifteen years, the Society has worked to increase the number of women in medical research. Several years ago, we launched our "Some Things Only A Woman Can Do" campaign to educate women about and encourage them to participate in clinical trials. Recently, the Society has added to this campaign to address issues related to the elderly women population served by CMS, which we believe is of critical importance since there

is very little data on women and drugs and devices in this age category. The Society has discussed with CMS the benefits that this expanded educational program may provide to coverage with evidence development. With the Society's expertise and experience running the previous "Some Things Only A Woman Can Do" campaign, we would be delighted to run a 1-year program focusing on elderly women and clinical trials.

The draft guidance specifically asks questions to be addressed by the Public. The Society has several comments to provide in two areas: "Factors Considered in Applying CED" and "Evidence Development Methods."

Factors Considered In Applying CED

The Society believes that sex differences criteria are critically important for consideration in applying coverage with evidence development decisions as medical research data has repeatedly shown. Several recent studies have revealed significant sex differences between men and women in the treatment and diagnosis of various diseases. For example, the CMS draft guideline mentions colon cancer. In a May 2005 study conducted by the University of Michigan, the National Cancer Institute, the University of Minnesota Cancer Center, the National Naval Medical Center and the Walter Reed Army Medical Center, it was determined that sex differences between men and women exist with respect to this disease, and that colonoscopy is the best screening method for women. According to Phillip Schoenfeld, M.D, assistant professor in the Division of Gastroenterology in the Department of Internal Medicine at the University of Michigan Medical School, these findings illustrate that "…Medical research conducted in men cannot routinely be applied to women. Women may be at a disadvantage if medical research is focused on men because women have unique biological differences that may require different diagnostic tools or treatments."

Another example of sex differences can be found in the diagnosis and treatment of Attention- Deficit/Hyperactivity Disorder (ADHD). A recent study showed that women with ADHD often display different symptoms than men, which causes the condition to remain undiagnosed. Further, women in the study displayed greater emotional symptom improvement than men when treated with the same drug.

The draft guidance poses the question of whether focus should be placed only on newer technologies and services, or on the entire spectrum. We believe that in terms of the Society's "Some Things Only A Woman Can Do" campaign, it is critical to look at the entire spectrum of technologies and services, not merely newer ones. Previously, many decisions were made based on young males, and did not examine the Medicare population, particularly older women.

Evidence Development Methods

The Society appreciates the study designs under consideration and feel that each could better answer the question of why men and women differ biologically. Regardless, the Society believes that these designs often lose opportunities to examine sex differences,

even when women are included in studies. Further, clinical trial designs need to include women in all types of clinical research, not merely in phase III clinical trials. Finally, a concerted effort should be made to report all data from trials, whether the results are positive, negative, or merely neutral, and this information should be stored in a repository of some kind so that it will continue to be available in the future.

Further, the Society believes that CMS should require a database, in order to delve into the comparative effectiveness of drugs and devices, a subject important to both women and men. A great deal of information on sex differences remains unknown; making the right choices difficult. We believe that databases should be required whenever possible to help improve this situation.

As CMS evaluates the quality of a proposed study design, we believe it is crucial that all of these proposed designs directly examine sex differences and report this data to CMS.

Thank you for providing this opportunity to comment on CMS's draft guidance on "Factors CMS Considers in Making a Determination of Coverage with Evidence Development." We hope that you will take our comments into consideration.

Organization: TrailBlazer Health Enterprises

- **Are there other stakeholder groups that should be included in discussions of priority setting?**

Although Medicare contractors (see below) should be important stakeholders in some facets of CED, involvement in the decision regarding when and how to apply CED might not be an appropriate role, since it could blur necessary boundaries between the LCD and NCD processes.

- **Who should have access to the data and in what form?**

It is essential that Medicare contractors have a key role in this process, particularly with respect to the formulation of registries. In the case of clinical trials, appropriate modifiers have been created such that claims can be properly adjudicated. However, less tightly prescriptive registry data may well need some internal controls such that "reasonable and necessary" can be supported at the claims processing level. Thus, strong consideration should be given to sharing of registry data with contractors, such that selective safeguards are instituted.

The confluence of registry development with claims processing should also involve targeted systems-oriented specialists, along with a CMD perspective. Therefore, at this juncture, TrailBlazer would like to nominate one of its key systems staff, Ms. Christine Griffith (chris.griffith@trailblazerhealth.com), along with Dr. Mitchell Burken (mitchell.burken@trailblazerhealth.com), to both represent this contractor perspective and, in turn, hopefully fulfill this potentially critical stakeholder role.

Organization: Washington Legal Foundation
Name:

(Comment on next page)

COMMENTS

of the

WASHINGTON LEGAL FOUNDATION

to the

CENTERS FOR MEDICARE AND MEDICAID SERVICES, U.S. DEPT. OF HEALTH AND HUMAN SERVICES

Concerning

CMS DRAFT GUIDANCE ON COVERAGE WITH EVIDENCE DEVELOPMENT

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VIA FIRST-CLASS MAIL AND E-MAIL (CAGInquiries@cms.hhs.gov**)**

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Re: CMS Draft Guidance, "Factors CMS Considers in Making a Determination of Coverage with Evidence Development"

Dear Dr. Phurrough:

The Washington Legal Foundation (WLF) is pleased to submit comments on the draft guidance released by the Centers for Medicare and Medicaid Services (CMS) concerning factors CMS considers in making a determination of coverage with evidence development (CED).

WLF appreciates the many efforts CMS has made to solicit public input on the CED initiative and to carry out a dialogue with Medicare's stakeholders on this important topic. We briefly summarize here some of the key points addressed in our comments on the draft guidance.

As described in the draft guidance, CED represents an approach in which "[c]overage may be limited to providers who participate in and beneficiaries who are enrolled into a defined prospective data collection activity, when this data collection activity constitutes part of the evidence required to ensure the item or service provided to that patient is reasonable and necessary."[1] Limiting Medicare coverage to patients who

[1] Draft guidance at 3. This description does not seem to encompass providing national coverage of a particular treatment to patients enrolled in a data collection system, but allowing contractors to cover the treatment for other patients who are not enrolled in a data collection system. While we have doubts about the practical utility of such an approach (since contractors may be disinclined to cover a treatment for patients who do

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enroll in a data collection system is a relatively new approach that could have important consequences for Medicare beneficiaries. WLF has a number of concerns about this approach, including the fact that it creates a risk of restricting patients' access to needed care. In addition, we do not believe these risks are necessary. That is, the draft guidance suggests that the principal purpose of the CED initiative is increasing the evidence base that physicians and patients can use in making treatment decisions (and CMS itself can use in refining future coverage policies). But CMS has many alternative tools to spur research on therapies relevant to the Medicare population that do not involve coverage limitations; by relying on these alternatives, CMS could avoid coverage restrictions that may reduce Medicare beneficiaries' access to needed care, and at the same time could advance its research goals more effectively. Consequently, we strongly encourage CMS to "de-couple" its National Coverage Determinations (NCDs) from its broader goal of generating a better evidence base for clinical decision-making, and use other mechanisms to fuel the evidence-development enterprise. While we cannot endorse the theory that the Medicare statute's "reasonable and necessary" provision authorizes coverage restrictions linked to the patient's participation in research endeavors, CED would represent a sub-optimal tool for achieving CMS' goals even if it were legally authorized.

