

**CLINICAL TRIAL POLICY: MCAC CONCEPT PAPER
DECEMBER 13, 2006 MEETING**

I. BACKGROUND

2000 Executive Memorandum for Clinical Trials

On September 19, 2000, the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services (CMS)) implemented a Clinical Trial Policy¹ through the national coverage determination (NCD) process. The Clinical Trial Policy was developed in response to a June 7, 2000 executive memorandum, issued by President Clinton, requiring Medicare to pay for routine patient costs in clinical trials.²

1995 and 2003 Regulations for Studies of Devices

CMS has also provided guidance (42 CFR 405.201-215, 411.15(o), and 411.406) on the coverage of clinical costs of devices with an FDA-approved investigational device exemption (IDE) in trials. IDEs are classified by the FDA as either Category A (experimental/investigational) or Category B (nonexperimental/investigational). Payment may be made for a Category B IDE device if all other coverage requirements are met. No payment is made for a Category A IDE device. This proposed NCD does not change existing CMS regulations on IDEs.

Identification of Each Research Study with a Unique Coding Scheme

CMS is developing a coding scheme that will be required on each claim form. The purpose of the coding scheme is to ensure that a study may be matched with all beneficiaries who participated in the study as well as all the claims associated with the clinical care received by the beneficiary. After the implementation of this coding scheme the Agency will be able to monitor expenditures by the program for clinical studies. The ability to track and monitor payments associated with clinical studies was recommended in the 2000 Executive Memorandum.

II. STANDARDS FOR MEDICARE COVERAGE OF STUDIES

The current policy specifies two sets of standards that a study must meet in order for routine clinical care costs to be covered by the program: 1) seven desirable characteristics, and 2) three Medicare specific characteristics. We propose to continue these two sets of standards but to clarify their interaction. The first set will be titled “Standards for a scientifically and technically sound study” and the second set “Medicare-specific standards.” The second set of standards are not distinct from the first but represent specific standards of a sound study in which CMS has special interest.

¹ http://www.cms.hhs.gov/manuals/downloads/ncd103c1_Part4.pdf

² <http://clinton4.nara.gov/WH/New/html/20000607.html>

A. Standards for Scientifically and Technically Sound Studies

The current policy lists seven standards of clinical trials that are termed “highly desirable characteristics.” These are standards that all good studies should meet but may not need individual assessment to qualify a study for CMS coverage of routine care costs.

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;
6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

While these seven desirable characteristics in the current Clinical Trial NCD are critical elements of a sound study, there may be other characteristics that make a study technically strong and scientifically sound.

We propose three options for your consideration in an endeavor to make the current set of general standards consistent with universally recognized criteria of scientifically and technically sound studies.

Option 1: Use a general definition of attributes that comprise a good clinical study.

CMS proposes two definitions: one adapted from the FDA and the other adapted from an epidemiology text. We believe these definitions are applicable to clinical trials and observational studies that may be used to evaluate the effectiveness and safety of technology (i.e., drugs, biologics, devices, procedures, and diagnostics) potentially beneficial to the Medicare population. We welcome additional or alternative definitions for the committee to consider.

1st Definition: A clinical study is any investigation in human subjects intended to discover or verify the clinical effects of an investigational product or procedure, and to identify any adverse reactions to an investigational product or procedure with the object of ascertaining its safety and effectiveness. Procedures to assure that the rights, safety, and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki must be followed.³

³ *Adapted from* FDA Guidance on General Considerations for Clinical Trials (ICH-E8) published in the *Federal Register* on December 17, 1997 (62 FR 66113).

2nd Definition: Clinical research is the observation of events in groups of individuals who share a particular characteristic, such as a symptom, sign or illness; or a treatment or diagnostic test provided for the symptom sign or illness. Inferences are made based on comparisons of rates of predefined outcomes among groups. Procedures to assure that the rights, safety, and well-being of study participants are protected; consistent with the principles that have their origin in the Declaration of Helsinki must be followed.⁴

Option 2: Endorse the current list of standards unchanged or with additional characteristics.

Option 3: Endorse existing standards.

Since other government agencies that oversee or conduct clinical research have established guidelines and standards for study protocols, we would like you to consider if endorsing existing standards is judicious and warranted. For example, the FDA Guidance on General Considerations for Clinical Trial (ICH-E8) published in the *Federal Register* on December 17, 1997 (62 FR 66113)). We welcome additional or alternative sources for the committee to consider.

