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Heart House
2400 N Street, NW
Washington, DC 20037-1153
USA

202.375.6000
800.253.4636
Fax: 202.375.7000
www.acc.org

May 10, 2007

Leslye K. Fitterman, Ph. D.
Centers for Medicare and Medicaid Services
Department of Health and Human Services
P.O. Box 8014
Baltimore, MD 21244-8014
Re: Draft National Coverage Decision (NCD) Memorandum on Clinical Trial Policy (CAG-00071R)

Dear Dr. Fitterman:

The American College of Cardiology (ACC; the College) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) draft National Coverage Decision (NCD) Memorandum (Draft Memo) on Clinical Trial Policy (CAG-00071R). The ACC is a 34,000 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 College supports most of the changes to the clinical trial policy proposed in the Draft Memo as written. We commend CMS for using its position in setting Medicare coverage policy to promote beneficiary participation in clinical trials by expanding coverage of routine medical care associated with such studies.

The ACC remains concerned as to several provisions of the Draft Memo that we believe could have a chilling, counter effect to CMS' stated goal of encouraging greater participation

of Medicare beneficiaries in clinical research. Of the ten issues CMS identified in the NCA reconsideration Tracking Sheet that need to be addressed by the new NCD, our reservations are focused on the following three proposed changes to the current policy:

> #3. Develop criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics;
> #4. Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials; and
> #6. Clarify the scientific and technical roles of Federal agencies in overseeing IND Exempt trials.

Our specific comments on each of the aforementioned proposals are as follows:

#3 - "Develop criteria to assure that any Medicare-covered clinical research study includes a representative sample of Medicare beneficiaries. by demographic and clinical characteristics:"

ACC Recommendation:
The ACC recommends that CMS engage stakeholders in a collaborative process to define what constitutes a sufficient "discussion of how the results will generalize to the Medicare population" in a given study's research protocol for clarification purposes and to minimize the creation of any potential disincentives for researchers to include Medicare beneficiaries in their studies.

Discussion:

As previously stated in our November 24, 2006 comment submission, the ACC appreciates CMS' concern in covering research that will, *inter alia,* benefit Medicare beneficiaries. The ACC did express reservations, however, with the lack of specificity with which the NCD would define standards for such research studies to achieve a "demographic balance." Further, we shared our concern that "[w]hile the goal of ensuring greater participation of Medicare beneficiaries in clinical trials is desirable, the potential means for achieving this could, in practice, prove to be a disincentive for researchers to include Medicare patients in their studies."

While we applaud CMS' decision not to employ any stringent "representative sample" requirement as a condition for CMS coverage of routine costs of care for trials, we remain concerned with the lack of specificity in what constitutes a sufficient "discussion of how the results will generalize to the Medicare population" in a given study's research protocol.

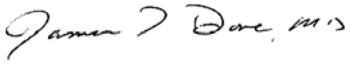
#4 - "Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials:"

ACC Recommendation:
The ACC recommends that CMS engage in a consultative process with stakeholders to develop guidance on the types of costs to be included and excluded under the definition of "routine care costs" as provided in the Draft Memo.
Discussion:
Although the College commends CMS for providing generalized categories of "routine care costs" vs. strict definitions and examples, we remain concerned that absent agency guidance practitioners will shoulder unnecessary risk for making good-faith errors in interpretation or application of various types of claims they believe to be covered by the categories provided in the Draft Memo. Without additional clarifying guidance, developed with the input of stakeholders, the ACC believes the proposed criteria for coverage of routine care costs unnecessarily invite potential risks for practitioners of incurring criminal and civil monetary penalties-thereby serving as a possible disincentive for researchers to include Medicare beneficiaries in their clinical studies.

#6 - *"Clarify the scientific and technical roles of Federal agencies in overseeing IND Exempt trials:"*
ACC Recommendation:
The ACC recommends that CMS clarify what is meant by its proposal to have IND-Exempt trials meet the "other criteria in this [Clinical Research (CRP) NCD] policy." Does this refer to the proposed requirement that a research protocol stipulate/discuss how the research to be conducted will benefit the Medicare population? If not, how then does CMS propose to review IND-Exempt trials without compromising its stated position that FDA retain full control of the IND and IND-Exempt regulatory frameworks?
Discussion:
As you are aware, in order to receive an "IND-Exempt" designation from the FDA, the study must meet certain requirements that, if met, justify the FDA's suspension of standard IND requirements for clinical trials. (See 21 CFR Part 312). Adding a separate layer of regulatory review that is independent from FDA jurisdiction unnecessarily adds administrative burdens for researchers that could serve as disincentives for researchers to include these populations in their studies. If the purpose of revising the Clinical Trials NCD is to encourage Medicare beneficiary participation in such research, the expansion of Federal oversight into areas where it is not needed can, in fact, be counterproductive at best and detrimental at worst.

*****

The ACC reiterates its appreciation to CMS for the opportunity to comment on the draft NCD memorandum on clinical trials. The College is eager to assist CMS in developing any further changes to this policy, and would welcome such an opportunity. If you have any questions, please contact Sergio A. Santiviago, Senior Specialist, Regulatory Affairs at 202.375.6392, or by e-mail at ssantivi@acc.org.
Sincerely,



James T. Dove, M.D., F.A.C.C.
President
cc: Jack Lewin

May 10, 2007

BY ELECTRONIC DELIVERY

Steve Phurrough, M.D.
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mailstop: C1-12-28
7500 Security Blvd.
Baltimore, MD 21244

Re: Proposed Decision Memorandum for Medicare National Clinical Trial Policy (CAG-00071R)

Dear Dr. Phurrough:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) Proposed Decision Memorandum for Medicare National Clinical Trial Policy (CAG-0007lR) (hereinafter "Proposed CRP") as a reconsideration of its national coverage decision (NCD) on Medicare coverage of clinical trials. BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the globe. BIO represents more than 1,100 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. Our research initiatives advance the understanding of disease pathology and therapeutic mechanisms of action, clinical effectiveness, health-related quality of life, and health economic impacts of therapies in addition to clinical safety and efficacy.

BIO strongly supports evidence-based medicine and is committed to increasing the body of evidence available regarding diseases and their treatments. Our members invest millions of dollars each year on clinical studies, both before and after Food and Drug Administration (FDA) approval of their therapies, 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 practice of medicine and patient care. BIO also is committed to ensuring beneficiary access to innovative biological therapies. To that end, we support CMS' efforts to revise its NCD on Medicare coverage of clinical trials. We believe that a clarification of Medicare's coverage policy

for clinical trials has the potential to strengthen the ability of biotechnology companies to develop and evaluate innovative therapies that will benefit Medicare beneficiaries.

As a general comment, BIO is concerned that the Proposed CRP diverges from the original intent of the agency's policy on Medicare coverage of clinical trials. In 2000, when the NCD on Medicare coverage of clinical trials first was developed, CMS (then the Health Care Financing Administration) recognized that beneficiaries should not be denied coverage of medically necessary care simply because that care was provided in the context of a clinical trial. The stated goals of the 2000 NCD were as follows: (1) to allow Medicare beneficiaries to participate in research studies, (2) to encourage research that adds to knowledge about therapies in the Medicare population and, by doing so, improve the quality of care that Medicare beneficiaries receive, and (3) to allow Medicare beneficiaries access to care that may have a health benefit, but for which unrestricted coverage is not yet available. [1]

BIO is concerned that the Proposed CRP not only moves away from these underlying goals, but that the Proposed CRP will in fact be in conflict with them. Specifically, we are concerned that CMS may be increasing the burdens on trial sponsors seeking Medicare coverage for reasonable and necessary care. In addition, although the Proposed CRP would greatly expand the scope of research studies subject to the requirements of the CRP, it also could create confusion about coverage of services that are currently covered, such as already-approved therapies, when provided in routine post-approval studies required by FDA. This confusion, and the potential bureaucratic burden it could impose on clinical researchers, could have a chilling effect on participation in clinical trials aimed at generating the very medical evidence CMS seeks.

BIO urges CMS to keep its underlying goals in mind when finalizing the CRP. The agency should clarify the requirements of the CRP in a manner that promotes Medicare beneficiary enrollment into clinical trials and assures them of coverage for their routine medical costs while enrolled in these clinical trials. Specifically, BIO requests that CMS include as "deemed" clinical trials exempt from the investigational new drug application (IND) process, at least until a separate centralized mechanism is established for approving these studies for inclusion. Second, BIO supports CMS' proposal to cover investigational clinical services in certain circumstances, and we seek additional clarification with regard to this proposal. Third, BIO believes that greater detail is needed in the implementation of certain of the Medicare-specific criteria in order to give beneficiaries, providers, and trial sponsors the certainty necessary to achieve the goals of the CRP. Fourth, BIO remains concerned that the CRP, and in particular those research studies that require Coverage with Evidence Development (CED), will impose additional data collection requirements on trial sponsors and asks CMS to consider ways to pay for some of the costs of those additional data requirements. Fifth, we urge CMS to address the Medicare Secondary Payer issues within the context of the CRP. Finally, BIO requests that CMS clarify the timeframe for implementation of the CRP and its applicability to research studies in various stages of development. These comments are discussed more fully below.