We are also concerned that the attempt to tie "reasonableness and necessity" to the broad range of evidence that could be helpful to physicians and patients in making decisions about alternative treatment strategies could inadvertently blur the distinction between better evidence and the evidence needed to meet the reasonableness and necessity standard, ultimately producing a shift in the "reasonableness and necessity" concept that could limit the choices available to Medicare beneficiaries and their physicians. The potential for the CED guidance implicitly to "redefine" reasonableness and necessity also illustrates a larger problem, which is that the term is not defined in the first place. Consequently, we encourage CMS to tackle this fundamental issue – the absence of well-defined, definitive coverage criteria – using a consensus-based process that can help to overcome the difficulties that have plagued past efforts to develop coverage criteria. Specifically, CMS should use the negotiated rulemaking process, which offers the Agency a vehicle for forging clearly-defined coverage standards grounded in a consensus among all of the Medicare program's stakeholders and a firm legal foundation.

Finally, on a more specific but critically important topic, we encourage CMS to act quickly to improve access to care for Medicare beneficiaries with cancer. In particular, the

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not participate in a data collection system once CMS issues a decision conditioning national coverage on data collection requirements), at least in theory it might ameliorate access limitations associated with CED policies and we are uncertain why it was left out of the CED description.

near-term steps CMS can take to advance its goal of enhancing access to cancer therapies include formalizing its commitment not to impose CED restrictions on medically accepted off-label uses of anti-cancer drugs; expanding the list of compendia and medical journals used in identifying medically accepted off-label uses of anti-cancer drugs, to help ensure that Medicare policy reflects the most current information; and reinforcing the Agency's current manual guidance authorizing contractors to cover off-label uses of anti-cancer drugs that are "medically accepted generally as safe and effective."[2] Given the importance of ensuring access to appropriate therapies for cancer patients, we encourage CMS to take these steps as promptly as possible.

I. INTERESTS OF COMMENTERS

WLF is a nonprofit public interest law and policy center based in Washington, D.C., with supporters nationwide. Since its founding in 1977, WLF has engaged in litigation and advocacy to defend and promote individual rights and a limited and accountable government, including in the area of patients' rights. For example, WLF successfully challenged the constitutionality of Food and Drug Administration restrictions on the ability of doctors and patients to receive truthful information about off-label uses of FDA-approved medicines. Washington Legal Found. v. Friedman, 13 F. Supp.2d 51 (D.D.C. 1998), appeal dism'd, 202 F.3d 331 (D.C. Cir. 2000). WLF has previously submitted comments to CMS, on February 10, 2004 and June 25, 2004, concerning Medicare coverage of off-label uses of FDA-approved cancer drugs under Part B, Part D, and the Section 641 demonstration program.

II. GOALS OF CED AND TOOLS FOR ACHIEVING THEM

The draft guidance suggests a number of different goals CMS may be seeking to achieve through the CED initiative, which apparently include generating additional evidence to help CMS evaluate the "reasonableness and necessity" of healthcare services, enhancing Medicare beneficiaries' access to promising therapies, ensuring that physicians obtain the information needed to make appropriate treatment decisions, and generating better evidence to help physicians and patients in making treatment decisions. Consistent with past CMS statements about CED, the draft places considerable emphasis on this latter goal of supporting physicians' and patients' decision-making needs. For example, the draft provides that evidence generated via CED policies will "assist doctors and patients in better understanding the risks, benefits and costs of alternative diagnostic and treatment options,"[3] that "[b]etter evidence will help doctors and patients get the most

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2 Medicare Benefit Policy Manual, Chap. 15 § 50.4.5.

3 Draft guidance at 4.

benefits at the lowest possible cost in our increasingly complex and individualized health care system,"[4] that difficulties in addressing practical questions in a pre-market clinical trial setting "highlight the value of a systematic expansion of practical clinical research efforts to address the information needs of health professionals and patients,"[5] and that CED policies "will provide useful information to doctors and patients faced with complicated clinical decisions and the need to personalize those decisions for individual patients."[6] Similarly, a CMS notice regarding the CED initiative spoke of "bridging the 'gaps in knowledge,' which is essential to increasing the evidence base that allows physicians and patients to select appropriate diagnostic and therapeutic services."[7]

Each one of the goals suggested by the draft guidance is important. However, we hope CMS will carefully evaluate how these various goals relate to the Medicare statute's "reasonable and necessary" provision (which is cited as the legal authority for CED) and whether they are best pursued by conditioning Medicare coverage of a particular healthcare service on the patient and provider participating in a clinical trial or registry (or another type of data collection system).

CMS has many options available for advancing research-related goals (such as generating additional evidence that may ultimately help physicians and patients in evaluating alternative treatment strategies, or help CMS itself to refine future coverage policies). Carefully considering whether these goals are most appropriately pursued through CED policies or other tools is essential, because limiting Medicare coverage to patients who enlist in research endeavors raises a number of serious concerns. As discussed further below, "de-coupling" coverage from a Medicare beneficiary's decision about whether or not to enroll in a data collection system could avoid these concerns. This approach would also enable CMS to advance all of its goals more effectively, by eliminating the need for tradeoffs between the goal of promoting better evidence and the goal of enhancing Medicare beneficiaries' access to promising therapies.

A. Alternative Tools For Promoting Research

CMS can use a wide variety of tools other than CED policies to spur additional research on healthcare services and products used by Medicare beneficiaries. Some examples of these alternative tools are outlined briefly below.

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4 Id.

5 Id.

6 Id. at 5.

7 CMS notice, "Improving Evidence Development."

First, CMS can use the process established by Section 1013 of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (the MMA) to advance its research priorities. Section 1013 authorizes the Agency for Healthcare Research and Quality (AHRQ) to "conduct and support research to meet the priorities and requests for scientific evidence and information identified by [Medicare and certain other programs]" regarding the outcomes, comparative effectiveness and appropriateness of healthcare items and services, while requiring that AHRQ "ensure that here is broad and ongoing consultation with relevant stakeholders in identifying the highest priorities for research."