B. Subset of Medicare-specific Standards

The current three Medicare specific criteria are discussed below:

1. The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).

This standard is a legal requirement for coverage of items and services by the Medicare program and may not be appropriately represented as criteria standard for clinical studies. Therefore, this statement will be incorporated into the policy, but no longer considered a standard.

2. The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.

We have received numerous inquiries requesting that we define more clearly what is meant by “therapeutic intent.” In addition, many commenters point out the need to differentiate what is meant by “therapeutic intent” when the intervention is a diagnostic test/procedure versus a therapeutic treatment. In the recent past, a number of safety and toxicity trials have begun to assess the benefit of the intervention under study but have been excluded from coverage since the primary objective has not been therapeutic intent. Thus, we believe that an appropriate definition would be that a qualified trial exhibits therapeutic intent when a major objective of the study seeks as its goal the diagnosis or treatment of disease including observation of benefit of the intervention under study. While this does not require that the primary objective of the trial be one of therapeutic intent, therapeutic intent must be of sufficient importance to the outcome of the study. We propose to define sufficient importance to the outcome of the study to mean that

⁴ *Adapted from* Rothman, Kenneth J., and Greenland, Sander. *Modern Epidemiology*. Second edition. Lippincott Raven. 1998.

the study has appropriate statistical power and planned analyses to ensure that the findings will substantially enhance the scientific knowledge base on the impact of the intervention under study on health outcomes. We would not expect that Phase I trials would commonly meet this definition. The Agency is directed in coverage decisions by a section 1862(a)(1)(A) of the Social Security Act and by a regulation regarding the medical management of a patient— 42 CFR 410.32(a).

3. Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

We propose to clarify the above criteria by stating that, “trials of therapeutic intent may assign patients to a control group.”

Additional Requirements to Be Considered for Inclusion in the Subset of Medicare-specific Qualifying Criteria

4. Registration of Medicare-covered Studies

The executive memorandum that led to the current Clinical Trial Policy stated that a registry for Medicare clinical trials be established for those trials for which the program would pay routine patient care costs. The purpose of this registry was to provide beneficiaries and providers a source of information as to trials covered by Medicare, a mechanism for the Agency to know the trials in which beneficiaries could participate, and enable post-payment review of claims.

Although a registry has not yet been established by CMS, we suggest that this requirement be continued. Concurrent with the implementation of the 2000 Clinical Trial NCD, the National Institutes of Health/National Library of Medicine (NIH/NLM) established a clinical trials registry (ClinicalTrials.gov) to meet the requirement of the 1997 Food and Drug Administration Modernization Act. After a thorough review of the NIH/NLM ClinicalTrials.gov website we believe that all studies covered under this policy should be registered in this registry prior to enrollment of the first subject. Many internationally and nationally recognized research organizations and peer-review publications have ratified the registration of clinical studies into the ClinicalTrials.gov registry. Registration into this registry assures that beneficiaries will have pertinent information about clinical research Medicare supports—an essential component of transparency to facilitate patient-provider informed decision making. The World Health Organization and International Committee of Medical Journal Editors (WHO/ICMJE) data elements are the required data elements in this registry. Information about this registry may be obtained at <http://www.clinicaltrials.gov/>.

5. Dissemination of Findings

Additionally, we suggest that study protocols explicitly address plans for the diffusion of study results and findings. It is imperative that studies for which Medicare has made payment of any clinical costs should be made available to the public regardless of the outcomes. We are aware that ClinicalTrials.gov does not currently have a mechanism for posting results and that most trial sponsors depend on the medical literature for announcing their results. This results in a lack of public knowledge on the results of many trials. CMS will work with other government agencies and the research community to develop routine outlets for release of these results. Until

that is completed, we are proposing that the results for all primary and secondary outcome measures (at each time point) must be made publicly available as the analyses are completed. These can be disseminated to the public in the form of a peer-reviewed publication or in a suitable public Internet-based database. If and when a Federal government database of results becomes available, this would be considered preferable to a sponsor-supported database. For now, a sponsor-supported database would be considered acceptable if it clearly states the sponsor, the relationship of the sponsor to the items being studied, and the methods of scientific review of the results.