I. **Coverage of IND-exempt Trials**

In the Proposed CRP, CMS proposes to remove IND-exempt trials from the list of research studies "deemed" in compliance with the CRP, but does not provide another mechanism for these trials to be covered. BIO is extremely concerned about this proposal. We believe that failure to grant deemed status to IND-exempt studies will have the effect of limiting research studies in which Medicare beneficiaries are able to participate, particularly in areas of unmet need such as oncology. BIO urges CMS to extend deemed status to IND-exempt research studies permanently. Alternatively, BIO urges CMS to include IND-exempt studies as "deemed" until a separate and centralized approval process can be established and implemented for these studies.

Exemption from the IND process is intended to apply primarily to researchers "who are beginning to explore new uses for marketed drugs *(i.e.* not pivotal studies) or who are using the drug as a research tool." [2] An IND-exempt investigation is permitted only where safety is not an issue and the investigation is not being conducted to support a labeling change such as a new indication or a comparative safety claim.[3] FDA expressly has encouraged use of this IND-exempt process for qualifying trials because these trials play an essential role in exploring innovative uses for approved therapies. For example, in 2004, FDA urged the oncology industry not to submit INDs for all clinical research for oncology products but instead to use the IND-exempt process where possible.[4] IND-exempt trials are a critical part of an established federal regulatory mechanism designed to expedite the approval of cancer therapies and encourage new uses of marketed products in cancer treatment. Outside the oncology setting, IND-exempt trials have been influential in the post-approval development of many important therapies, and this is increasingly true as more companies seek to use the IND-exempt process, at FDA's urging.

Designating IND-exempt trials as "deemed" qualified for Medicare coverage will reduce uncertainty among patients and providers regarding Medicare coverage for routine clinical services. While sponsors currently may seek coverage from local contractors, this process is inefficient and may result in varying coverage decisions, which poses challenges for research studies occurring in multiple sites. Failure to provide a clear centralized approval process for routine clinical services to be covered when part of an IND-exempt trial could render Medicare beneficiaries unable to obtain consistent coverage for therapies received during research studies that otherwise would be reimbursed outside the investigator-initiated trial. This will deter seniors from enrolling in potentially beneficial investigator-initiated studies and will deter publication of outcomes and data that could help improve the lives of Medicare beneficiaries. The inability of Medicare beneficiaries to participate in these critical research studies will undermine the fundamental goal of the CRP.

BIO appreciates CMS' acknowledgement that there is a "need to explore alternative processes for approving other types of studies such as IND exempt studies and studies of orphan drugs."[5] We support CMS' statement that it, along with the Agency for Healthcare Research and Quality (AHRQ), will seek public input in a discussion of

various options. Nonetheless, BIO is concerned that this process may not be established in a timely manner. In issuing the NCD for clinical trials in 2000, CMS included as "deemed" IND-exempt trials only until other qualifying criteria could be developed. These criteria never were developed, and, as a result, IND-exempt trials have continued to operate as "deemed" under this temporary status. Failure to continue to deem IND-exempt trials, combined with delays in establishing a separate process for IND-exempt trials, will deny Medicare coverage to beneficiaries who could benefit from these clinical research studies. Leaving beneficiaries without access to coverage for these critical studies as well as without access to potential new therapies under study. It is imperative that CMS establish a clear and immediate avenue for centralized approval of IND-exempt trials. BIO urges CMS to undertake this effort expeditiously and to continue to cover IND-exempt studies under the CRP until such processes can be implemented. This is necessary to ensure that Medicare beneficiaries have access to the full range of research studies being conducted and that they are able to participate in the studies that are most appropriate for their conditions.

II. Coverage of Investigational Clinical Services

BIO supports CMS' proposal to cover investigational clinical services in Medicare-covered research studies both (1) where coverage for such services is a Medicare defined benefit, and (2) when the service is required as a condition of coverage pursuant to a NCD using CED. In order to achieve the CRP's goal of promoting Medicare beneficiary participation in clinical research, it is critical that a beneficiary be able to obtain coverage for the items and services that would be covered outside the context of a research study. In some research studies, the item or service being studied is not experimental and already has been deterrl1ined to be reasonable and necessary for purposes of Medicare coverage. In these circumstances, Medicare should cover the investigational item or service within the context of a research study to the same extent as coverage otherwise is available to Medicare beneficiaries. BIO urges CMS to finalize this proposal and to clarify that coverage for the investigational item or service is available to beneficiaries participating in a research study in the same manner and to the same extent coverage is available to those beneficiaries not participating in the research study. BIO also urges CMS to include in the definition of investigational clinical services coverage for off-label indications for approved drugs and biologicals in Phase III studies.

In addition, BIO believes that CMS must not use the CRP to limit coverage for items and services currently covered by Medicare outside the context of a research study. Under Parts A and B, Medicare reimburses for drugs and biologicals in a range of settings. This includes coverage for on-label indications as well as off-label indications for cancer therapies when the indication is listed in an approved compendia and for medically accepted uses of other drugs and biologicals at the discretion of each Medicare contractor. We urge CMS to clarify that it does not intend the CRP to narrow that existing coverage or to require these covered uses to be part of CED or another study subject to CRP. Instead, Medicare coverage of approved therapies should not change depending on whether the therapy is part of a research study. Specifically, these therapies

must continue to be covered consistent with existing reimbursement rules when provided as part of a research study that meets the requirements of the CRP.

BIO also supports coverage of the investigational item or service required as part of a NCD using CED. This will help to make CED a more feasible approach for trial sponsors, promote Medicare beneficiary enrollment into clinical trials, and increase the medical knowledge about therapies that have important implications for Medicare beneficiaries. Again, however, we are concerned that CMS not use the CRP to require otherwise covered therapies to be in a research study with CED in order for Medicare coverage to be available.

III. Implementation of the Medicare-Specific Criteria

As a general comment, BIO is concerned that many details regarding the implementation of this CRP are not clear. In particular, it is not apparent from the Proposed CRP how clinical trial sponsors or Medicare beneficiaries will know when a particular trial has met the criteria set forth in the CRP and thus the trial has been approved for coverage. This is particularly true with respect to the Medicare-specific criteria, and we believe more detailed guidance is needed with respect to the process for approving these criteria in order for trial sponsors to have certainty regarding Medicare coverage before enrolling beneficiaries in a clinical research study.

CMS proposes to clarify in the CRP that "CMS will use routine processes to ensure that the Medicare-specific standards and any standards required through the NCD process using CED are met."[6] We urge CMS to provide greater detail on how this approval process will work and to ensure that it is implemented in a manner that assures trial sponsors of certainty of Medicare coverage in advance of a research study and not retroactively. We understand that CMS may be considering a process by which it would review a random selection of research studies on a retrospective basis. We are extremely concerned that this approach would make both providers and beneficiaries reluctant to participate in research studies. These results would render the fundamental purpose of the CRP meaningless. If an approval process is established for Medicare-specific criteria, we encourage CMS to require submission of only the aspects of the protocol related to the Medicare-specific criteria rather than submission of the entire protocol.

Also with respect to the Medicare-specific criteria, BIO supports CMS' efforts to include certain Phase I trials in the CRP and requests certain clarifications of CMS' approach. Early phase trials are the building blocks for the development of approved therapies, and it is important to ensure that trial sponsors are not inappropriately burdened in the conduct of these studies in order to further the participation of Medicare beneficiaries. BIO also is concerned that some of the Medicare-specific criteria may not be appropriate for all research studies. BIO urges CMS to establish its standard regarding the consideration of certain subpopulations as well as the criteria related to the consideration of Medicare-specific issues in trial design in a manner that recognizes the wide range of research studies. We have discussed each of these comments in more detail below.

A. **Coverage for Beneficiaries Participating in Phase I Research Studies**

Under the Proposed CRP, one of the proposed Medicare-specific criteria is that the clinical research study not be designed to exclusively test toxicity or disease pathophysiology. The proposed criterion goes on to state that "[r]esearch 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."

BIO believes it is critical that CMS expand its coverage policy to include expressly all Phase I studies except for those conducted in healthy volunteers/subjects, as well as include all Phase II studies. The current coverage requirement that clinical trials have therapeutic intent unfortunately leads to confusion and inconsistent coverage determinations. Under the existing NCD, coverage for Phase I studies frequently is denied and, under some narrow interpretations of the existing NCD, coverage is limited only to Phase III studies. BIO believes that this harms Medicare beneficiaries' access to promising new investigational drugs in the early stages of their development, particularly for diseases where there exists no current standard of care or where other treatment options have failed. Moreover, Phase I trials have an implicit therapeutic intent as part of research into the development of new therapeutic interventions, and it is only as a result of the conduct of these early phase trials that later phase studies are feasible. BIO supports CMS' proposal to expressly include certain Phase I trials under the CRP.