Second, CMS can work with stakeholders such as sister agencies with a research mission, medical societies and other provider groups, patient groups, and manufacturers of healthcare products to identify research priorities and promote research of particular importance to the Medicare population. In fact, MMA Section 1013 specifically envisions such collaborative efforts, providing in part that the HHS Secretary shall "work in voluntary collaboration with public and private sector entities to facilitate the development of new scientific knowledge regarding health care items and services," and shall identify options that could be undertaken in voluntary collaboration with private and public entities for the provision of more timely information on topics such as the outcomes and quality of patient care. Voluntary collaborative efforts with relevant public and private sector stakeholders would also provide CMS with a valuable mechanism for keeping abreast of research efforts that are already underway or planned, helping the Agency to target its resources most effectively; in fact, CMS noted the need for such a mechanism in its discussion of cancer drug trials, stating that "we are interested in some systematic way of obtaining input [on] current and planned clinical studies."[8]

Third, CMS could use the Centers for Education and Research on Therapeutics (CERTs) program to advance its research goals. CERTs is a national initiative "to conduct research and provide education that advances the optimal use of therapeutics (i.e., drugs, medical devices, and biological products)."[9] The program is administered as a cooperative agreement between AHRQ and FDA, and consists of seven research centers and a coordinating center. The CERTs receive funds from public and private sources, with AHRQ providing core financial support, and the CERTs Steering Committee includes representatives from CMS as well as AHRQ, FDA, and private sector groups.[10] As a recent AHRQ publication on Medicare use of CERTs research noted, "[s]everal CERTs projects have been conducted in Medicare populations and even more have generated

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8 Draft guidance at 8.

9 "Centers for Research and Therapeutics: Overview," AHRQ Publication No. 02-P-025, April 2004, http://www.ahrq.gov/clinic/certsovr.htm.

10 Id.

results applicable to these groups"; because the CERTs data sources can be used for large population-based studies, "CERTs research results can be useful to the Medicare program when evaluating policy options and assessing the effects of policy decisions."[11] A number of the CERTs centers also have worked with Medicare's Quality Improvement Organizations in carrying out projects relevant to Medicare.[12]

Fourth, CMS can make additional payments to Medicare providers for collecting data of interest to CMS, but without conditioning coverage of the underlying treatment on collection of the data. This is the approach CMS has taken in its current demonstration project paying physicians to collect certain assessment data on chemotherapy patients, which CMS initiated "to identify and assess certain oncology services in an office-based oncology practice that positively affect outcomes in the Medicare population." [13]

Fifth, CMS can use its Clinical Trials NCD[14] more effectively to promote research. The Clinical Trials NCD provides national coverage for routine costs of "qualifying" clinical trials. Although CMS has noted previously that the Clinical Trials NCD "is designed to help the Medicare program answer questions about the effectiveness of therapies on Medicare patients,"[15] the NCD was issued in 2000 but has not yet been fully implemented.

Under the Clinical Trials NCD, "qualifying" trials must have certain "desirable characteristics" (e.g. the trial's principal purpose must be to test whether the intervention potentially improves health outcomes, the trial design must be appropriate to answer the research question being asked, the trial must comply with federal regulations on protection of human subjects), and certain trials are "deemed" to have these characteristics.[16] The NCD also provides for AHRQ to convene a multi-agency panel charged with developing criteria to identify trials with a strong probability of exhibiting the desirable characteristics

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[11] "Medicare Use of Research from CERTs," AHRQ Publication No. 05-P010, March 2005, http://www.ahrq.gov/clinic/certmedicare.htm.

[12] Id.

[13] CMS Transmittal No. 14, "Chemotherapy Demonstration Project" (Dec. 30, 2004).

[14] Medicare National Coverage Determinations Manual, § 310.1.

[15] October 5, 2000 Decision Memo for Pelvic Floor Electrical Stimulation for Urinary Incontinence (CAG-00021N).

[16] "Deemed" trials include: (1) trials funded by NIH, the Centers for Disease Control and Prevention, AHRQ, CMS, the Defense Department, or the Department of Veterans Affairs; (2) trials supported by centers or cooperative groups funded by the agencies listed above; (3) trials conducted under an investigational new drug application (IND); and (4) IND-exempt drug trials.

listed in the NCD; once these criteria are developed, trials other than "deemed" trials can be qualifying trials if the principal investigator certifies that the trial meets the criteria. However, CMS has not yet established the self-certification process contemplated by the NCD, even though the AHRQ-led panel developed recommendations regarding the self-certification criteria.[17] Consequently, only "deemed" trials are currently covered by the Clinical Trials NCD. By establishing the self-certification process and bringing more trials within the Clinical Trials NCD, CMS could encourage Medicare beneficiaries to participate in more clinical trials – and thereby obtain better evidence about the effectiveness of therapies for Medicare patients – without using coverage restrictions.

Finally, in some cases CMS may be able to obtain useful information on the benefits and risks of certain therapies simply by analyzing data normally submitted on Medicare claims. For example, in a recent coverage policy that did not impose CED requirements, CMS noted that "[a]s with all items and services, CMS will perform post-coverage analysis of claims data to continue to examine the net health benefit of [the treatment in question]."[18]

B. Concerns Raised By Promoting Research Through CED Policies

We hope that CMS will seriously consider methods for promoting research such as those outlined above (as well as other vehicles outside the coverage process), because conditioning Medicare coverage on the patient's enrollment in research endeavors raises a number of significant concerns. At the same time, the NCD process may not offer the best vehicle for forging research priorities and generating high-quality research results in a cost-effective fashion.

Most importantly, CED policies may create the risk of restricting Medicare beneficiaries' access to needed services. Among other things, some patients may be unable or unwilling to participate in clinical trials or registries. For example, certain patients may be ineligible to participate in a clinical trial due to its exclusion criteria

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[17] In a coverage policy on PET scans used in diagnosing dementia, CMS conditioned coverage on the patient's participation in a trial that met four criteria (written protocol containing specified information on file, IRB review and approval, scientific review and approval by two qualified individuals who are not part of the research team, and certification that researchers have not been disqualified), and described these criteria as the same criteria that the multi-agency panel led by AHRQ recommended using as the basis for the self-certification process contemplated by the Clinical Trials NCD. See Sept. 15, 2004 Decision Memo for Positron Emission Tomography (FDG) and Other Neuroimaging Devices for Suspected Dementia (CAG-00088R).

[18] April 27, 2005 Decision Memo for Ultrasound Stimulation for Nonunion Fracture Healing (CAG-00022R).

(which is not uncommon with elderly patients due to factors such as comorbidities); likewise, some patients may be unable to travel to trial sites, reluctant to participate because they might need to change physicians or other healthcare providers, or fearful of enrolling in a randomized trial because they could be assigned to an arm of the trial that did not involve the treatment recommended by their physician.