6. *Representative Study Samples and Coverage of Clinical Care Costs Under this Policy*
Congress recognized the lack of representation in many research studies in the NIH Revitalization Act of 1993.⁵ The National Institutes of Health implemented the statute in the *Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001*.⁶

The NIH is a recognized leader in the design and conduct of clinical research and has incorporated the NIH Revitalization Act of 1993 into its approval process. Incorporating this concept in the Medicare Clinical Research Policy is warranted to assure this standard is included for clinical research the Medicare program supports. In addition to the subpopulations addressed by the NIH, CMS serves a unique population encompassing the elderly and disabled. Therefore, we suggest that unless there are clear data documenting that no important differences exist within relevant subpopulations, as defined by gender, race/ethnicity, age, or other factors, the study must enroll sufficient numbers of these populations to ensure a valid analysis of the intervention effects.

7. *Representative Study Samples in Research to be Considered for National Coverage*
The Agency wants to support studies that allow Medicare beneficiaries to participate in research studies and encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive. However, a major weakness of many of the high-quality studies that the Agency reviews when considering evidence for an item or service in an NCD is the exclusion of populations that represent the burden of the disease being investigated. This commonly results in scientifically inadequate representation of racial, ethnic, age and gender subgroups in studies, such that subgroup analyses cannot be conducted in a valid manner. Well-designed studies should have protocols that define the populations with the disease being studied and if data is not available that clearly demonstrates a lack of differences of clinical importance in subgroups as defined by gender, race/ethnicity, age, or other relevant subpopulations, then the protocol should discuss the necessary steps to enroll sufficient numbers of these populations to ensure a valid analysis of the intervention effects. Specifically, sufficient Medicare-aged populations must be included to arrive at clinically and statistically significant conclusions if this data is to be used in a subsequent Medicare coverage decision.

⁵ Public Law 103-43.

⁶ http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

8. Study Standards as Stated in an NCD Using Coverage with Evidence Development (CED)
In July 2006, the Agency posted guidelines entitled, “National coverage determinations with data collection as a condition of coverage: Coverage with evidence development.” If an NCD determines that a technology is only covered when used within a research study, the NCD will define the standards such a required study should meet. All CED-required studies will need to meet the general definition of a good study as outlined above. The NCD may define additional or different Medicare-specific standards.

III. PROCESSES TO ENSURE THE STANDARDS ARE MET

Processes Included in the Current Policy

In the current policy, CMS “deems” or considers trials to be qualified if they are:

1. funded by NIH, CDC, AHRQ, HCFA, DOD, or VA;
2. supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, HCFA, DOD, or VA;
3. conducted under an investigational new drug application (IND) reviewed by the FDA; or
4. conducted under the exemption from having an IND under 21 CFR 312.2(b)(1). These studies are deemed automatically qualified until qualifying criteria are developed and the certification process is in place. At that time, the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial and will not be used to retroactively change the earlier deemed status.

The current policy recognized that the standards applied by Federal agencies in their review and funding processes were sufficient to judge the quality of the studies by allowing trials to be deemed to have met the seven highly desirable characteristics of a qualified trial if funded by a Federal agency.

Federally Funded Studies

We propose to continue the first three processes outlined above with some changes. We propose to no longer list each Federal agency in #1 & #2. We will replace the list with “Federal agency.” In addition, we propose to add language that ensures that a Federal agency will have reviewed and approved the study as meeting that agency’s definition of a good study prior to the funding decision.

IND Exempt Studies

21 CFR part 312 requires sponsors who wish to study a drug or biological product in humans to submit an investigational new drug application (IND) to the FDA. However, these regulations also provide for the exemption of some studies from the requirement to submit an IND if they meet certain criteria. For example, clinical investigators of drug products lawfully marketed in the U.S. are exempt from the IND requirements if all of the following apply:

1. The study is not intended to support FDA approval of a new indication or any other significant change in the product labeling.
2. The study is not intended to support a significant change in the advertising for the product.

3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
4. The study is conducted in compliance with Institutional Review Board (IRB) and informed consent regulations set forth in 21 CFR parts 56 and 50.
5. The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).

The 2000 Clinical Trial Policy NCD gave drug trials that are IND exempt the “deemed” status on an interim provision, until the self-certification process was implemented. That process was never developed. We propose that the “deemed” status of IND exempt studies be removed and that IND exempt studies meet the same standards as any other study covered under this policy.