We suggest, however, that CMS revise the language to more closely mirror that proposed by the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) or AHRQ in finalizing this standard. Specifically, we are concerned that the statement that "[r]esearch 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" can reasonably be construed to mean that all research studies, not just Phase I studies, may be covered only if the disease being studied is chronic, life threatening, or debilitating. We do not believe that CMS means to preclude Medicare coverage of any research study that does not meet this standard. Instead, we suggest that CMS revise this criterion to state that "The research study must not be designed primarily to test toxicity or disease pathophysiology in healthy individuals. Phase I trials that have therapeutic intent as one of the objectives may meet this standard if the disease is chronic, life-threatening, or debilitating." This revised language would more clearly indicate what trials may not be covered under the CRP and would limit the restriction in coverage to those Phase I trials studying healthy volunteers/subjects.

B. Registration on Clinicaltrials.gov

BIO supports the concept of trial registration, particularly as a means for Medicare beneficiaries and others to learn about the research studies particularly relevant to their condition. We request that CMS provide study sponsors a reasonable way to comply with this requirement, such as specifying that posting on clinicaltrials.gov must

occur within 30 days of a trial's approval by an institutional review board (IRB) or first patient visit. We ask that CMS work to make the website more user friendly for Medicare beneficiaries. In addition, CMS should provide links from Medicare.gov for beneficiaries interested in participating in trials and clarify that research study participation should not result in lack of coverage for routine care.

C. Participation of Medicare Beneficiaries in Research Studies

BIO supports CMS' goal of encouraging more Medicare beneficiaries to participate in research studies, and we believe that CMS' efforts to clarify Medicare coverage of clinical trials by developing a new CRP could have the effect of making clinical trials more available to Medicare beneficiaries. We appreciate CMS' efforts to develop guidelines regarding the representation of Medicare beneficiaries in Medicare-covered trials in a manner that reflects the challenges of enrolling Medicare beneficiaries and fosters the goal of increasing the participation of such patients. With respect to the Proposed CRP standard that the research protocol "must have explicitly discussed inclusion criteria and considered relevant subpopulations," however, BIO is concerned that this standard does not reflect the nature of the wide range of studies that will be subject to the CRP. BIO recognizes the importance of including relevant subpopulations where appropriate in clinical research. However, we are concerned that this standard, as proposed, will eliminate smaller studies from the CRP. Many trials covered under the current NCD involve only small numbers of patients. In a small trial, including many Phase II studies, it may not be possible to assess results by certain subpopulations. This standard would have the effect of denying Medicare beneficiaries access to a wide range of small trials.

BIO also appreciates CMS' recognition that establishing stringent criteria regarding the enrollment of Medicare beneficiaries could have the effect of limiting beneficiary access to trials. This is critical in ensuring that Medicare coverage is available to those beneficiaries who do qualify for and choose to enroll in research studies. Many of the therapies in biotech companies' pipelines target conditions that primarily affect seniors, an important and growing population in need of new drug development for conditions common in later life. Member companies long have sought innovative therapies for Medicare's disabled population. It is critical that those Medicare beneficiaries who are able to qualify for a clinical trial be able to participate without concern that their care will not be covered. This, in turn, will better enable sponsors to include Medicare beneficiaries their research studies.

In sum, with respect to the Medicare-specific criteria, BIO urges CMS to design any approval process in a manner that provides sufficient detail and consistency so that trial sponsors, clinical researchers, or patients have a reasonable level of certainty regarding Medicare coverage when enrolling Medicare beneficiaries in a research study. We also urge CMS to clarify its proposed implementation of these Medicare-specific criteria in a manner that better recognizes the appropriate role of Medicare coverage in a research study as well as provides trials sponsors, researchers, and providers with adequate certainty regarding Medicare coverage during a research study.

IV. New Data Collection Requirements

We greatly appreciate CMS' efforts to clarify the interaction between CED and the CRP. Nonetheless, we continue to have some serious concerns regarding the potential application of CED to drugs and biological products. Most relevant to the CRP, we are concerned about the imposition of data collection requirements in addition to those required by FDA. We urge CMS to minimize additional data collection requirements and to set any data collection standards in a manner that can achieve its specific goals while imposing minimal burdens for patients, providers, and clinical trial sponsors. We also urge CMS to consider covering the costs of additional data collection requirements imposed by a NCD with CED.

The data collection required by CMS, when in addition to any FDA required data, adds to the costs of a clinical trial. We urge CMS to take every effort to minimize these costs and to pay particular attention to the costs imposed on beneficiaries and providers. Beneficiaries' cost of care should not increase as the result of increased data collection requirements. If beneficiaries are forced to incur greater costs for receiving care in Medicare-covered clinical trials they will choose other, potentially less appropriate, care options. CMS also must minimize physicians' costs in operating clinical trials. Physicians who participate in clinical trials often donate considerable amounts of time and resources to evaluating patients' eligibility for trials, data collection, and drug administration services that frequently are not reimbursed by trial sponsors. One option for appropriately compensating these costs would be to permit coverage of administrative costs specifically related to a NCD with CED. In the Proposed CRP, CMS has clarified that administrative services will not be covered by Medicare. Yet BIO urges CMS to consider covering certain administrative services when required by a NCD with CED, much like the Proposed CRP policy on covering investigational clinical services when those services are required pursuant to a NCD with CED. This would reduce the burden of collecting additional data, as is required by CED.

In determining whether additional data collection is necessary for Medicare-covered trials, we urge CMS to balance carefully the value of the information gathered against the burden of collecting it, align any data collection requirements with FDA's clinical study requirements and with other research priorities to ensure that our research resources are used efficiently, and require that data collection continue only as long as important questions remain and the effort and resources required to collect these data are justified by the potential value of the information to be collected. We believe it is critical that data collection needs be determined at the outset so that the study will produce the data needed to satisfy CMS' needs and to ensure that any coverage decisions relying in part on such data will be made in an efficient and timely manner. We also urge CMS to consider ways to compensate physicians more appropriately for the data collection activities they undertake, as well as services they provide relating to evaluating patient eligibility and drug administration.

V. Medicare Secondary Payer Issues

In the Proposed CRP, CMS states that it will address Medicare Secondary Payer (MSP) issues separately from the Proposed CRP. Although BIO appreciates that a different office within CMS may have responsibility for MSP issues more broadly, we urge CMS to address these issues directly within the context of the CRP, and we reiterate our concerns here. It is critical to ensuring beneficiary participation in research studies that CMS clarify that when a clinical trial sponsor, study site, or investigator assures a study subject that he or she will not be responsible for out-of-pocket payments for medical services resulting from a trial-related illness or injury, that assurance will not turn the sponsor, site, or investigator into a primary payer, and render Medicare a secondary payer.

The Medicare statute requires payment for items and services that are reasonable and necessary for the treatment of illness or injury.[7] It is clear that medically necessary services provided to treat complications arising in the course of a clinical trial are intended to be covered by Medicare. Indeed, CMS regulations specifically authorize Medicare payment for complications arising from clinical trials involving the use of medical devices.[8] In addition, the current NCD itself calls for coverage by defining routine costs in qualifying clinical trials to include items and services for the treatment of complications.[9]

The MSP statute provides that Medicare payment "may not be made...with respect to any item or service to the extent that payment has been made or can reasonably be expected to be made" under a "primary plan."[10] The statute defines "primary plan" to include (1) a group health plan or large group health plan and (2) a worker's compensation law or plan or automobile or liability insurance policy or plan (including a self-insured plan) or no fault insurance.[11] Nothing in the MSP statute or its legislative history suggests that Congress intended to expand the reach of the MSP provisions to preclude Medicare payment for covered items and services when the sponsor of a clinical trial offers in an informed consent document and related clinical trial agreement to make payment for *uncovered* expenses relating to illness or injury resulting from the trial. In effect, such an interpretation of the MSP statute would turn clinical trial sponsors into primary health care insurers - a result surely not intended by Congress, and one that runs contrary to the policy of encouraging the participation of Medicare beneficiaries in clinical trials. Accordingly, BIO urges CMS to explicitly clarify that a promise by a clinical trial sponsor or study site to pay for uncovered trial-related illness or injury will not result in the sponsor being viewed as a "primary plan," or render the sponsor, site, or investigator a "primary payer," under the MSP provisions. CMS should assure beneficiaries that they will not be denied coverage merely because they have volunteered to participate in a clinical trial.

In addition, we ask that CMS clarify that neither the MSP statute, nor the exclusion from Medicare coverage for items or services for which a person has no legal obligation to pay[12,] operates to eliminate Medicare coverage for otherwise covered items where the sponsor has agreed to cover those clinical care costs that would not, in any event, have been recognized as an expense covered by insurance (e.g., the costs of care for uninsured trial participants). CMS should make clear that beneficiaries may not be

denied coverage for otherwise covered items or services as a result of having volunteered to participate in a clinical trial whose sponsor has agreed to cover those clinical care costs that are not, for any particular patient, normally (i.e., absent the trial) covered by insurance.