Patients also could face access restrictions under CED policies if their providers decided not to participate in the data collection system because it imposed extra costs that were not reflected in their Medicare payments. While the draft guidance emphasizes the need for data collection systems that keep costs and burdens to providers as low as possible,[19] it also contains passages suggesting that participating in these systems could nevertheless be a costly enterprise.[20] Even if CMS increased providers' payments to account for the costs of the data collection requirements, however, this would also increase beneficiary copayments for the service, which might itself create barriers to access in certain cases.

In addition, some CED policies have called for clinical trials or registries that do not yet exist. For example, CMS' recent policy on using FDG-PET scans to diagnose certain cancers acknowledged "the complex nature of the prospective clinical studies discussed in this [policy]," and noted that "no clinical study will be fully operational by the effective date of this decision"; consequently, "while this coverage decision is effective, it will not be fully implemented until a clinical study is ready to enroll providers and patients."[21] In these kinds of circumstances where a CED policy's implementation lags behind its effective date, any Medicare beneficiary who needed a service subject to the CED policy would be denied coverage until the trials or registries required by the policy were designed and put into operation.

Given the risks of reduced access to care associated with CED, CMS might better achieve all of its goals – including "enhancing access to medical technologies and services

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[19] See, e.g., draft guidance at 5, 14.

[20] For example, the draft guidance provides that "[e]ach evidence development enterprise should appoint an individual with appropriate clinical, scientific and technical expertise to oversee all aspects of the data collection"; "[p]roviders involved in the evidence development enterprise must be educated about the reasons for the study, receive training about data collection, and be informed of all aspects of the study's purpose and design"; and "[t]here should be a data auditing system to ensure data integrity for continuous quality improvement." Draft guidance at 13-14.

[21] Jan. 28, 2005 Decision Memo for Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers (CAG-00181N).

that improve health outcomes"[22] – by relying on vehicles outside the coverage process to further its research objectives.

Apart from access problems, CED policies also may not be a good vehicle for allocating research resources prudently. Medicare coverage policies are developed in a relatively short period of time, and they involve specific items or services. Coverage policies with data collection requirements will necessarily divert resources from other research endeavors, and it is not clear that Medicare's coverage process is an appropriate vehicle for establishing national research priorities and allocating scarce research resources in the most prudent fashion. The coverage process was not designed to gather and evaluate the wealth of information and expertise that should be brought to bear in designing research protocols and setting research priorities. Similarly, the coverage process does not involve the "broad and ongoing consultations with relevant stakeholders" that Congress required in authorizing AHRQ to support research meeting Medicare priorities,[23] which helps to ensure that research priorities are defined through a well-informed, transparent process that improves the quality of the resulting decisions.

Generating evidence through coverage restrictions may also needlessly increase the cost of answering the research questions in which CMS is interested. This approach requires all Medicare patients who need a particular treatment to enroll in the research effort (or to forego coverage), even though in many instances CMS' research questions could be answered by less costly, smaller-scale studies that only involved a sample of the relevant Medicare population.

Finally, CED policies may also raise legal and ethical concerns associated with patient privacy and informed consent.

As a "health plan," CMS is a "covered entity" under the HIPAA Privacy Rule; most healthcare providers that serve Medicare patients also are covered entities.[24] Covered

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22 Draft guidance at 1.

23 MMA § 1013.

24 Covered entities include "health plans," "covered health care providers," and "health care clearinghouses." "Health plan" means "an individual or group plan that provides, or pays the cost of, medical care," specifically including Medicare parts A-C. 45 CFR § 160.103. As explained by HHS, "where a public program meets the definition of 'health plan,' the government agency that administers the program is a covered entity. Where two agencies administer a program jointly, they are both a health plan. For example, both the Health Care Financing Administration [now CMS] and the insurers that offer a Medicare & Choice plan are 'health plans' with respect to Medicare beneficiaries." 65 Fed. Reg. 82462, 82578 (Dec. 8, 2000).

entities that wish to use or disclose protected health information (PHI) for research[25] purposes must obtain the patient's authorization to do so, unless an exception to the Privacy Rule's general requirement for authorization applies (or unless the data is "de-identified," in which event it is no longer "PHI" but may have limited utility for research purposes). Subject to specified exceptions, a covered entity "may not condition the provision to an individual of treatment, payment, enrollment in the health plan or eligibility for benefits on the provision of an authorization."[26] Where patient authorization is required to use or disclose PHI for research purposes, it is not clear how CMS could deal with the prohibition on "conditioning" eligibility for benefits on the patient providing an authorization. The draft guidance does not address this issue, or explain CMS' plans for complying with the HIPAA Privacy Rule generally.

Similarly, CED policies may raise questions about whether patients can freely consent to participate in research when denial of Medicare coverage for the treatment of choice is the price of not participating. Voluntary informed consent, obtained without undue influence, is a bedrock principle of ethical research. As articulated in the 1979 Belmont Report commissioned by HEW:

> [I]nformed consent requires conditions free of coercion and undue influence . . . . Undue influence . . . occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance . . . .

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[25] "Research" is broadly defined under the Privacy Rule as a "systematic investigation, including research development, testing and evaluation, designed to contribute to generalizable knowledge." 45 CFR § 164.501. "Research" includes the creation of a research database or repository, and the use or disclosure of PHI from such a database or repository for research. NIH, "Research Repositories, Databases, and the HIPAA Privacy Rule" at 2.

[26] 45 CFR § 164.508(b)(4) (emphasis added). Exceptions to this prohibition on conditioning of authorizations are as follows: (1) "[a] covered health care provider may condition the provision of research-related treatment on provision of authorization for the use or disclosure of [PHI] for such research"; (2) authorization is sought "for the health plan's eligibility or enrollment decisions relating to the individual" (or for its underwriting or risk rating determinations) and the authorization does not involve psychotherapy notes; or (3) the covered entity conditions the provision of health care "that is solely for the purpose of creating [PHI] for disclosure to a third party" on provision of an authorization for disclosure of the PHI to the third party. Id.

> . . . [U]ndue influence would include actions such as . . . threatening to withdraw health services to which an individual would otherwise be entitled.[27]

This same principle is currently reflected both in HHS regulations on the protection of human subjects (which generally apply to any research involving human subjects conducted or supported by a federal agency),[28] and in similar FDA regulations. Both sets of regulations provide that investigators must seek the informed consent of research subjects "only under circumstances . . . that minimize the possibility of coercion or undue influence,"[29] and both require informing prospective research subjects "that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled."[30]

Whether CED is viewed as a penalty for failure to participate in research or a reward for participation, it can raise concerns about beneficiaries' ability to give genuinely voluntary informed consent. Because CED policies often involve costly treatments, the

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[27] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm. As HHS has noted, "[t]he principles underlying the Belmont Report . . . have served for over 20 years as a leading source of guidance regarding the ethical standards that should govern research with human participants in the United States." 66 Fed. Reg. 45998, 45999 (Aug. 31, 2001).