Post-approval Studies

Many items cleared or approved by FDA for marketing have requirements for continued data collection. These are known as post-approval studies. Post-approval studies for devices are not IDE studies and thus do not meet the requirements of the IDE regulation (42 CFR 405.201). Since FDA does not fund these trials, they also do not meet the criteria of the current Clinical Trial Policy. Post-approval studies for drugs also do not meet the current Medicare coverage criteria. We are proposing that any FDA-required or -approved post-approval studies be deemed to have met the definition of a good study.

With these changes, studies will be deemed to have met the definition of a good study if:

1. The study is reviewed, approved and funded by a Federal agency.
2. The study is supported by centers or cooperative groups that are funded by a Federal agency that has reviewed and approved the study.
3. The study is conducted under an investigational new drug application (IND) reviewed by the FDA and authorized to proceed with the study if no deficiencies are identified by the FDA.
4. The study has been required and reviewed by the FDA as a post-approval study.

Self-certification

The current Clinical Trial Policy suggested a process that allowed principal investigators to self-certify that their studies met the standards of good clinical trials. CMS did not implement that process and does not intend the new policy to include that option. We believe that some oversight is both beneficial to the trial designers as well as prudent for CMS. We are proposing to remove that option.

Additional Options to Ensure Standards of a Good Study Are Met

CMS strongly believes that an alternate process for studies without Federal funding is integral to assuring broad access to clinical research participation for all Medicare beneficiaries. CMS agrees with many comments submitted following the posting of the tracking sheet opening the reconsideration of this policy that funding source should not be the only criterion for obtaining Medicare coverage. Therefore, we are listing several options for the MCAC to discuss that could be used to ensure that studies meet the definition of a good study.

1. Approved but Not Funded by a Federal Agency

One option would be to use the processes that the other Federal agencies currently employ to review study proposals and to cover those that are approved but not funded for coverage under this policy. While this would increase access to clinical trials, there are concerns that not all of the trials at the bottom of the priority list would be of a similar quality as those above the funding line.

2. Establish a Federal Inter-agency panel to Review Study Protocols for Medicare Coverage of Clinical Costs

CMS has received comments during the original Clinical Trial Policy development process and during this current reconsideration that a Federal inter-agency panel be formed to review study protocols for Medicare coverage. This group would establish a process to routinely review study protocols and determine if the above standards are met. CMS would need to establish and provide resources towards a process to receive protocols, determine their completeness, prepare them for submission to the panel, collect the panel's recommendations and inform the submitter of the results. Timing and funding are issues that need to be discussed.

3. Establish a Multi-stakeholder Panel to Review Study Protocols for Medicare Coverage of Clinical Costs

Many commenters encouraged CMS to convene a multi-stakeholder panel to develop criteria for covering the costs associated with "non-deemed" trials. They urged that a study's qualifications should be based on scientifically sound criteria, not its funding source. As in the Federal panel (described in #2 above), this multi-stakeholder panel would establish a process to routinely review submitted protocols to determine adherence to the required standards. CMS would also need to establish and provide resources towards the protocol submission process as discussed above. While we strongly support the collaboration between stakeholders, we are concerned whether or not a sustained commitment on the part of multiple stakeholders is possible. This proposal also presents enormous funding and administrative support issues.

4. Federal Agencies Incorporate Medicare-specific Criteria in the Study Panel Scoring Process

Federal agencies that routinely review study protocols could include, as a review item, this policy's definition of a good study with a requirement for the reviewer to recommend whether the study under review meets this definition. This option utilizes current agency processes and reviewers. Since the standards most Federal agencies apply are consistent with CMS standards, this additional step might not impose significant burdens on the reviewers. However, we are concerned about any additional burden in time and effort this endeavor would impose on members of study sections that review studies. Further, proposals submitted for review may increase and thus impact the budget that supports the study sections.

5. Standards for Coverage of Clinical Services when Coverage with Evidence Development (CED) Is the NCD Requirement

As discussed above, CMS may require participation in a clinical study as a condition of coverage. For completeness and consistency, we are listing CED as one means of approving specific clinical studies.

IV. DEFINITIONS TO IDENTIFY COVERED CLINICAL SERVICES

The definitions of covered services must be clear enough to ensure that investigators and providers, as well as Medicare contractors who process claims, can apply them in a consistent manner.