VI. Implementation of the CRP

In implementing the CRP, BIO urges CMS to grandfather existing clinical trials, including any new trial sites for ongoing clinical trials. Where an ongoing clinical trial adds a new trial site, it is important that that new sites be able to operate under the same protocol as those sites that had studies underway prior to implementation of the CRP. At a minimum, the guidance on the timing of the CRP implementation and how it applies to different types of studies already underway is critical. Also, we urge CMS to provide clear guidance on exactly when the CRP will go into effect for new trials, taking into consideration research studies that already have been approved and are about to begin enrolling patients. It could be extremely disruptive to these research studies to have to reconfigure protocols in order to comply with the CRP on the eve of enrolling patients.

VII. Conclusion

BIO appreciates this opportunity to comment on CMS' Proposed CRP. We hope that our recommendations are useful to the agency in developing a final CRP that establishes Medicare coverage of clinical trials in a predictable manner that ensures beneficiary access to innovative drugs and biologicals. Specifically, we urge CMS to:

- Expressly designate clinical trials exempt from the IND process as "deemed," at least until another centralized approval process for these research studies is established and implemented;
- Clarify that coverage of investigational services is available in a research study consistent with existing Medicare coverage of these items or services, as well as that the CRP does not intend to narrow existing Medicare coverage to require that already covered items or services must be part of a CRP research study in order to continue to maintain coverage;
- Include coverage of off-label indications for approved drugs and biologicals in Phase III studies in the definition of "investigational clinical services";
- Make clear how the CRP will be implemented in a manner that gives trial sponsors, providers, and Medicare beneficiaries sufficient certainty regarding coverage;
- Include Phase I studies in the CRP where the disease studied is chronic, life threatening, or debilitating;
- Ensure that standards regarding the inclusion of subpopulations can be applied in the context of a wide range of research studies, including smaller studies;
- Set any data collection standards in a manner that achieves CMS' specific goals without imposing undue burdens on patients, providers, and clinical trial sponsors;
- Explain that Medicare coverage of a clinical trial is not conditioned on the clinical trial sponsor serving as a primary payer for medical costs that may be associated with the trial; and

• Clarify how the implementation of the CRP will apply to research studies in various stages of development at the time the CRP becomes effective, and grandfather trials and sites already underway as well as those studies about to begin.

We look forward to working with CMS to encourage increased Medicare beneficiary access to and participation in clinical trials. If you have any questions regarding our comments, please contact me at 202-312-9281. Thank you for your attention to this very important matter.

Respectfully submitted,
/s/
John Siracusa
Manager, Medicare Reimbursement
& Economic Policy

[1] Proposed CRP at 4.

[2] 48 Fed.Reg. 26720,26721 (June 9, 1983); *see also* 52 Fed.Reg. 8798, 8799-8800 (Mar. 19, 1987). FDA permits a clinical investigation of a drug product lawfully marketed in the United States to be exempt from the IND process only if certain requirements are met. 21 C.F.R. § 312.2(b); 52 Fed. Reg. 8798, 8801 (Mar. 19, 1987) (noting that "a study of a marketed drug involving an indication contained in the product's approved labeling would be subject to all relevant [IND] requirements" but would be "exempt from IND submission requirements if it met the conditions of § 312.2").

[3] Id

[4] Food and Drug Administration, "Guidance for Industry, IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer", January 2004, available at www.fda.gov/cder/guidance/6036fnl.htm.

[5] Proposed CRP at 24.

[6] CRP at 24.

[7] 42 U.S.C. §§ 1395(d) (entitlement to have payment made for inpatient hospital services), 1395k(a)(I) (entitlement to have payment made for medical and other health services), 1395y(a)(1)(A) (exclusion for items that are not reasonable and necessary for treatment of illness or injury).

[8] 42 C.F.R. § 405.207(b). The regulation calls for payment even when the device itself is unapproved, making clear that coverage also is compelled where the device is an approved one.

[9] Medicare Coverage, Clinical Trials, Final National Coverage Decision, *available at* http://www.cms.hhs.gov/coverage/8d2.asp.

[10] 42 U.S.C. § 1395y(b)(2)(A).

[11] *Id.* In the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Congress amended the definition of "primary plan" to state that "[a]n entity that engages in a business, trade, or profession shall be deemed to have a self-insured plan if it carries its own risk (whether by a failure to obtain insurance, or otherwise) in whole or in part." Social Security Act § 1862(b)(2)(A).

[12] 42 U.S.C. § 1395y(a)(2).

The Medical Oncology Association of Southern California (MOASC) is a leading oncology society that advances and protects the ability of cancer patients to obtain, and the ability of the oncology physicians to provide, optimal cancer care representing more than 350 medical oncologists in California.

Thank you for affording MOASC the opportunity to review and comment on CMS' Proposed Decision Memorandum for Medicare National Clinical Trial Policy, CAG0071R.

MOASC whole-heartedly supports and endorses the comments made by our national organizations: American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO).

Our additional comments are:
At present, the payment for patients on clinical trials is not reporting any abuse or problems. Therefore any changes should help the system be more equitable and comprehensive, and not more cumbersome or more demanding in terms of paperwork or resource utilization.

IV. Discussion with Review of Comments and MedCAC and AHRQ Input; B. Standards; 2. Medicare-Specific Standards; Release of Study Results: Regarding public release of outcomes, the PI should make a report of all results and toxicities to a public site maintained by CMS and FDA. It should not be in lieu of publication.

IV. Discussion with Review of Comments and MedCAC and AHRQ Input; B. Standards; 2. Medicare-Specific Standards; Medicare Populations: All studies in their final analysis should discuss the ability to generalize to specific age groups, including those over 65, not just to Medicare populations. Trials should not have to prove the ability to generalize to Medicare before payment under the clinical trials regulation.

IV. Discussion with Review of Comments and MedCAC and AHRQ Input; C. Approval Processes; 1. Current "Deemed" Processes; Trials conducted under an Investigational New Drug application (IND) reviewed by the FDA:
All trials approved by the FDA, or which are conducted under an IND, or which are IND exempt, and also are approved by an IRB, should be deemed qualified for payments for standard care. This will reduce the burden of establishing new committees or new regulations for certification, and shorten the time to trial completion and reduce the cost of trials. CMS may establish this new system and analyze resulting claims paid on an annual basis to see if there is any abuse.

Any increased review or certification should be viewed as violation of the Paperwork Reduction Act, since the new regulations are not being established because of Medicare fraud or abuse findings.

Your consideration of these comments is greatly appreciated.

If you have any questions, please do not hesitate to contact the MOASC office at (909) 985-9061.

Sincerely,

Robert A. Moss

Robert A. Moss, M.D.
President

Sincerely,

Cary A. Presant, M.D.

Cary A. Presant, M.D.
Chairman of the Board

Sincerely

DYSTONIA
MEDICAL
RESEARCH
FOUNDATION
serving all dystonia-affected persons

May 9, 2007

Stephen Phurrough, MD
Center for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Dear Dr. Phurrough

The Dystonia Medical Research Foundation (DMRF) appreciates the opportunity to provide its comments on the Centers for Medicare and Medicaid proposed National Clinical Trial Policy (CAG-00071R).

DMRF supports the Centers for Medicare and Medicaid's proposed decision, published April 10, 2007, not to include a separate provision for Humanitarian Use Devices and to continue to allow local carriers to exercise their discretion on coverage determinations for Humanitarian Use Devices with a Humanitarian Device Exemption. This direction underscores the importance of individual consideration, critically important for dystonia patients.

One such device of enormous importance -- and even greater promise -- to some dystonia patients, is Medtronic's Activa® for Deep Brain Stimulation (DBS).

Dystonia is a neurological movement disorder that causes the muscles to contract and spasm involuntarily, forcing the body into repetitive and often painful, twisting movements and abnormal postures. DBS is often the treatment sought after years of failed pharmacological interventions. Recent literature reflects the clinical comments the Foundation has received from physicians treating dystonia indicating that DBS for dystonia is emerging as an effective therapy for those for whom other treatments have not been effective. In short, DBS is an important treatment option for some Americans suffering from Dystonia.

Although local coverage determinations are not a perfect solution, we have found that, working with local carriers and private insurers, we have been able to ensure access to this therapy for all patients who meet the DBS eligibility criteria.

We urge the Centers for Medicare and Medicaid to make final the National Clinical Trial Policy (CAG00071R) as proposed.

Thank you for your consideration of these comments.

Sincerely,

Janet L. Hieshetter

Janet L. Hieshetter
Executive Director

AMERICAN ACADEMY
OF OPHTHALMOLOGY
The Eye M.D. *Association*

Suite 700
1101 Vermont Avenue NW
Washington, DC 20005-3570
Tel. 202.737.6662
Fax.202.737.7061
http://www.aao.org
Federal Affairs Department

May 10, 2007
Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Center for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD

RE: Administrative File CAG-0071R Clinical Trial Policy
Proposed decision memorandum for Medicare National Clinical Trial Policy

Dear Dr. Phurrough:

On behalf of the American Academy of Ophthalmology (Academy) I am writing to comment on the 2007 proposed decision memorandum for Medicare National Clinical Trial Policy released on April 10, 2007. The Academy is the world's largest organization of eye physicians and surgeons, with more than 27,500 members. Over 16,000 of our members are in active practice in the United States.

