MCAC QUESTIONS WORKSHEET

A. Standards for Medicare Coverage of Studies

The clinical trial policy currently defines two separate sets of standards that clinical trials must meet to qualify for CMS coverage. The first three are specific standards that affect Medicare only. The second set of seven "highly desirable characteristics" are general standards for good clinical trials.

General Standards

In this reconsideration, we are asking the MCAC to consider two options for the general standards; 1.) develop a broad definition of a good clinical study, or 2.) recommend that CMS endorse standards of good clinical research as defined in existing guidance documents and texts. If the MCAC recommends a general definition, we would like this body to then consider whether or not the definition should include specific characteristics.

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

CMS provides the following general definitions of clinical studies for discussion:

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 wellbeing of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki must be followed.[1]

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 wellbeing of study participants are protected; consistent with the principles that have their origin in the Declaration of Helsinki must be followed.[2]

Option 1.b. Using the existing "highly desirable characteristics" to define a good clinical study (i.e. no change in current definition)

A good clinical study includes the following attributes: The principal purpose of the study is to test whether the intervention potentially improves the participants' health outcomes; the study is well-supported by available scientific and medical information or it is intended to clarify or

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

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

establish the health outcomes of interventions already in common clinical use; the study does not unjustifiably duplicate existing studies; the study design is appropriate to answer the research question being asked in the study; the study is sponsored by a credible organization or individual capable of executing the proposed study successfully; the study is in compliance with Federal regulations relating to the protection of human subjects; and all aspects of the study are conducted according to the appropriate standards of methodological and scientific integrity.

Option 1.c. Endorsing external sources that describe characteristics of a good clinical study (e.g., FDA Guidance on General Considerations for Clinical Trial (ICH-E8) published in the *Federal Register* on December 17, 1997 (62 FR 66113)).

Question 1	
How should CMS define a good clinical study? (Option 1.a, 1.b, or, 1.c)	
Recommend any changes/other options	

Medicare-specific standards.

CMS will continue Medicare-specific requirements in the revised clinical trial policy. There are currently three Medicare-specific criteria. The first is a statutory issue and not a clinical study standard and will be removed from consideration.

The remaining two current standards are:

- The study must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent. The trial must enroll patients with the diagnosed disease.
- 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.

Question 2.a	
Should these two current standards remain in the revised policy?	Yes/No
Recommend any modifications:	

Discussion Question: CMS seeks to clarify the definition of therapeutic intent. A proposed definition is that "a qualified study exhibits therapeutic intent when a major objective of the study seeks as its goal the diagnosis or treatment of disease including the observation of benefit of the intervention under study". Do you concur with the proposed definition or do you suggest an alternative definition for therapeutic intent? (If suggesting an alternative, please elaborate) Should CMS define therapeutic intent differently for studies evaluating diagnostic services?

Question 2.b	
CMS is proposing several new Medicare-specific standards. Should CMS add the following standards?	Yes/No
1. The study must be registered on the ClinicalTrials.gov website.	
2. The study protocol must specify method and timing of public release of results regardless of outcome or completion of trial.	
3. The study must have explicitly discussed consideration of relevant subpopulations (as defined by age, gender, race/ethnicity, or other factors) in the study protocol.	
4. If the study results are to be used to inform Medicare coverage policy, the study must contain an explicit discussion of how the enrollment process will ensure that sufficient Medicare populations are included to clinically and statistically determine that Medicare populations benefit from the intervention.	
5. Any standard required through a national coverage determination using coverage with evidence development (CED).	
Recommend modifications or other options.	

B. Processes to Ensure the Standards are Met

The current clinical trial policy does not outline a process to ensure that the Medicare-specific standards are met. CMS contractors have assumed that responsibility in some instances and CMS will clarify that process in its proposed decision memorandum using the usual and customary national coverage determination procedures that communicate instructions to providers and contractors.

The clinical trial policy currently "deems" that the broadly defined characteristics of a clinical trial have been met if the conditions listed in question 3 are met. Thus, if a study meets any one of the following, that will be sufficient by itself for the study to be deemed to have met the

definition of a good clinical study. CMS is asking the MCAC to recommend if the first three should be continued, if the fourth should be removed and if another should be added. Please note that we have clarified "funded" to include reviewed and approved.

In addition, the current clinical trial policy suggested a process that allowed principal investigators to self-certify that their study met the standards of a good clinical trial. CMS did not implement that process and does not intend the new policy to include that. However, CMS is interested in other avenues for studies to be approved and is asking the MCAC to recommend appropriate methods.

Question 3	
Should studies continue to be "deemed" to have met the definition of a good clinical study if:	Yes/No
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.	

Question 4: The current policy listed a fourth temporary option for studies to be 'deemed' to have met the current standards:

> "The drug under study is exempt from having an IND under 21 CFR 312.2(b)(1)."

This option was to have been removed once the self-certification process was implemented. IND Exempt studies, as stated in 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 parts 56 and 50 (21 CFR parts 56 and 50).
5. The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).

Question 4	Yes/No
Since the self-certification did not occur and CMS does not intend to include this in the revised policy, CMS is proposing to require IND Exempt studies to follow the other processes allowed under the revised policy. Does the panel agree?	

Question 5	Yes/No
Should CMS consider studies that have been approved by but not funded by a Federal agency as "deemed?"	

Question 6	Least Desirable 1 ↓ Most Desirable 5
Should CMS adopt additional methods to approve studies for Medicare coverage such as:	
1. Any study required through a national coverage determination using coverage with evidence development (CED).	
2. Establish a Federal inter-agency panel to review study protocols.	
3. Establish a multi-stakeholder panel to review study protocols. (Discuss funding issue).	
4. Work with other Federal agencies to incorporate into their current study panel scoring process an item that asks "Does this study meet the requirements of the Medicare Clinical Trial Policy?"	

C. Clarification to Definition of Clinical Services:

The current clinical trial policy defines those items and services that are to be covered in clinical trials as "routine care costs." The policy 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:
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> - 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.

CMS is proposing that the term "routine costs" be changed to "routine clinical services" and that the definition be changed to the following:

Routine clinical services are those items and services that are:

a. Available to Medicare beneficiaries outside of a clinical study, not including items or services that meet the definition of investigational clinical services;
b. Used for patient medical management within the study;
c. Required for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent);
d. Required for the clinically appropriate monitoring of the effects of the item or service (e.g., blood tests to measure tumor markers); or
e. Required for the prevention, diagnosis or treatment of complications.

Question 7	
Do you believe this change clarifies the definition?	Yes/No
What changes would you suggest?	

CMS is also proposing that additional categories of "administrative services" and "investigational clinical services" be added.

Question 8a	
Should CMS adopt the following definition?	Yes/No
Administrative services are all non-clinical services such as investigator salaries; protocol development; recruiting participants; data quality assurance activities, statistical analyses; dissemination of findings; and study management. Administrative services are not covered.	
What changes would you suggest?	

Question 8b	
Should CMS adopt the following definition?	Yes/No
Investigational clinical services are those items and services that are being investigated as an objective within the study for its effect on health outcomes including items and services involved in the control arm of the study. Investigational clinical services meeting one of the following conditions are covered.	
1. The item or service is currently available to the Medicare beneficiary outside the study.	
2. The item or service is required through the NCD process for CED and is being evaluated for its effect on health outcomes.	
3. 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.	
What changes would you suggest?	