[28] The Basic HHS Policy for Protection of Human Research Subjects is contained in 45 CFR Part 46 Subpart A. These regulations provide that "research that is conducted or supported by a federal department or agency . . . must comply with all sections of this policy." 45 CFR § 46.101(a)(1). "Research" means "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge"; activities meeting this definition "constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes." Id., § 46.102(d). The policy contains limited exemptions, including research and demonstration projects designed to study: "(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under these programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs." 45 CFR § 46.101(b)(5). HHS interprets this exemption as applying to programs that deliver a public benefit ("e.g., financial or medical benefits as provided under the Social Security Act"), if certain additional criteria are satisfied — in particular, "[t]he research or demonstration project must be conducted pursuant to specific federal statutory authority." http://www.hhs.gov/humansubjects/guidance/exmpt-pb.htm.

[29] 45 CFR § 46.116 (HHS-wide regulations); 21 CFR § 50.20 (FDA regulations).

[30] 45 CFR § 46.116(a)(8); 21 CFR § 50.25(a)(8).

financial consequences of declining to participate in the research may effectively foreclose this option for many Medicare beneficiaries, creating a tension between CED and principles of voluntary informed consent. [31] Like all of the other considerations discussed above, this would counsel in favor of stimulating research through alternative tools divorced from coverage policy, even if CMS had the legal authority to adopt CED policies.

III. THE MEDICARE STATUTE'S "REASONABLENESS AND NECESSITY" PROVISION

A. The Connection Between "Reasonableness and Necessity" and Data Collection Requirements

The draft guidance cites the "reasonableness and necessity" provision in the Medicare statute as the legal authority for CED policies.[32] This provision generally prohibits Medicare payment for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[33] As a logical matter, there is a temporal problem with basing decisions about the "reasonableness and necessity" of a treatment on yet-to-be-developed evidence. Thus, it is unclear how the "reasonableness and necessity" of a treatment can hinge on data collection requirements aimed at generating future information regarding the treatment's reasonableness and necessity; NCDs are necessarily based on the information that exists at the time they are made, not speculation about what future data collection efforts might or might not demonstrate.[34]

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[31] For example, one commenter on CMS' draft policy on ICDs stated that it "falls within the definition of undue coercion as defined by both the Office of Human Research Protections and the Food and Drug Administration"; another stated that "patients should not be forced to participate in a study as a condition of receiving benefits."

[32] Draft guidance at 6.

[33] Social Security Act (SSA) § 1862(a)(1)(A) (codified at 42 U.S.C. § 1395y(a)(1)(A)).

[34] At least as we understand the draft guidance, however, it appears that CMS is (appropriately) not relying on the idea that data collection requirements will generate future evidence as its legal justification for CED. As discussed below, it appears that the legal theory for CED is that requiring patients to enroll in a data collection system is itself something that improves their care (by requiring that their physician obtain the information needed to make good treatment decisions) and in this way boosts the patient's treatment to the "reasonable and necessary" level. However, the discussion of "Legal authority for coverage with evidence development" in the draft guidance does not crisply articulate CMS' legal theory and may be subject to misinterpretation.

The draft guidance states that in some cases "CMS will determine that an item or service is only reasonable and necessary when specific data collections accompany the provision of the service," and then describes "two general circumstances under which clinical care provided may only be reasonable and necessary in the context of protocol-driven data collection."[35] These two circumstances involve cases: (1) where "a particular medical intervention may have been demonstrated to improve health outcomes in a broad population of patients, but the evidence would only be adequate, and the service reasonable and necessary for the individual patient, when specific data is collected and reviewed by the provider at the time the service is delivered";[36] and (2) where "a particular medical intervention has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests the intervention may provide an important benefit."[37]

In both circumstances, the draft guidance basically appears to suggest that data collection requirements can boost an intervention to the "reasonable and necessary" level by requiring that healthcare providers collect and review information needed to evaluate the patient and develop an appropriate treatment strategy. For example, the draft guidance states that data collection requirements "support appropriate treatment decisions" (e.g., they "may require the physician to reevaluate the original conclusions, [and] alter the management plan"); data collection "help[s] ensure individual patients are being provided with care that is appropriate to their clinical circumstances and delivered by skilled, informed providers"; care may be reasonable and necessary only in the context of data collection "because the additional care in clinical decision making and monitoring of the patient offers greater assurance that the benefits of receiving the service will exceed the risks"; clinical trial designs for cancer therapy "ensure individualized analysis and evaluation of patients' response to chemotherapy and their health status"; data collection requirements associated with FDG-PET scans may improve care by "helping physicians

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[35] Draft guidance at 6.

[36] The draft guidance does not specify why "the evidence would only be adequate, and the service reasonable and necessary for the individual patient," when specific data is collected. However, the guidance cites CMS' recent policy on implantable cardioverter defibrillators (ICDs) as an example of the first circumstance, and explains that while the benefits of ICDs have been demonstrated in two major high-quality clinical trials reported since 2002, "many important questions remain about which patients are most likely to derive benefits from the device." Consequently, the first circumstance apparently involves cases where benefits have been demonstrated in a broad patient population, but further information on the benefits to specific patient subgroups would be helpful.

[37] The draft guidance cites two recent policies on off-label use of certain colorectal cancer drugs and on FDG-PET scans used in cancer diagnosis as examples of this second circumstance.

appropriately evaluate the PET scan results in the context of critical, relevant clinical information"; and care provided under data collection protocols "generally involves greater attention to appropriate patient evaluation and selection, as well as the appropriate application of the technology."[38]

The theory that reasonableness and necessity can hinge on data collection requirements because they prompt physicians to review information needed to make appropriate treatment decisions is both troubling and unfounded, since it implies that ordinarily physicians make treatment decisions without relevant information. The draft guidance does not cite any evidence supporting such an assumption, nor is it reasonable. Regardless of whether Medicare imposes data collection requirements, physicians treating cancer patients will "ensure individualized analysis and evaluation of patients' response to chemotherapy and their health status," and physicians ordering PET scans will "appropriately evaluate the PET scan results in the context of critical relevant clinical information." These kinds of activities are normal features of good patient care, not anything unique to "protocol-driven" patient care. Moreover, even if one assumed that physicians often make treatment decisions without reviewing relevant clinical information, there is no reason why such conduct would be more common in circumstances where the chosen intervention warrants further research. Instead, the theory that physicians will fail to review relevant information unless prompted to do so by data collection requirements implies that few services would be reasonable and necessary without such requirements – and that the data collection requirements should continue indefinitely, since their purpose is to compel physicians to act responsibly.