We appreciate the opportunity to comment on the proposed guidance. The Academy and its members have a long standing interest in all aspects of ophthalmic research and support the agencies goals to clarify payment criteria for Medicare-supported clinical research studies. We also agree with the CMS goal of providing access to Medicare services for beneficiaries by ensuring their participation in scientifically sound clinical research projects. Finally, we also applaud the CMS efforts to begin including national coverage decisions (NCD) as part of the coverage with evidence development (CED) process within the research study process. We are hopeful that these changes will allow Medicare participation in clinical trials like the upcoming NEI trial that will compare the effectiveness of two similar drugs used to fight wet macular degeneration. This will help the agency make sound decisions about the most appropriate, cost-effective treatments for our nation's seniors.

Disorders of the eye and eye diseases are more common in the aging population, especially cataracts, glaucoma, macular degeneration and diabetic retinopathy. Advances in ophthalmology will allow more people to maintain good vision as they grow older but those advances should not come at a significant sacrifice to Medicare patients. Medicare payment for clinical services within a study that are paid by the program for similar care provided outside of a study will help ensure that advances in eye care can be brought forward for Medicare patients. The Academy supports the change that allows such research costs to be paid for by the Medicare program. It is also imperative that CMS support research that not only improves the quality of patient care but ensures beneficiaries receive effective services for the lowest cost – preserving the trust fund for future seniors. We strongly agree with the changes that allow for clinical costs incurred as part of research into the effectiveness and appropriate products and technology to be covered by Medicare.

Finally, the Academy supports registration on the ClinicalTrial.gov website for all Medicare-supported research studies, as well as the publication of the results of such studies in peer-reviewed journals or other similar means. Thank you for your consideration of our comments.

Yours truly,

Michael X. Repka, M.D.
AAO Secretary, Federal Affairs

Government Relations
1400 K Street NW, Suite 1212
Washington, DC 20005
t: (202) 371-9746 f: (202) 371-2760

JDRF Juvenile Diabetes Research Foundation international

dedicated to finding a cure

May 10, 2007

Leslye K. Fitterman, Ph.D.
Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
U. S. Department of Health and Human Services
Mailstop:
7500 Security Blvd.
Baltimore, MD 21244-1850

Re: Proposed Decision Memorandum for Medicare National Clinical Trial Policy (CAG-00071R)

Dear Dr. Fitterman:

The Juvenile Diabetes Research Foundation (JDRF) appreciates the opportunity to comment on the Center for Medicare and Medicaid Services' (CMS) Proposed Decision Memorandum for the reconsideration of the Medicare National Clinical Trial Policy.

JDRF was founded in 1970 by parents of children with type 1 (juvenile) diabetes and is the leading charitable funder and advocate of type 1 diabetes research worldwide. Since its founding, JDRF has funded more than $1 billion in diabetes research, including over $122 million in FY 2006 alone. More than 80 percent of JDRF's expenditures directly support research and research-related education. As part of its research efforts, JDRF has more than two dozen human clinical trials under way or in preparation.

JDRF supports CMS' goal of maintaining and expanding coverage and access for items and services provided to Medicare beneficiaries participating in clinical trials or research protocols. JDRF believes that the national policy put in place following President Clinton's Memorandum ("Increasing Participation of Medicare Beneficiaries in Clinical Trials") was an important step in providing beneficiaries access to services they otherwise may not have received because of their participation in clinical research. The practical effect of this policy has been the generation of needed evidence that has added to the knowledge base about the effectiveness of certain therapies in the Medicare population.

By continuing to provide and improve access to care and encourage beneficiary participation in clinical trials, JDRF supports CMS' efforts to refine the existing coverage of routine -- and in some cases experimental -- costs of items and services provided during enrollment in a clinical trial or participation in a clinical research protocol. We also support CMS' efforts in assuring that qualifying clinical trials and research protocols meet certain standards to assure that they are both designed and implemented in a methodologically appropriate and rigorous fashion. If appropriately implemented, the new policy will continue to drive robust clinical research and encourage new studies focused on emerging technologies for the Medicare population.

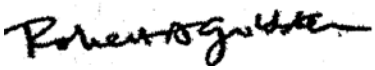
JDRF hopes that by establishing a clear, transparent, and streamlined process through which Medicare beneficiaries can participate in clinical research, CMS can achieve two important goals. First, Medicare beneficiaries will gain access to promising new treatment options which can help

improve their quality of life in the near term. Second, the knowledge and clinical evidence generated by this research will provide patients and physicians with the information needed to manage, treat, and hopefully cure diseases like type 1 diabetes. We encourage CMS to move forward in finalizing a policy that will remain consistent with these important goals and continue to expand, not contract, Medicare coverage.

JDRF also supports CMS' proposal to cover certain investigational items and services provided in approved clinical research where coverage would have otherwise been available to beneficiaries outside of these efforts or when the item or service is covered under a national coverage determination (NCO) with coverage with evidence development (CEO) conditions. In some studies, the item or service being studied is not experimental and may have already been determined to be reasonable and necessary for purposes of Medicare coverage. Therefore, coverage for these items or services within the clinical trial or research protocol should be the same as otherwise is available to beneficiaries outside of the specific trial or research study.

JDRF appreciates the opportunity to submit these comments, and we look forward to continuing our work with you in this important area. We are encouraged by CMS' goal of improving Medicare beneficiary access and participation in clinical research, and we hope that any revisions to the existing policy remain focused on this important goal. If you have any questions or concerns regarding our comments, please feel free to contact Cynthia Rice, JDRF Director of New Technology Access, at (202) 465-4159 or crice@jdrf.org.

Sincerely,



Robert Goldstein, MD, PhD
Chief Scientific Officer
Juvenile Diabetes Research Foundation

cc: Barry Straube, MD, Director, Office of Clinical Standards and Quality
Steve Phurrough, MD, MPA, Director, Coverage and Analysis Group

Vanderbilt University School of Medicine
Gordon R. Bernard, M.D.
Melinda Owen Bass Professor of Medicine
Room T-1208 MCN, Nashville TN 37232-2650

Phone (615) *343-0077*
Fax (615) 343-4479
Gordon.Bemard@Vanderbilt.edu

May 4, 2007
Leslye K. Fitterman, PhD., Lead Analyst
Centers for Medicare & Medicaid Services
Mail Stop C1-10-23
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: Comments to the Proposed CMS Clinical Research Policy

Dear Dr. Fitterman:

On behalf of Vanderbilt University, I would like to express our appreciation to the Centers for Medicare & Medicaid Services (CMS) for the opportunity to submit Comments on the proposed revisions to the National Coverage Decision for the CMS Clinical Trial Policy (CAG-00071 R). Vanderbilt University is an independent, private research university located in Nashville, Tennessee comprised of a well-recognized academic medical center and a highly-respected university offering degrees from several undergraduate, graduate, and professional schools and colleges. Vanderbilt's growing research enterprise exceeds $300 million in total research expenditures, and the Vanderbilt-Ingram Cancer Center is designated as a comprehensive cancer center by the National Cancer Institute. The Vanderbilt University Medical Center is a Level 1 Trauma Center comprised of several hospitals and institutes, including the Vanderbilt University Hospital, the Vanderbilt Children's Hospital, the Vanderbilt Stallworth Rehabilitation Hospital, the Vanderbilt Clinic, and the Vanderbilt Heart Institute.

We appreciate the work and effort that CMS has invested in revising the Clinical Trial Policy and welcome CMS's further consideration of this important policy for Medicare beneficiaries. In particular, we commend CMS for the clarification of coverage for routine clinical services and investigational clinical services. We are concerned, however, that some of the other features of the new policy could lead to confusion and the possibility that research institutions might submit bills to Medicare for clinical research studies that, unbeknownst to the research institution, do not qualify for coverage. We would appreciate your consideration of the following Comments.

COMMENT 1: Harmonization of General Standards and Medicare-specific Standards

General Standard: *The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.*

Medicare-specific Standard: *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 the standard only if the disease being studied is chronic, life-threatening, or debilitating.*

In order for a clinical research study to satisfy both of these requirements, there may be some unintended confusion. A strict reading of these two provisions together seems to narrow the scope of clinical studies that would meet both standards to only clinical research studies that (a) include therapeutic outcomes as a primary objective and (b) study chronic, life-threatening, or debilitating diseases.

First, the use of the word "principal" in the General Standard seems to imply that therapeutic outcomes must be a primary endpoint or objective for the study, while the Medicare-specific standard implies that therapeutic outcomes only need to be one of the objectives as opposed to primary. Secondly, it is also unclear whether the requirement that the disease being studied is chronic, life-threatening, or debilitating applies to just Phase I studies that test toxicity or all clinical research studies.

We believe that the intent of the provisions, taken together, was to include clinical research studies that have therapeutic outcomes as one of the objectives regardless of the seriousness of the disease being studied, unless the study tests toxicity or disease pathophysiology as a primary endpoint. If the study tests toxicity or pathophysiology as a primary endpoint, then it must involve the study of a chronic, life-threatening, or debilitating disease. We would also respectfully suggest that the phrase "or condition" be added after disease to include injuries and other medical conditions not caused by an underlying disease, and that the term "intervention" be modified to include both therapeutic and diagnostic interventions to prevent any confusion about Medicare coverage for clinical research studies of diagnostic interventions.

