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**Comments also submitted electronically at:
<http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=186>**

RE: Proposed Decision Memo for Clinical Trial Policy (CAG-0071R)

Dear Dr. Phurrough:

The Association of American Medical Colleges is a nonprofit association representing all 125 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems, including 68 Department of Veterans Affairs medical centers; and 94 academic and scientific societies. Through these institutions and organizations, the AAMC represents 109,000 faculty members, 67,000 medical students, and 104,000 resident physicians. The AAMC is pleased that CMS is revising its policy on payment for items and services for Medicare beneficiaries who participate in clinical trials and appreciates this opportunity to provide comments. We welcome the Agency's consideration of the many viewpoints expressed about this policy and the thoughtful proposals that have been put forward for comment.

As part of the process for reviewing this proposal, the AAMC spoke to many of the individuals at our member institutions who will be charged with implementing the clinical research policy (CRP). These discussions have led the AAMC to conclude that the new policy, although containing many commendable features, requires additional changes and clarifications, described below, that will allow CMS to issue a clear, understandable policy that can be implemented without institutions having fears of inadvertently submitting an incorrect bill to Medicare for the items and services covered by the CRP.

Conflict Between Standards for a Good Clinical Trial and Medicare-Specific Standards and Clarification of Regarding Phase I Studies

For a trial to qualify for Medicare coverage, it must first meet the eight "standards for a good clinical trial." Once these standards are met, a trial must meet a minimum of 5 Medicare-specific standards (or more if the trial is being conducted under the coverage with evidence development process). The first requirement for a good clinical trial is that:

The *principal purpose* of the research study is to test whether a particular intervention potentially improves the participants' health outcomes. (emphasis added)

The first Medicare-specific standard appears to be contradictory to this, as it says that:

The clinical research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols commit to *measuring therapeutic outcomes as one of the objectives*, may meet this standard only if the disease being studied is chronic, life threatening, or debilitating. (emphasis added)

The AAMC requests that CMS clarify whether a study that has “measuring therapeutic outcomes as one objective” could also have as its “principal purpose” to test whether a particular intervention potentially improves the participant's health outcomes. If not, then the policy would not allow for the coverage of any Phase I studies. CMS could provide clarity to this issue by revising the first general standard for a scientifically and technically sound clinical research study as follows:

One purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.

The AAMC also requests that CMS clarify that the requirement in the Medicare-specific standard that the “disease is chronic, life threatening, or debilitating” only applies to Phase I trials. The language suggested by AHRQ provides more precision, and should be considered for inclusion in the final CRP:

The research study must not be designed primarily to test toxicity or disease pathophysiology. Phase I trials that have therapeutic intent as one of the objectives may meet the CMS beneficiary protection standard only if the disease is chronic, life threatening, or debilitating.

Need for Grandfathering Certain Trials—Registration on ClinicalTrials.gov and Protocol Discussions

The AAMC strongly supports the registration of all clinical trials on ClinicalTrials.gov. However, the proposed CMS requirement is mandates that the registration occur “prior to the enrollment of the first study subject.” The AAMC also supports the three proposed requirements related specifically to the contents of the protocol (though with modifications that will be discussed below). However, AAMC suggests the need for CMS to grandfather trials under two different circumstances:

1. **On-going trials not registered on ClinicalTrials.gov.** Trials that currently are being paid under the 2000 national coverage decision, but are not registered on ClinicalTrials.Gov should be grandfathered because it will be impossible for them

to meet this standard since the first study subject already is enrolled. If these trials suddenly becomes ineligible for Medicare coverage, both the institutions where the studies are being conducted and the study participants will face hardship. Institutions negotiated payment with sponsors based on the reasonable belief that some of the costs of these trials could be billed to Medicare. Should this anticipated payment disappear, it is possible that some of these trials could not continue, to the detriment of those already enrolled in them. An alternative would be for CMS to require that on-going trials that meet the standards of the 2000 NCD be registered on ClinicalTrials.gov within 60 days of the effective date of the CRP if they wish to remain eligible for Medicare payment.

2. **Protocols that have been submitted to an IRB, but are not yet approved as of the effective date of the CRP.** The development of a protocol to the point where it is submitted to an institutional review board (IRB) is a long and intensive process. Protocols submitted prior to the effective date of the CRP may not contain the required elements regarding release of all pre-specified outcomes; discussion of inclusion criteria and considered relevant subpopulations; or a discussion of how the results will generalize to the Medicare population. If, as of the effective date of the CRP, the studies have been submitted to an IRB, they should qualify for Medicare payment as long as they would have qualified under the 2000 NCD. Only studies submitted to an IRB on or after the effective date of the CRP should be required to comply with its requirements.

To minimize problems related to on-going studies and studies already submitted to an IRB, the AAMC further suggests that the effective date of the CRP be at least 30 days after the final policy is published on the CMS website.

Finally, CMS indicates in the proposed CRP that it will ‘review adherence’ to the requirement for registration on ClinicalTrials.gov. The AAMC requests that CMS clarify whether CMS intends to audit only that a trial actually is registered, or whether adherence depends on the inclusion of certain information on the ClinicalTrials.gov site. If the latter, please specify the information that must be included in the registration for the purposes of a CMS audit.