In short, the draft guidance does not provide a cogent or empirically-supported explanation as to why a particular service could "only [be] reasonable and necessary when specific data collections accompany the provision of the service." Consequently, the theory that CMS has the legal authority to limit coverage of a treatment to patients who enroll in a data collection system is not well-founded. If one assumes that physicians can use their professional judgment to determine what information is needed to make sound treatment decisions, and that they review such information on their own initiative, then physicians will engage in those data collection activities that are medically necessary without CMS requiring this; a CMS requirement for extra data collection activities would only make physicians perform additional tasks that were not reasonable and necessary for patient care, ostensibly by authority of the "reasonable and necessary" provision.

While developing better evidence is important, this does not require re-shaping the Medicare statute's reasonable and necessary provision into a tool for conscripting Medicare patients into the research enterprise. CMS has commendable goals – and it has

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[38] Draft guidance at 6-9.

appropriate tools outside the coverage process to pursue them – but the draft guidance demonstrates that linking the "reasonable and necessary" provision to a patient's enlistment in research endeavors requires reliance on theories unsupported by evidence or logic.

B. Distinguishing Between Evidence that Supports Better Decision-making and Evidence Needed to Establish Reasonableness and Necessity

As noted earlier, the draft guidance appropriately emphasizes the importance of developing better evidence on healthcare interventions that can help physicians and patients to choose between alternative treatments (as well as help CMS itself to refine future coverage policies). Consistent with this focus, the draft includes an "initial list" of nine circumstances "in which coverage with data collection might be valuable," most of which are quite broad – e.g., where "[t]he available clinical studies may not have adequately described risks and benefits in specific patient subgroups, or in patients with disease characteristics that exclude them from clinical trials"; where "assessment of important outcomes has not been evaluated in the available clinical studies" (which outcomes include but are not limited to "long-term risks and benefits, quality of life, utilization, costs, and other real-world outcomes"); where "[t]here may remain questions about the comparative effectiveness of new items or services compared to existing alternatives or to usual care"; or where the evidence "shows statistically significant benefits but the clinical significance of the outcomes may not be well understood."[39]

The various circumstances that CMS describes are all cases where better evidence could be valuable to physicians and patients in deciding on a treatment strategy. However, we are concerned that the draft guidance often seems to blur the distinction between "better" evidence and the evidence needed for Medicare coverage, implicitly creating a new concept of "reasonableness and necessity" with troubling implications for beneficiary access.[40] For example, the draft guidance states that CMS expects to apply CED in cases where "better evidence to support decision-making by patients and clinicians is an essential part of reaching a conclusion that a treatment is reasonable and necessary."[41]

The universe of evidence that may support clinical decision-making goes far beyond the evidence needed for Medicare coverage, and "better evidence to support decision-making by patients and clinicians" has never historically been the standard for

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[39] Draft guidance at 9-10.

[40] Again, this is a consequence of attempting to tie the statute's "reasonable and necessary" language to a broader research agenda.

[41] Draft guidance at 2.

reasonableness and necessity determinations. Nor has it traditionally been the case that a medical intervention was "non-covered" if it "has yet to conclusively demonstrate an improvement in health outcomes, but existing information clearly suggests [it] may provide an important benefit": a circumstance where the draft guidance describes CED as increasing access "compared to the alternative of non-coverage."[42]

To gain some perspective on reasonableness and necessity, it is worth recalling that the "reasonable and necessary" language in the Medicare statute was enacted in 1965 at Medicare's inception: a period predating the era of evidence-based medicine, when Congress would not have envisioned reasonableness and necessity as requiring randomized clinical trials demonstrating a treatment's benefits – let alone requiring randomized clinical trials plus supplemental research studying issues such as "real world outcomes" or benefits to specific patient subgroups. As the American Medical Association noted in a 2000 letter to CMS "[t]he effectiveness of the vast majority of treatments that are covered by Medicare today for its aged and disabled beneficiaries has not been demonstrated in peer-reviewed scientific literature" and "[e]ven where the effectiveness of treatments has been demonstrated in a study population under certain study conditions, it is highly unlikely that effectiveness in routine clinical use in the Medicare population will have been demonstrated in peer-reviewed scientific literature."[43]

In fact, the Medicare statute's text allows coverage for items and services that may be reasonable and necessary, but that do not have the evidence needed "to conclusively demonstrate an improvement in health outcomes."[44] By its terms, the statute provides that Medicare generally may not pay for items and services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[45]

The concept of allowing coverage for services lacking "conclusive" evidence of benefits (but where there is no evidence demonstrating that the service is ineffective, or harmful) has been recognized in past CMS decisions. Some of these decisions have required national coverage, while others determined that the evidence did not warrant national coverage – or national non-coverage – and the coverage issue should thus be left

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42 Draft guidance at 7 (emphasis added).

43 May 9, 2000 AMA letter to Dr. Hugh Hill, Acting Director of the Coverage and Analysis Group in the Health Care Financing Administration (now CMS).

44 Draft guidance at 7.

45 SSA § 1862(a)(1)(A) (emphasis added).

to the discretion of local contractors.[46] Consistent with this latter approach, CMS has previously described the local coverage process as "giv[ing] Medicare the opportunity to test new, experimental treatments before enough clinical evidence is available to warrant national coverage."[47]

For example, in a 2000 decision regarding biofeedback as a treatment for urinary incontinence, CMS required national coverage for patients who had previously failed pelvic muscle exercises (PME) or were unable to perform PME, and left coverage of biofeedback for other patients to carrier discretion. Calling the scientific evidence "inconclusive," CMS observed that "[t]here is limited direct empirical evidence on whether biofeedback improves outcomes in patients who have failed PME or are unable to perform PME" but that "[d]espite this, we felt that [national] coverage was warranted, given the combination of suggestive scientific evidence and broad positive expert testimony."[48] In another 2000 decision, concerning augmentative and alternative communication devices for speech impairment, CMS concluded that: "[T]o make a national determination to cover AAC devices, sufficient medical evidence . . . must be presented. Upon review of the supporting documentation presented . . . we determined that we need more information to support issuance of positive national coverage guidelines. Until we receive . . . additional information, we are reversing our national non-coverage decision, and permitting carriers to make local coverage [decisions]."[49]

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[46] As CMS noted in a 1999 notice regarding the NCD process, one possible result was "[n]o national coverage decision (which allows for local contractor discretion)," in which case CMS "will also identify the deficiencies in the evidence and the types of information that we will require to reach a national coverage decision." 64 Fed. Reg. 22619, 22622 (Apr. 27, 1999).