Thus, we request clarification on the following points:

1) Is a clinical study required to list therapeutic outcomes as a primary endpoint (as opposed to one of several endpoints/objectives)?
2) Must all clinical studies involve a chronic, life-threatening, or debilitating disease, or only studies that test toxicity as a primary endpoint?

We would respectfully propose that the Standards be revised as follows:

General Standard: One purpose of the research study is to test whether a particular therapeutic or diagnostic intervention potentially improves the participants' health outcomes.

Medicare-specific Standard: The clinical research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols include testing toxicity or disease pathophysiology as the primary objective, but which nevertheless also commit to measuring therapeutic outcomes as an additional objective, will not meet the General Standard regarding therapeutic health outcomes unless the disease or condition being studied is chronic, life-threatening, or debilitating.

COMMENT 2: Approval of IND Exempt Studies and Internally-Funded Studies

We respectfully request that CMS reconsider including IND exempt studies as approved clinical research studies under the new Medicare Clinical Research Policy. We understand that CMS is concerned about the lack of FDA oversight in the IND exempt process as compared to the traditional IND process under 21 CFR Part 312. However, we respectfully disagree and would propose that IND exempt clinical research studies are in fact subject to appropriate levels of review. Under 21 CFR 312.2, IND exempt studies are limited to drugs already approved for marketing by the FDA and the studies must be reviewed and approved by a duly constituted institutional review board. An institutional review board (IRB) is a Federally-regulated body under 45 CFR 46 and 21 CFR Parts 50 and 56 with Federally-delegated oversight obligations as well as reporting requirements for both the FDA and the U.S. Department of Health and Human Services through the Office of Human Research Protections. Additionally, many IRBs have obtained further accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP). The website for AAHRPP is located at http://www.aahrpp.org/www.aspx.). Specifically, IRB's are charged with review of clinical research to ensure such research meets acceptable scientific standards, is conducted by appropriately trained individuals and that the risk to benefit ratio is acceptable. Therefore, these studies have already received two levels of review: the FDA has reviewed and approved the drug and a duly constituted IRB must review the study.

As an alternative to deleting IND exempt clinical research studies from the new Medicare Clinical Research Policy, we respectfully recommend that IND exempt research studies that are reviewed and approved by an IRB accredited by a national organization such as AAHRPP should be deemed to have met the standards of the new Medicare Clinical Research Policy.

COMMENT 3: Coverage for INO Exempt Studies and Exclusions Under Section 5

We are concerned about the availability of Medicare coverage for clinical items and services provided to Medicare beneficiaries in connection with an IND exempt study or a study excluded under Section 5 of the new Clinical Research Policy. If these clinical items and services would otherwise qualify for Medicare coverage outside of a clinical research study, will Medicare coverage be lost for these clinical services if they are administered in connection with any non-qualifying clinical research study, particularly if the clinical item or service at issue is the investigational article in the study? This would not seem to be within the spirit of the new Medicare Clinical Research Policy which

stated that the intent was to allow Medicare beneficiaries to participate in research studies.

Thus, we respectfully request clarification as to whether items and services that are determined to be reasonable and necessary under Section 1862(a)(1)(A) of the Social Security Act will still be covered by Medicare if such items and services are administered in connection with a non-qualifying clinical research study that is not deemed to be approved under the new Medicare Clinical Research Policy such as an INO exempt study, a study excluded under Section 5 of the Medicare Clinical Research Policy, or an internally-funded study, particularly if the item or service at issue is the investigational article in the research study.

COMMENT 4: Methods of Public Release of Clinical Research Study Outcomes and Results

Medicare-specific Standard: The research study protocol specifies and fulfills method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated earlier.

We are unsure of the methods envisioned by CMS to fulfill this requirement, in particular for studies with negative outcomes that may have difficulty being published. As the competition for publication intensifies, we feel that this requirement might unnecessarily exclude less noteworthy but nevertheless valuable research studies.

Respectfully, we would like to recommend that the Standard be revised to explicitly state that a sponsor or investigator may satisfy this Standard by placing the outcomes or results of a clinical research study on a publicly accessible sponsor or institutional website for a pre-determined period of time.

COMMENT 5: Studies Approved by Federally-Funded Research Centers or Cooperative Groups

Approval Process: Studies reviewed and approved by health care research centers or cooperative health care research groups, funded by one of the above Federal Agencies, 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.

We are concerned that the research community will not always have visibility into the review process required of Federal Agencies by this provision.

We respectfully request clarification as to how CMS expects the relevant Federal Agencies to inform the research community about the status of specific research centers and cooperative groups so that the research community can determine in advance whether or not any particular center or group meets this Standard.

COMMENT 6: Clinical Trial Registry Requirement

Clinical Trial Registry: *The research study is registered on the ClinicalTrials.gov website prior to the enrollment* of *the first subject.*

While we understand CMS's desire to ensure its beneficiaries have pertinent information about the research CMS supports, we are concerned that CMS's requirement that the research study be registered "prior to enrollment of the first study subject" could lead to unintended consequences. For example, in a large multi-center study with over 100 centers (including foreign study centers), an individual study center would have no knowledge of the enrollment activities of the other centers. If anyone of these other centers inadvertently enrolled a participant before the study was registered by the sponsor, then all of the Medicare charges made by the remaining centers would have been submitted in violation of the Clinical Trial Policy with no knowledge of the disqualifying early enrollment. As an alternative, we would respectfully suggest that the Medicare-specific standard should only require that a clinical research study be registered on ClinicalTrials.gov but not before the enrollment of the first study subject. Instead we would propose that any clinical research study that is registered on ClinicalTrials.gov should qualify for the Medicare-specific standard with a caveat that any clinical services for study subjects who are enrolled before the study is registered will not be covered. Then, any study subjects who are enrolled after the research study is registered would still be covered by the Clinical Research Policy, regardless of the enrollment of subjects at other study centers prior to registration of the study.

Thus, we would respectfully propose that the Medicare-specific standard for clinical trial registry be revised as follows:

Medicare-specific Standard: The research study is registered on the ClinicalTrials.gov website. Coverage, however, will not be available for any clinical services provided to a study subject prior to the registration of the research study.

COMMENT 7: Inclusion Criteria for Relevant Subpopulations

Medicare-specific Standard: The research study protocol must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic or other factors).

Institutional Review Boards (IRBs) routinely assess proposed exclusion criteria during their review to ensure that patient subpopulations are appropriately, and not systematically, excluded. Unless data is available clearly showing differences between subpopulations, the subpopulations should be allowed access to a clinical study. A better way of controlling this is to explicitly define relevant subpopulations that the study should not enroll as exclusion criteria. Examples of this would be patients who the intervention was unlikely to be beneficial to or patients who the intervention is more likely to be harmful. These patients are usually better defined according to disease processes as opposed to strict demographics. If patients do not fall into one of the

exclusion criteria, the risk/benefit ratio for the intervention being studied is favorable to them and they should be allowed to be enrolled. Since study population is a routine assessment of risk/benefit ratio performed by IRBs, we recommend that this be left to the discretion of the IRB.

In addition, the requirement to have specific inclusion criteria language based on demographics may prohibit participation by a Medicare beneficiary in a clinical study simply because it is not explicit that they can participate. In these instances, Medicare beneficiaries may miss out on a potential intervention. Furthermore, once the study is completed, the results will not be able to be extrapolated to a Medicare subpopulation, because patients were not explicitly included. In order for these results to apply to the Medicare subpopulation, an additional study would have to be done, exposing additional patients to the risks of the study.

Finally, not all Medicare beneficiaries fit one specific demographic. Some non-elderly beneficiaries may be excluded from a clinical trial because the foresight of including explicit language about their condition or situation may not have been included in the protocol inclusion criteria.

Thus, we would respectfully propose that the Medicare-specific standard for inclusion criteria for relevant subpopulations be revised as follows:

Medicare-specific Standard: The research study protocol should not explicitly exclude relevant subpopulations without an explanation.

COMMENT 8: Generalization to the Medicare Population

Medicare-specific Standard: The research study protocol contains a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients may benefit from the intervention. In particular, 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.

This Standard proposes that the study be powered to address outcomes in each subgroup separately. This is a very inefficient method of conducting research. It places additional participants at unnecessary risk. The reason that subpopulations are analyzed separately is because they are thought to be different from the general population with respect to their response to the intervention or the adverse effects of the trial. In these instances, reasonable data exist suggesting that the subpopulation is different. Unless the Medicare population differs from the other included populations, ensuring that the study is powered sufficiently to draw conclusions specifically about the Medicare population will unnecessarily require additional Medicare participants to be placed at risk in the study in order to answer this question. If the outcome in the Medicare patients in the study is congruent with the overall study outcome, the results can be extrapolated to that population. This would require fewer Medicare participants to be enrolled. Also, there are too numerous to count subpopulations enrolled into each clinical trial, and the division of subpopulations is arbitrary.