Method and “Fulfillment” of Timing and Public Release of All Pre-Specified Outcomes

The AAMC strongly supports the requirement that trials qualifying for Medicare payment must publicly release all pre-specified outcomes and encourages our members to commit to such release of all trial results. Rapid communication of results is particularly important in the case of either clear problems with the trial that leads to termination, or the determination of a clear benefit. The AAMC suggests that when a termination occurs public release of the reasons for the termination decision should occur within no more than 7 days of the termination.

Of concern to the AAMC is the requirement for “fulfillment” of the public release of information. The sponsor may be responsible for release of the results, and thus it may not be possible for the hospital to control whether or when such release is made. It also is possible that a journal will not accept publication of the study results, or that publication may be delayed. Institutions should not face the possibility that Medicare will request the return of “overpayments” for a clinical trial if, for reasons outside of their control, the public release is not “fulfilled.” The AAMC recommends that CMS delete the requirement for “fulfillment.”

While study results can be posted on the web, CMS acknowledges that there is no site that is supported by either the government or a neutral private party. At this time such posting is most likely to occur on a sponsor’s website and would not be subject to review by outside bodies. It would be preferable if there were a governmental or other neutral-party repository where information is made publicly available. The most direct way to accomplish this would be to authorize and enable ClinicalTrials.gov to develop this capability. The AAMC would be happy to work with CMS and other federal agencies on the establishment of such a site.

Generalizing the Study to the Medicare Population

The AAMC agrees that it is important that any study that merits payment by Medicare by one that may be of benefit to the Medicare population which includes both the aged and the disabled. Therefore, it is reasonable that the study protocol contain such a discussion. However, CMS also is proposing that:

The protocol describes the potential impact of age-specific and other factors on outcomes and whether the research study is powered sufficiently to draw conclusions with respect to the Medicare population.

The AAMC is concerned that this sentence imposes a further requirement on study design, i.e. that sufficient Medicare patients be enrolled such that a valid scientific conclusion can be reached based on analysis of **only** the Medicare patients. The consequence of such a requirement would be the need for a far greater number of subjects potentially causing sponsors to **exclude** Medicare patients in order to control study costs. General Standard 4 already addresses study design: “The research study design is appropriate to answer the research question being asked in the study”. To avoid unintended and unnecessary exclusion of Medicare patients from studies which can benefit them, AAMC supports using the MedCAC recommended revision instead:

“The protocol must contain a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients benefit from the intervention and whether the results are generalizable to Medicare beneficiaries.”

Routine Clinical Services

The AAMC appreciates the changes that CMS has made to this requirement. Payment for “routine clinical services” rather than “routine costs” adds much clarity to this policy.

Deemed Studies

CMS lists five types of studies that will be “deemed” to have met the eight standards for a good clinical trial. The second type of “deemed study” is one that is reviewed and approved by a health care research center or cooperative health care research group, funded by a Federal agency, provided that:

The Federal Agency reviews and approves the applicant research centers’ or cooperative research groups’ subcontract and sub-grant funding requirements, selection procedures and oversight methods, and determines that those processes provide the same level of protocol review as provided by the supporting Federal Agency.

It will not be possible for hospitals to determine if this review and approval has occurred as there is no place they can turn to find this information. This puts them at risk for incorrectly billing Medicare if they submit bills for any studies that would fall into this category. If CMS retains this requirement, it should consider entering into agreements with the relevant Federal agencies to require that they report the results of this review and approval to a web site that will be publicly accessible to any institution that needs to know if a study qualifies under this deemed category.

IND-Exempt Trials

The AAMC is sympathetic to the concern expressed by CMS that many IND-Exempt trials do not have an “external process for ensuring that the standards of this Medicare policy are met.” We also recognize that many IND-Exempt trials involve new combinations of drugs or new uses of drugs that may be of direct benefit to the Medicare population. The exclusion of most IND-Exempt studies from Medicare payment may be an impediment to much useful research. In its recommendation, MedCAC suggested that “CMS develop a mechanism to certify other entities to deem research studies,” such as “professional societies, private foundations, academic health centers, and university scientific review panels.” The AAMC supports this idea as an alternative to the elimination of most IND-Exempt studies from Medicare coverage and would be pleased to work with CMS and others to implement it.

Medicare Secondary Payer Rule and Medicare Advantage Enrollees

The AAMC remains concerned that even with revisions and clarifications to the clinical trials policy, the outstanding questions regarding the interaction of this policy with the MSP rules remain an impediment to the enrollment of Medicare beneficiaries. That is equally true of the inherent disadvantages to Medicare Advantage enrollees who may

wish to participate in a clinical trial but could be discouraged by the stiff out-of-pocket costs that they would incur. We urge all relevant parts of CMS to work in concert to produce a clinical research policy that addresses all remaining concerns and removes barriers to the enrollment of Medicare beneficiaries in clinical trials.

If you have any questions, please contact Ivy Baer, Division of Health Care Affairs, at 202-828-0499 or ibaer@aamc.org.

Sincerely,

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