[47] GAO, "Medicare: Divided Authority for Policies on Coverage of Procedures and Devices Results in Inequities," at 45 (April 2003) (CMS comments on GAO's report).

[48] Oct. 6, 2000 Decision Memo for Biofeedback for Urinary Incontinence (CAG-00020N).

[49] April 26, 2000 Decision Memo for Augmentative and Alternative Communication Devices (CAG-00055). See also, e.g. June 12, 2000 Decision Memo for Air-Fluidized Beds for Pressure Ulcers (CAG-00017N) (deciding to continue Medicare's existing NCD covering air-fluidized beds for patients who failed conservative treatment for wound healing, even though CMS had issued a request for information on, among other things, "[e]vidence of clinical benefit or change in outcome" from air-fluidized beds and "[n]one of the information that was submitted was responsive to our questions"); May 5, 2005 Decision Memo for Mobility Assistive Equipment (CAG-00274N) (covering mobility assistive equipment for patients with a mobility deficit impairing mobility-related daily living activities, and noting that: "Not unlike many other aspects of medical practice, the use of mobility assistance equipment has arisen from a base of collective clinical experience and inference of benefit. In this light, we believe that the best available evidence is found largely in the expertise of impartial practitioners").

In short, the Medicare statute's "reasonable and necessary" provision does not require the broad range of evidence cited in the draft guidance – all of which can be valuable to doctors and patients in making individual treatment decisions – as a prerequisite to Medicare coverage. Nor does the statute bar coverage for items and services lacking "conclusive" evidence of improved outcomes. CMS can cover such items and services (or leave the issue to contractor discretion) without imposing data collection requirements,[50] and it can spur the development of better evidence through vehicles outside the coverage process. While the desire for better evidence is widely shared by all of Medicare's stakeholders, Medicare beneficiaries and their physicians could have restricted treatment options if better evidence were equated with the evidence needed for coverage.

C. Developing a Consensus-Based Rule Defining Reasonableness and Necessity: A Path Forward

As the discussion above illustrates, the draft CED guidance highlights the fact that basic issues regarding Medicare's coverage standards have not yet been addressed in definitive CMS guidance, which can make coverage standards a "moving target" and produce a lack of predictability for Medicare's stakeholders. These basic issues include, for example: (1) what type and level of evidence is needed to establish affirmatively that a treatment is reasonable and necessary; (2) what evidence is necessary or sufficient to support a national noncoverage decision (i.e., a conclusion by CMS that a particular treatment is "not reasonable and necessary" and cannot be covered by contractors); and (3) what are the respective roles of NCDs and coverage decisions by local carriers (including both formal coverage policies and claim-by-claim decisions), and whether or to

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[50] This is important to be clear about because the draft guidance sometimes seems to suggest that CED somehow gives CMS a new freedom to cover items lacking conclusive evidence, as if the statute otherwise would prohibit coverage until a robust body of definitive evidence emerged. For example, the draft states that "[r]ather than waiting for definitive studies to be completed to address all key questions related to whether the use of a particular technology is reasonable and necessary, CMS can now provide coverage along with an assurance that appropriate data will be collected to ensure that the item or service is reasonable and necessary and to answer specific, important remaining questions." Draft guidance at 6 (emphasis added).

Like treatments lacking "conclusive" evidence of benefits, proven treatments where further evidence concerning specific patient subgroups would be useful also can be covered without CED requirements. Ironically, the ICD policy CMS cited as an example of this first scenario where a treatment is only reasonable and necessary when accompanied by data collection requirements was based on what has always been considered "gold standard" evidence.

what extent the evidentiary requirements for coverage or noncoverage differ at these two levels.

While CMS states that it "intend[s] to discuss in greater detail the interpretation of 'reasonable and necessary' in the context of coverage determinations in future guidance documents,"[51] Medicare's coverage criteria are critically important to the program's beneficiaries and their healthcare providers, and they deserve to be fleshed out in a definitive, binding form – i.e., through the rulemaking process.

In abandoning a long-standing effort to adopt regulations defining reasonableness and necessity in 2003, CMS cited "substantial competing interests about the coverage criteria."[52] Similarly, a CMS official stated recently at an open door forum that the public was "not ready" for CMS to develop regulations on coverage criteria, and another CMS official has described the failure to issue such regulations as "reflect[ing], in part, the inability of the primary stakeholders – employers, drug and device manufacturers, private payers, patient advocates, and organizations representing medical professionals – to reach a consensus."[53]

However, the controversy associated with Medicare's coverage criteria does not warrant giving up on the rulemaking effort, particularly when CMS and its contractors must make coverage decisions on an ongoing basis with or without regulatory standards to guide these decisions. The fact that "reasonableness and necessity" raises difficult questions of great importance to Medicare's stakeholders is all the more reason to thrash these issues out through the notice-and-comment rulemaking process. And a special variant of notice-and-comment rulemaking – negotiated rulemaking – is designed specifically for building the stakeholder consensus needed to develop rules on particularly important and controversial topics. This process, detailed in the Negotiated Rulemaking Act,[54] uses a committee of stakeholder representatives that operates in accordance with the transparency requirements of the Federal Advisory Committee Act to develop consensus recommendations on a proposed rule, which is then subject to the Administrative Procedure Act's full requirements for notice-and-comment rulemaking.

Negotiated rulemaking would thus allow CMS to engage representatives of all Medicare's stakeholders – CMS itself, patients, physicians and other healthcare providers,

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51 Draft guidance at 3.

52 68 Fed. Reg. 55634, 55635 (Sept. 26, 2003).

53 Sean R. Tunis, "Why Medicare Has Not Established Criteria for Coverage Decisions," N. Eng. J. Med. 350, no. 21 (2004): 2196-2198.

54 5 U.S.C. §§ 561-570.

and manufacturers of healthcare products – in a structured, open dialogue aimed at forging consensus recommendations that would then be reflected in a proposed rule and further refined through the APA's notice-and-comment process. This is not a new idea for confronting the difficulties associated with developing a regulation spelling out Medicare's coverage criteria; a coalition of device manufacturers reportedly filed a citizen petition in 1998 urging CMS (then HCFA) to engage in a negotiated rulemaking on coverage criteria.[55] But using negotiated rulemaking to develop well-defined coverage standards embraced by Medicare's stakeholders still offers the best path forward today, as the need for consensus and clarity only grows in importance. We urge CMS to consider pursuing this approach, which offers the best opportunity for developing predictable, consensus-based coverage criteria with a firm legal foundation.

IV. IMPROVING ACCESS TO CANCER CARE

In its recent NCD concerning off-label uses of certain colorectal cancer drugs, CMS expressed its commitment to expanding access to anti-cancer medicines for Medicare beneficiaries; similarly, the draft guidance refers to this NCD as producing a "net expansion of coverage," by ensuring that all Medicare contractors provide coverage for any patient enrolled in certain clinical trials listed in the NCD.[56] Whether the colorectal cancer drug NCD will ultimately expand coverage remains unclear at this point; however, CMS' goal of expanding access to cancer therapies is critically important and there are a number of simple steps CMS could take to enhance access to care for Medicare patients with cancer.

Subsequent to the issuance of the draft CED guidance, CMS representatives have clarified that the Agency will not impose CED restrictions in circumstances where Congress has already specified that particular treatments meet the reasonableness and necessity standard, including in the statutory provisions defining "medically accepted indications" for anti-cancer drugs.[57] This is an important clarification to the draft guidance that CMS should formalize in written guidance to alleviate concern that the CED initiative could result in a retrenchment of coverage for medically accepted indications of anti-cancer drugs.

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[55] Susan B. Foote, "Why Medicare Cannot Promulgate a National Coverage Rule: A Case of Regula Mortis," 27 J. Health Politics, Policy and Law 707, 718 (Oct. 2002).

[56] Draft guidance at 8.

[57] SSA § 1861(t)(2)(B) (codified at 42 U.S.C. § 1395x(t)(2)(B)). The definition of medically accepted indications for anti-cancer drugs was added to the Medicare statute by a provision in the Omnibus Budget Regulation Act of 1993 entitled "Uniform Coverage of 'Off-Label' Anticancer Drugs."

CMS could also help to enhance patients' access to anti-cancer drugs by expanding the list of compendia used in identifying medically accepted indications for these drugs;[58] for example, CMS could add the National Comprehensive Cancer Network compendium or other compendia to the list to help ensure that coverage of off-label uses of anti-cancer drugs reflects the most current information. Similarly, we encourage CMS to consult with organizations and individuals involved in cancer treatment to identify any medical journals that should be added to the list of journals (in Chapter 15 § 50.4.5 of the Medicare Benefit Policy Manual) that contractors currently use to identify medically accepted off-label indications for anti-cancer drugs.

Finally, we hope that CMS will clear up the concerns about access raised by its NCD on off-label uses of certain colorectal cancer drugs. As noted earlier, CMS issued this NCD in order to expand access to off-label uses of these drugs, by providing uniform national coverage for all beneficiaries enrolled in certain clinical trials. However, many commenters on the draft version of this coverage policy expressed concern about its failure to mention CMS' existing manual guidance allowing coverage of off-label uses "determined by the carrier to be medically accepted generally as safe and effective,"[59] and the final policy also did not specifically mention this guidance. Thus, while the policy seeks to expand coverage, CMS still needs to reaffirm explicitly that contractors may continue to cover off-label uses "medically accepted generally as safe and effective." By doing so, CMS could ensure that a policy designed to expand coverage for certain off-label uses in the clinical trial setting cannot be misconstrued as *constricting* coverage in other cases. This is important because any perceived restriction on contractors' discretion to cover off-label uses could leave many cancer patients with few treatment options. Due to factors such as toxicity to certain agents, the rapidly changing nature of cancer progression, and underlying comorbidities, the viable treatment alternatives available to cancer patients are often quite limited, and any additional restrictions on Medicare coverage of off-label uses would exacerbate this problem.

V. ABANDONING "COVERAGE WITHOUT CONDITIONS"

The draft CED guidance states that while a number of older NCDs do not impose conditions on coverage (i.e., the item or service is covered for all patients with a particular clinical condition, without further restrictions), CMS does "not anticipate issuing

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[58] SSA § 1861(t)(2)(B) lists American Hospital Formulary Service – Drug Information, USP – Drug Information and AMA Drug Evaluations (which is no longer in print), and permits CMS to revise this list as appropriate.

[59] Medicare Benefit Policy Manual, Ch. 15 § 50.4.5.

additional decisions of this type."[60] The draft provides no explanation for this statement, which should be retracted. Abandoning "coverage without conditions" would have serious implications for beneficiary access, particularly if the message that providing broad access to particular treatments is somehow "outmoded" spills over to the local coverage process. In any event, the announcement of a new policy abandoning coverage without conditions does not appropriately belong in a guidance document intended only to address CED; if CMS believes that abandoning coverage without conditions would be prudent, the issue could best be addressed through a negotiated rulemaking process concerning Medicare's coverage criteria generally.

Similarly, the description of the types of possible coverage decisions in the draft guidance refers to a national noncoverage decision as a decision that the evidence is "not adequate to conclude that the item or service improves net health outcomes for the patient,"[61] and does not mention the option of leaving coverage to contractor discretion in circumstances where CMS considers the available evidence inadequate to warrant a positive national coverage decision. We hope this option was inadvertently omitted from the draft guidance and CMS did not mean to suggest that it would no longer issue decisions of this type. Preserving contractor discretion in circumstances where the evidence does not warrant national coverage (but does not demonstrate that the service is ineffective or harmful) can be important in allowing access to promising therapies without the body of evidence often needed today to support national coverage, particularly as premature evaluation of the value of a new medical intervention can reduce the flexibility Medicare needs when embodied in a national non-coverage decision.

VI. FACILITATING PUBLIC COMMENTS ON THE CED GUIDANCE

The draft guidance has a broad scope, and raises a wide range of important issues. We are concerned that this will make it more difficult for many stakeholders to provide comments fully addressing all of the questions and issues raised by the document. For example, the draft guidance includes 29 separate questions for the public, and many of these questions would call for extensive comment by themselves (e.g., two of the questions are "Under what circumstances should CMS require a database? A longitudinal data collection? A prospective study? A clinical trial?" and "How should CMS decide whether the evidence collected suggests patients are either harmed or not benefited by the item or service?"). Given the breadth of the draft guidance and the importance of the numerous topics it subsumes, we strongly encourage CMS to adopt procedures that help to facilitate public comment. At a minimum, this would involve extending the deadline for

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[60] Draft guidance at 2.

[61] Draft guidance at 3.

comments on the draft, and then releasing a revised draft for a new round of public comments.

CONCLUSION

For the reasons set out above, WLF respectfully requests that the draft CED guidance be withdrawn and revised. WLF appreciates the opportunity to comment on the draft CED guidance, and we hope CMS will find these comments useful as it continues to evaluate the CED initiative. We would be glad to provide any further information concerning the points addressed in these comments that would be of assistance, and look forward to working with CMS on efforts to develop policies that improve Medicare beneficiaries' access to care and to the development of better evidence on the treatments they need.

Respectfully submitted,

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