The Standard also suggests an alternative of analyzing the subgroups together and then testing for an interaction. Unfortunately, the power to test for an interaction in any study is considerably smaller than the overall power of the study. In order to obtain enough power to see anything other than a very large interaction, the number of enrollees must be increased significantly. This proposal will then, place additional participants at risk by increasing the number of participants needed to complete the study.

We respectfully recommend that the Medicare-specific standard for generalization to the Medicare population be deleted.

COMMENT 9: Transition Period

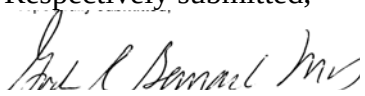
The effective date for the new Medicare Clinical Research Policy has not yet been determined, so we are unsure about the application of the new Policy to existing research studies. Many of the new requirements for this Policy apply to the content of the protocol itself, which is usually prepared in the earliest stages of a research study. Most studies would need to submit amended protocols to their institutional review board and possibly the FDA for review in order to meet the Medicare-specific standards, and study participants would not be eligible for coverage during the interim while amendments to study protocols are being reviewed. We are concerned about the ability of current Medicare beneficiaries to continue receiving benefits for these ongoing clinical research studies, so that ongoing clinical care is not interrupted which might jeopardize the health, safety, or welfare of research participants.

We respectfully suggest that the effective date of the new Medicare Clinical Research Policy apply only to clinical research studies which have not yet submitted a written protocol to either the FDA or an institutional review board for approval to allow for ample time to revise the protocols before they are submitted for review.

We are also concerned about the coverage status of study participants currently enrolled in ongoing IND exempt studies that are "deemed" to meet the eligibility requirements of the existing Clinical Trials Policy if CMS decides to delete IND exempt studies from the new Clinical Research Policy. We respectfully request that these participants be "grandfathered" under the new Clinical Research Policy and be permitted to receive benefits coverage under the existing Clinical Trials Policy until the completion of their studies.

If you have any questions, please feel free to contact me at 615-343-0077 or email to gordon.bernard@vanderbilt.edu. Thank you for your time and consideration.

Respectively submitted,



Gordon R. Bernard, M.D.
Melinda Owen Bass Professor of Medicine
Assistant Vice Chancellor for Research

Sent to you in behalf of Dr. Patrick Price, Medicare Medical Director, Wheatlands Administrative Services

To Whom It May Concern:

First, the national coverage decision (NCO) is thoughtful and will be a building block in the construction of a framework to support clinical research which benefits Medicare patients. Laws and administrative directions are written in general terms in order to give those entities which implement them latitude to apply the intent to specific scenarios. Below I have pasted the basis in Law for the NCO and the administrative guidance.

Two questions follow, these are important because of issues raised in the citations attached to this email. Question number one is the following: Can contractors refuse to pay for clinical trials because the protocol does not assure a representative number of Medicare beneficiaries will be included? Do contractors have the authority to refuse to pay if issues like the ones cited in the article by HGC Van Spall, *Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals* JAMA 2007; 297: 1233 - 1240?

A second question is-- Can contractors deny payment because of flaws in the protocol design? Equivalence trials can be used as a generic example. Peter C. Gotzsche, M.D. stated the following: *"In addition, only20% of the trials the authors surveyed provided the* 4 *necessary basic requirements: noninferiority or equivalence margin defined, sample size calculation taking this margin into account, both intention-to-treat and per-protocol analyses and confidence interval for the result If justification for the margin is included, which is an important regulatory requirement only*4% *of these trials complied with reporting requirements."* JAMA March 8, 2006 vol 295 no.10 1172 – 1174

More scrutiny of trial design at different levels might decrease the 30% refutation of the most-cited clinical research (JAMA July 13, 2005 vol 294 no 10 218 -228). Notwithstanding, protocol evaluation is work intensive. Unless administrative law judges (ALJs) are aware the MACs and contractors can deny reimbursement based upon protocol design, the granting entity, for example the National Institute of Health (NIH) will be the last level of protocol critique. The body which awards the grant does not have an incentive, necessarily, to consider the inclusion of Medicare beneficiaries.

The articles cited have been written in a time period when the current trial evaluation by the Food and Drug Administration (FDA), NIH and other bodies exists. Is the intent of the Centers for Medicare and Medicaid Services to supplement the protocol evaluations performed by the agencies listed in the NCO?

III. Authority

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under Title XVIII of the Social Security Act section1869(f)(1)(8). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part 8, must not be otherwise excluded from coverage, and must be reasonable and necessary as defined in section1862(a)(1)(A).

Section 1862(a)(1)(A) states:

> *Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services-which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member...*

One of the succeeding subparagraphs to section 1862(a), section 1862(a)(1)(E) of the Act states:

> *Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services-in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section...*

Section 1142 in pertinent parts provides:

> (a)(1) IN GENERAL.-The Secretary, acting through the Administrator for Health Care Policy and Research[2] shall-
>
> (A) conduct and support research with respect to the outcomes, effectiveness, and appropriateness of health care services and procedures in order to identify the manner in which diseases, disorders, and other health conditions can most effectively and appropriately be prevented, diagnosed, treated, and managed clinically;
>
> (2) EVALUATIONS OF ALTERNATIVE SERVICES AND PROCEDURES. – In carrying

Conclusion

We believe that the changes CMS is proposing to the current Clinical Trial Policy are consistent with the original Executive Memorandum and with the goals we stated at the beginning of this process:

• Allow Medicare beneficiaries to participate in research studies;
• 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; and,
• Allow Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or service is insufficient to allow for full, unrestricted coverage.

We are especially encouraged by the support and recommendations to strengthen the approval processes to ensure that our beneficiaries, when participating in research studies, have greater assurance that the study will be of good quality and of benefit not only to them but to all Medicare beneficiaries.

The following is a summary of the proposed changes to the current policy:

The Centers for Medicare & Medicaid Services (CMS) is proposing the following revisions to the Medicare National Clinical Trial Policy:

1) Rename the policy, the Clinical Research Policy (CRP).
2) Add a definition of research.
3) Continue the seven highly desirable characteristics and rename them "general standards for a scientifically and technically sound clinical research study" and add an additional standard: "The research study must *have* a written protocol."
4) Revise the requirements that qualify a clinical study for Medicare coverage by renaming them "Medicare-specific standards," eliminating the first, and combining and modifying the second and third requirements for greater clarity. Add the following Medicare-specific requirements:

- The research study must be registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.
- The research study protocol must specify and fulfill method and timing of public release of results.
- The research study must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic, or other factors) in the study protocol.
- The protocol must contain a discussion of how the results will generalize to the Medicare population.

5) The NCO process may establish additional standards through Coverage with Evidence Development (CEO).
6) Rename routine costs to "routine clinical services" and clarify the definition.

Thank you,

Patrick Price, M.D., FACS
Medicare Medical Director
Wheatlands Administrative Services

Attachments 3

NOTE: The three attachments are the JAMA articles, which I wanted to attach to this email for your convenience. However, because they are scanned documents, I am unable to send them as attachments. Therefore, / will provide them to you by way of the postal mail with a copy of this email as a cover. Please look for them.

Perhaps a more efficient commenting method could be utilized on your website; one that allows transmission of attachments.

H. Lee
MOFFITT
Cancer Center & Research Institute
A National Cancer Institute
Comprehensive Cancer Center
At the University of South Florida

William S. Dalton, Ph.D., M.D.
Chief Executive Officer
and Center Director
Professor of Oncology
and Medicine
University of South Florida

12902 Magnolia Drive
SRB-CEO
Tampa, Florida 33612-9416
Phone (813) 745-4261
Fax (813) 745-4268
Dalton@moffitt.usf.edu

May 9, 2007

Stephen Phurrough. MD, MPA
Director
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: Proposed Decision Memorandum for Medicare National Clinical Trial Policy (CAG-00071R)

Dear Dr. Phurrough:

On behalf of the H. Lee Moffitt Cancer Center & Research Institute, a National Cancer Institute Comprehensive Cancer Center, I am writing to comment on the Centers for Medicare & Medicaid Services' Proposed Decision Memorandum for the Medicare National Clinical Trial Policy, as published on CMS's website on April 10, 2007.

We are in agreement with the detailed comments submitted by The Alliance of Dedicated Cancer Centers, an alliance of ten nationally recognized cancer institutions, including the Moffitt Cancer Center. I would like to take this opportunity, however, to reinforce those concerns and summarize my comments.

The Moffitt Cancer Center strongly supports the policy objective of the original clinical trial national coverage decision (NCO) to expand the availability of clinical trials to the Medicare population. However, there has been significant confusion and ambiguity regarding the application of the current NCO, especially regarding whether it is appropriate to bill for particular services and a lack of assurance that these costs will be covered. CMS has addressed some of the issues in the Proposed Decision, but the following ambiguities or concerns remain.

• In the Proposed Decision Memorandum, CMS recommends a definition of clinical research. We request that the agency clarify the examples of the types of clinical research that would be supported under this policy. We believe the agency should expand coverage for cancer prevention trials in high risk patients.

• We are supportive of CMS' explicit inclusion of Phase I trials in this standard and for stating that measuring therapeutic outcomes must be but *one* of the objectives of the trial. We ask for specific criteria by which to determine if a trial satisfies this standard. What evidence is needed to establish that a Phase I trial has demonstrated sufficient therapeutic intent?

• We agree that clinical trials should be registered on the ClinicalTrials.gov website. However, CMS should state explicitly who is responsible for trial registration and when patients can be enrolled relative to registration of the trial. We suggest a grace period from the time of trial opening to the trial registration, and that no financial or other penalties be imposed during this period.

• We ask CMS to clarify the requirement for public release of trial outcomes. We suggest that the trials be published when completed, rather than by a specific date. In addition, we would like to bring to your attention that it may not be possible to publish all results in peer-reviewed journals.

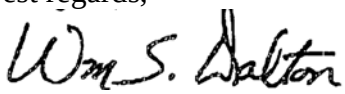
• We strongly urge the agency not to tie clinical trial qualification to patient demographics or other characteristics. Other federal government agencies already require researchers to be aware of health disparities. We are also not supportive of trial eligibility that is related to the type of insurance an individual carries, such as Medicare, or other socioeconomic factors.

• We request that CMS confirm that cancer centers that follow NCI core grant guidelines satisfy the standard of federal review for IND-exempt clinical trials. We believe that the real issue with regard to INO-exempt trials is to have in place a rigorous scientific review of the proposed trials. At the Moffitt Cancer Center, and other NCI-designated cancer centers, there is a strict review for scientific merit and statistical justification of investigator-initiated trials by a scientific review committee, followed by further review by an Institutional Review Board for human subject protection and scientific merit. Active trials are closely monitored for toxicity, response, adherence to stopping rules, and timely accrual by a protocol monitoring committee, and, at Moffitt, audited annually by the Compliance Department. It is difficult to imagine institutions that are more qualified to review investigator-initiated IND-exempt trials than an NCI-designated Cancer Center.

• Finally, we request that CMS clarify in the final revised NCD that the new NCD is not retroactive and will only affect trials that commence after the new NCD is published.

I appreciate the opportunity to comment on the Proposed Decision.

Best regards,



William S. Dalton, Ph.D., M.D.
President & Chief Executive Officer

FLORIDA SOCIETY OF CLINICAL ONCOLOGY

May 1, 2007

Leslye K. Fitterman, PhD
Centers for Medicare and Medicaid Services
7500 Security Blvd., Room C1-12-04
Mail Stop C1-09-06
Baltimore, MD 21244-1850

Re: Proposed Decision Memo for Clinical Trial Policy (CAG-00071R)

Dear Dr. Fitterman:

The Florida Society of Clinical Oncology (FLASCO), with more than 400 members, is the Voice of Oncology in the State of Florida. We are a State Affiliate of the American Society of Clinical Oncology (ASCO).

On behalf of FLASCO, I want to convey that our State Society completely supports the letter that ASCO sent to you on April 27, 2007.

Like ASCO, our Society is concerned to see that CMS is proposing to abandon coverage for IND-exempt trials, a move that we believe has the potential to create havoc in both clinical cancer research and quality cancer care for beneficiaries.

We urge reconsideration of this policy change, at least as it applies to clinical cancer studies and perhaps to studies in other therapeutic areas as well.

Sincerely,

Robert Cassell, MD
FLASCO President

3709 W. Jetton Ave· Tampa, Florida 33629-5111 • 813.253.0541 • Fax 813.254.5857

BUX-MONT ONCOLOGY HEMATOLOGY MEDICAL ASSOCIATES, P.C.

Oncology • Hematology • Internal Medicine

Alan Kaufman, M.D.
Thomas Siesholtz, M.D.
Mitchell Alden, D.O.
Howard Zipin, M.D.
Lorraine Dougherty, M.D.
Anthony Magdalinski, D.O.
Jay Ziegenfuss Jr., M.D.
Kenneth Baab, Practice Administrator

Debbie Draus, RN, OCN
Sheryl Ehst, RN, BSN, OCN
Nancy McGrath, RN, BSN, OCN
Susan Beaver, RN, OCN
Lisa Martella, RN, OCN
Patty McCartney, RN, OCN
Deborah Hittle, RN, OCN
Nancy Barry, RN, BSN, OCN

May 7, 2007

Leslye K. Fitterman, PhD
Centers for Medicare and Medicaid Services
7500 Security Boulevard, Room C1-12-04
Mail Stop C1-09-06
Baltimore, MD 21244-1850

Re: Proposed Decision Memo for Clinical Trial Policy (CAG-000071R)

Dear Dr. Fitterman:

Bux-Mont Oncology Hematology Medical Associates is a private group practice in hematology/oncology, comprised of six physicians. We are located in Bucks County, Pennsylvania, and have four offices and actively lead cancer programs in the regions four hospitals. We actively encourage our patients to participate in a variety of research protocols that are available through our collaboration with Fox Chase Cancer Center and the University of Pennsylvania, and other resources.

We are members of the American Society of Clinical Oncology (ASCO) and have supported their leadership and collaboration with CMS, FDA, and NCI in the extension of coverage of patient care costs to "IND-exempt" trials that have been designated by the FDA.

We wish to express our strong opposition to CMSs proposal to abandon coverage for IND-exempt trials. Our interest is in the oncology field, and with the broad array of interested parties that fashioned the current policy several years ago, it is surprising that CMS is proposing to abandon it.

We believe that it will limit patient access to meaningful studies. We are concerned that the FDA will be hard-pressed to respond to the flood of applications that will be necessitated by this change in policy. This will result in confusion as we try to ascertain how to go about studying the modest changes in protocols that we undertake on a routine basis.

We are also concerned to learn of ASCOs assertion that they saw no evidence that CMS conferred with the FDA before initiating this proposal. There are many interested and knowledgeable parties that will be affected by this change, and we ask CMS to redouble its efforts to involve them and to keep the present practice in place.

We appreciate the opportunity to add our name to the long list of those opposing this proposed change.

Thank you.

Sincerely,

Alan Kaufman, MD on behalf of Bux-Mont Oncology Hematology Medical Associates

AK/KMB

The Summit, South • 920 Lawn Avenue, Sellersville, PA 18960 • telephone: 215-257-6858 • fax: 215-257-1892
1021 Park Avenue, Quakertown, PA 18951 • telephone: 215-536-4121 • fax: 215-536-5743
700 Horizon Circle, Suite 102, Chalfont, PA 18914 • telephone: 215-997-1134 • fax: 215-997-8890
The Pavilion at Doylestown Hospital, Suite 302 • 599 West State St., Doylestown, PA 18901 • telephone 215-345-8444 • fax 215-345-8298

This comment to proposed changes to the Medicare policy on clinical trials is submitted on behalf of the *Cherishing Our Hearts and Souls Coalition (COHS)* and the advisory groups to its cancer clinical trials initiative *Breaking It Down: Our Health Our Way (BID).* COHS is a community coalition coordinated by the Program to Eliminate Health Disparities, Division of Public Health Practice, at the Harvard School of Public Health, and based in the Roxbury neighborhood of Boston, MA. COHS promotes health, wellness, and community participatory action approaches towards the elimination of racial/ethnic disparities in health and healthcare. In February 2006, COHS began the *BID Initiative*, which seeks to combat the causes of racial and ethnic disparities in cancer clinical trial (CCT) participation that are influenced by a lack of knowledge, cultural sensitivity, awareness among clinical trial investigators, community residents and health providers. The BID initiative is sponsored by funding from the Education Network to Advance Cancer Clinical Trials, with support from the Lance Armstrong Foundation. The advisory groups to the BID Initiative are a project specific Planning Committee and the Roxbury Community Research Advisory Board (CRAB).

Our review of the proposed changes has yielded the following observations:

1. Requiring trials to be listed under the clinicaltrials.gov website before a patient is enrolled is ideal in terms of assuring the database is a complete reflection of federally sponsored clinical trials that are enrolling patients. We also believe that the Medicare administration should recognize that clinical investigators have a number of options of clinical trials websites on which to post their trials, therefore strategies/mechanisms to ensure that investigators register with clinicaltrials.gov is needed.
2. Also, the term "therapeutic intent" is too vague. There are some trials that are done with therapeutic benefit in mind, with an emphasis on learning more about the disease or therapy to benefit future generations; these are also very important (i.e. Phase I clinical trials).
3. We believe that there should be increased access to clinical trials for currently underrepresented groups (i.e. elderly, people of color) and endorse the intent of proposed requirement that "a research study must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic, or other factors) in the study protocol". Additionally it is important that a plan be outlined a priori to enhance "considered relevant populations" in clinical trials' design. Such plans should include education of clinical trials staff and investigators around communicating with diverse populations (i.e. CLAS standards) and for the prospective participants there should be clear explanation of the study protocol and their rights.
4. There is also the unmentioned issue of costs to the participant of a clinical trial that fall outside the realm of clinical intervention or administrative costs of research facility and staff (i.e. transportation). This is particularly important when we talk about inclusion of Medicare recipients in clinical research, a population that is elderly or disabled.

Brian Gibbs HARVARD School of Public Health