Routine Costs

The current Clinical Trial Policy limits coverage to routine care costs and defines those as:

“...all items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in either the experimental or the control arms of a clinical trial except:

- The investigational item or service, itself;
- Items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

“Routine costs in clinical trials as currently implemented include coverage for:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service--in particular, for the diagnosis or treatment of complications” (NCD Manual § 310.1).

Several clarifications of what is meant by “routine costs” have been proposed. We propose to now refer to routine costs as “routine clinical services.” The following clarifications for what is considered to be a routine clinical service are proposed:

- a. Routine clinical services include items and services that are available to Medicare beneficiaries outside of a clinical study, other than items or services that meet the definition of investigational clinical services.

- b. Routine clinical services include only those items and services used for patient management within the study.
- c. Routine clinical services include items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent),
- d. Routine clinical services include the clinically appropriate monitoring of the effects of the item or service (e.g., blood tests to measure tumor markers), and
- e. Routine clinical services include those required for the prevention, diagnosis or treatment of complications (e.g., blood levels of various parameters to measure kidney function).

Administrative Services

The current Clinical Trial Policy does not define the administrative services provided within clinical studies. We are proposing to define that as “all non-clinical services, such as investigator salaries; protocol development; recruiting participants; data quality assurance activities, statistical analyses; dissemination of findings; and study management.” The activities associated with this definition of administrative services would explicitly be non-covered.

Investigational Clinical Care Services

The current Clinical Trial Policy does not define investigational items or services, though it does exclude them from the definition of routine costs even if that particular item or service would have been covered outside the trial. We believe that to be inappropriate. Therefore, we are proposing a definition of investigational clinical services and the circumstances under which they would be covered. The proposed definition is “those items and services that are being investigated as an objective within the study for their effects on health outcomes, including items and services involved in providing sham procedures.” We are also proposing that we cover investigational clinical services under specific conditions:

a. The item or service is currently available to the Medicare beneficiary and thus eligible for coverage outside the trial. It is unclear why the current Clinical Trial Policy prohibited payment for the item or service under investigation even if that item or service was currently available outside the trial. We propose to change that.

b. The item or service is required through the NCD process for CED and is being evaluated for its effect on health outcomes. One of the goals of the CED process is to increase access to promising technologies. As we have discussed in our CED guidance document⁷, we propose to cover the technology if it is the item or service under investigation.

c. The item has been designated by the FDA as an HUD, has received HDE status and is the investigational item or service in a study that meets the requirements of the policy. Since 1990, Congress has required the FDA to approve certain devices that are designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States. FDA categorizes these devices as Humanitarian Use Devices (HUD) and may provide a Humanitarian Device Exemption (HDE) that allows the device to be marketed for the limited condition. In order for the FDA to authorize the marketing of an HUD, the device manufacturer must submit an HDE application, which has some similarity to a pre-market approval (PMA) application, but

⁷ http://www4.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8

need not present clinical data addressing the effectiveness of the device. Through the review of the application and information provided, the FDA must be able “to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.”⁸ In addition, the manufacturer must show that no comparable devices are available for treatment or diagnosis of the disease or condition, and there are no other means by which the device may be brought to market. The device can have other indications and the affected population can be a small subset of a disease or condition. The HDE holder is required to ensure that an approved device is only used in facilities having an Institutional Review Board (IRB) that continually reviews and approves the use of this device. In addition, the amount charged for the device cannot exceed the costs of the device’s research, development, fabrication, and distribution. Finally, the FDA can require annual reports of the number of devices used to determine continued HUD status.

The FDA requires that labeling for an HUD must state that the effectiveness of the device for the specific indication has not been demonstrated. This level of evidence would generally not reach the level required for national coverage. Several HUDs are currently noncovered by CMS. However, we do believe that this limited population should have access to these technologies. Because of the lower level of evidence for HDEs, we believe it appropriate that the use of these devices in the Medicare population be under closer supervision than other covered devices. In keeping with the FDA regulatory requirements for an IRB and some limited data collection, we are proposing that CMS provide coverage for HUDs with an HDE in studies under this policy when the HUD is the item or service under investigation. We are interested in the MCAC’s recommendations as to whether this should include those HUDs that are currently noncovered by an NCD.

⁸ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm>