BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

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BY ELECTRONIC DELIVERY

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Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mailstop: C1-09-26
7500 Security Blvd.
Baltimore, MD 21244

Re: Proposed Decision Memorandum for Second Reconsideration of the Medicare Clinical Trial Policy (CAG-00071R2)

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 Second Reconsideration of the Medicare National Clinical Trial Policy (CAG-00071R2), renamed the Clinical Research Policy (hereinafter "Proposed Revised CRP"). 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.

On May 10, 2007, BIO submitted comments to the April 10, 2007 proposed CRP, seeking clarification and expressing a number of concerns, including: divergence from the original agency intent to provide coverage for Medicare patients who participate in clinical trials; limitations on the research studies that would have been deemed to comply; failure to cover items and services in a study that would be covered outside of a study; and the potential for minimized participation of Medicare beneficiaries in clinical trials. On July 3, 2007, BIO submitted a letter to CMS conveying our concerns regarding a proposed interpretation of the pending CRP.

BIO appreciates CMS' attention to the concerns we have raised in this correspondence. We understand that the agency has devoted substantial effort in seeking to develop a workable policy that will protect the interests of Medicare beneficiaries who participate in clinical trials and promote such participation and the development of valuable clinical trial results. However, we remain concerned about the implications of this policy for Medicare beneficiaries and for clinical research involving this population. Further, given the new provisions set forth in the July 19, 2007 Proposed Revised CRP, we have additional concerns regarding the scope of the policy, the potential legal exposure for sponsors that self-certify, and the difficulties inherent in meeting some of the standards that would apply to sponsors seeking Medicare coverage for items and services provided in a clinical research study. In light of the fact that many of the changes set forth in the July 19 Proposed Revised CRP are unprecedented and represent a drastic departure from both the current National Coverage Decision (NCD) for Clinical Trials and the April 10 proposed CRP, we believe notice and comment rulemaking is warranted. Accordingly, we urge CMS to withdraw the Proposed Revised CRP and to issue a notice of proposed rulemaking (NPRM) on these important issues instead. Finally, we remain concerned about whether CMS has the legal authority to adopt the Proposed Revised CRP at all, denying Medicare beneficiaries access to reasonable and necessary care merely because they are enrolled in a clinical trial for which the sponsor failed to self-certify.

These issues are addressed in more detail below.

I. Procedural Flaws

BIO's July 3, 2007 letter endorsed the Hogan & Hartson, LLP June 12, 2007 White Paper (White Paper), which addressed the significant procedural flaws

presented by the April 10, 2007 proposed CRP, contrary to both the Administrative Procedure Act (APA) and the agency's authority to adopt NCDs. The APA provides that a federal agency must provide adequate notice to interested persons by publishing in the *Federal Register* all "substantive rules of general applicability adopted as authorized by law, and statements of general policy or interpretations of general applicability formulated and adopted by the Agency"[1] to provide "actual and timely notice" of a matter prior to an adverse effect on a stakeholder.[2] As discussed in the White Paper, NCDs have specific notice and comment requirements[3] and the proposed CRP interpretation failed to meet them. Indeed, CMS recognized in its July 9, 2007 Decision Memo, with regard to the "additional Medicare policies and statements that are not identical to the coverage provided under the proposed April 10, 2007 CTP," that "the public has not had an adequate opportunity to comment on those changes."

Similarly, the changes in the July 19, 2007 Proposed Revised CRP are substantial and warrant adequate notice and opportunity for the public to comment. A notice of proposed rulemaking published in the *Federal Register*, not a draft decision memorandum, is the appropriate method of notifying the public of these changes in policy and accepting comment on them. The Proposed Revised CRP would alter the landscape of Medicare coverage for clinical trials significantly—by removing the process by which a study can be deemed and by creating a poorly-defined self-certification process. CMS in fact states in the Proposed Revised CRP that "significant changes are proposed in this second reconsideration"[4] and also states that "CMS is considering rulemaking to resolve these issues."[5] Further, during the Special Open Door Forum on the CRP Proposed NCD hosted by CMS on August 7, 2007, Dr. Steve Phurrough indicated that the agency would be initiating a rulemaking process on certain aspects of this policy around the time that a final NCD is issued. CMS also indicated that the proposed rule might address the issue of "deeming," and that some of the provisions of such a proposed rule may differ from the revised CRP Proposed NCD. BIO is concerned about the

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[1] National Res. Def. Council v. EPA, 279 F.3d 1180, 1186 (9th Cir. 2002) (" NRDC II") (citing National Res. Def. Council v. EPA, 863 F.2d 1420, 1429 (9th Cir.1988) (" NRDC I")).

[2] 5 U.S.C. § 522(a)(1). This publication requirement, like the notice requirement that applies to APA rulemaking, is to ensure that individuals who are affected by an agency action are aware of it so that "actions can be guided and strategies planned." Northern Calif. Pwr. Agency v. Morton, 396 F. Supp. 1187, 1191 (D.D.C.), aff'd mem. sub. nom. Northern Calif. Pwr. Agency v. Kleppe, 176 U.S. App. D.C. 241, 539 F.2d 243 (D.C. Cir. 1976).

[3] SSA § 1862(l)(3).

[4] Proposed Decision Memo for Clinical Trial Policy (CAG-00071R2), Section IV, July 19, 2007, http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=210.

[5] Id.

confusion that will be created by finalizing this NCD while a pending rulemaking is underway to address important issues that presumably relate to and affect implementation of such a policy.

In addition, the NCD process is not an appropriate or legal mechanism for CMS to use to deny coverage for broad and unspecified items and services. As detailed in the White Paper, CMS' authority to adopt an NCD that withdraws coverage derives from Section 1862(a)(1)(A) of the Social Security Act (SSA), which prohibits Medicare program payment for "items or services" that are not "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." CMS may make coverage determinations on a national basis under section 1862(l) regarding "whether *a particular* item or service is reasonable and necessary."[6] It is contrary to this authority, as expressly interpreted by CMS itself,[7] for CMS to say to beneficiaries for whom an item or service would otherwise be covered as "reasonable and necessary" that they lose their coverage merely because it is furnished in what CMS now defines as a non-qualifying clinical trial. Simply stated, Section 1862(l) does not authorize use of the NCD process to deny coverage except with respect to *particular* items or services. The NCD process is not the correct pathway for addressing coverage of clinical trials, especially if CMS intends to use an NCD to withdraw coverage for broad categories of items and services.

CMS has never before interpreted its authority to create NCDs to allow it to be used to withdraw coverage for broad categories of items and services. In its own notice setting forth the NCD procedure, CMS specifies that, "For over 30 years, we have exercised these authorities to make a coverage determination regarding *whether a specific item or service meets one of the broadly defined benefit categories* and can be covered under the Medicare program."[8] CMS continues, "In general, an NCD is a national policy statement granting, limiting, or excluding Medicare coverage for *a specific medical item or service*."[9] This definition of an NCD was codified by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 at Section 1862(l)(6)(A), and every NCD issued since the amendment became effective on January 1, 2004 has applied to "a particular item or service." Every description by CMS of how to exercise the

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[6] SSA § 1862(l)(6) (emphasis added).
[7] 68 Fed. Reg. 55634. This notice, which went into effect on October 27, 2003, replaced the previous notice published in the Federal Register on April 27, 1999 (64 Fed. Reg. 22619).
[8] 68 Fed. Reg. 55635 (emphasis added).
[9] Id (emphasis added).

NCD authority is likewise addressed to specific items or services.[10] Accordingly, CMS has issued NCDs that apply to individual items such as: specific anti-cancer drugs and biologicals, cardiac pacemakers, corsets used as hernia supports, and infusion pumps; or to individual services such as acupuncture, endoscopy, and sterilization. The only exception to CMS' long history of issuing NCDs on specific items and services is the current clinical trial policy NCD. This NCD was issued in 2000, before the statutory definition of an NCD as applying to particular items and services was enacted. Moreover, it was intended to *expand* access to care in clinical trials, not to limit coverage of items and services that were already covered. If the Proposed Revised CRP were adopted, the Clinical Research NCD would become the *only* NCD that purports to determine that unspecified items and services are not reasonable and necessary for the treatment of unspecified diseases and conditions.[11]

Thus, not only is the Proposed Revised CRP unprecedented and beyond the scope of the agency's NCD authority, but the changes proposed by CMS are likely to result in elimination of Medicare coverage of items and services delivered as part of certain clinical trials and will have a significant impact on the participation of Medicare beneficiaries in such trials, as well as on the operation of the trials themselves. These changes present issues of first impression and are not a logical outgrowth of previously published policies.[12] The Proposed Revised CRP should be characterized as a substantive rule, as it would affect the rights of Medicare beneficiaries, as well as providers of items and services. Accordingly, the APA requires that notice and comment rulemaking be employed prior to adoption of the Proposed Revised CRP.[13] We urge CMS to withdraw the Proposed Revised CRP and to issue a NPRM on these important issues instead.

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[10] See, e.g. 64 Fed. Reg. 22621 (CMS may initiate the NCD process where necessary, for example, if (1) "*the service* represents a significant medical advance, and no similar service is currently covered under Medicare," (2) "*the service* is the subject of substantial controversy among medical experts as to its medical effectiveness;" (3) "*the service* is currently covered but is widely considered ineffective or obsolete;" or (4) "there are program integrity issues surrounding significant underutilization or overutilization of *the service*") (emphasis added).

[11] CMS has also stated that it may exercise its NCD authority to make "scope of benefit" determinations, e.g., deciding "whether a particular device is considered durable medical equipment" or describing "certain specific services" for which Medicare prohibits payment (e.g. cosmetic surgery.) 67 Fed. Reg. 54534, 54536 (Aug. 22, 2002) (proposed rule). Assuming that this authority exists, it still applies only to "particular" or "specific" items or services, not to *all* items and services that may be furnished in the context of a clinical trial.

[12] Citizens for Better Forestry v. Dep't of Agric., 481 F. Supp. 2d 1059, 2007 WL 966985, at *11 (N.D. Cal., 2007) (quoting NRDC II, 279 F.3d at 1188).

[13] 5 USC §§ 551(4) and 553.

If CMS decides to finalize the Proposed Revised CRP while the rulemaking process mentioned in the decision memorandum is under way, then BIO believes it will be necessary for CMS to delay the effective date of the finalized clinical research policy and blend the comments from the NPRM with those received for the CRP NCD. This would avoid the significant implementation challenges that will occur if sponsors, principal investigators, and providers are forced to first comply with the issuance of a final clinical research policy NCD, and then change to new rulemaking. Although the Social Security Act (SSA) mandates a 60-day deadline after the close of a NCD comment period for the agency to make a final decision on the request, the statute does not specify a time period when the NCD must become effective.[14] Instead, the SSA requires only that CMS "assign a temporary or permanent code" and "implement the coding change" made in response to a request for an NCD no later than 60 days after the conclusion of the comment period.[15] Here, there are no coding changes to implement, so the 60-day time limit does not apply to this implementation of this NCD.

Further, BIO believes that, CMS has not interpreted this statute to require it to implement coding changes in that timeframe. As CMS has explained, the agency and its contractors need time after a decision is released to make any necessary coding, payment, and systems changes.[16] As a result, CMS often delays implementation of coding changes in order to allow contractors and providers sufficient time to implement billing requirements. For example, when CMS granted a request for an NCD to cover smoking and tobacco-use cessation counseling and had to create new codes for the services, it implemented those codes over three months after it issued the NCD.[17] Because CMS has not interpreted the statute's clear provision regarding the timing of implementation of coding changes to mean that those changes must be made within 60 days of the completion of the comment period, the agency should not interpret the statute to mean that the NCD itself must be effective on that date.

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[14] SSA § 1862(l)(3).

[15] SSA § 1862(l)(3)(C)(iv).

[16] 68 Fed. Reg. at 55,640 ("We expect to make any payment changes or other systems changes dictated by the NCD instructions effective within 180 calendar days of the first day of the next full calendar quarter that follows the date we issue the decision memorandum.").

[17] Transmittal 562, Change Request 3834, May 20, 2005 (noting that new codes would be implemented July 5, 2005 in response to an NCD issued on March 22, 2005).

Finally, we remind CMS that it is not required to issue a final decision memorandum in the statutory timeframe that changes Medicare's clinical trial policy. CMS has the option of issuing a final decision memorandum announcing that it is not changing the clinical trial policy at this time. With the exception of two changes to the policy, this is exactly what CMS did on July 9, when it released the final decision in the first reconsideration of the clinical trial policy.[18] CMS correctly recognized that it had not provided adequate opportunity for comment on its proposed changes, so it decided to "preserve the status quo" and open another reconsideration. As described in our comments below, many significant questions about coverage of clinical trials remain unresolved in the Proposed Revised CRP, and CMS will need further consultation with stakeholders to resolve these issues. Rather than issuing a decision that is likely to cause more confusion, we urge CMS to conclude this reconsideration process without changing Medicare's policy and to open another reconsideration of the NCD to continue the dialogue with stakeholders about coverage of these critical items and services.

II. Scope

BIO is concerned by the Proposed Revised CRP's elimination of the deeming process, whereby certain trials automatically qualified for Medicare coverage. For example, Medicare currently automatically grants coverage for trials funded by the National Institutes of Health (NIH), the Centers for Disease Control (CDC), the Agency for Healthcare Research and Quality (AHRQ), CMS, the Department of Defense (DOD) and the Veteran's Administration (VA). In addition, studies of drugs and biologicals conducted pursuant to an Investigational Drug Application (IND) reviewed by the Food and Drug Administration (FDA) have been treated by CMS as "deemed." Deeming certain trials funded and regulated by other government agencies is reasonable and straightforward, and conserves both public and private resources. In particular, allowing IND trials that have already undergone significant review to be covered without an additional certification process would enable such studies to proceed, with the knowledge that they have met rigorous FDA standards. CMS states in the Proposed Revised CRP that the proposed standards are intended to assure that clinical studies are conducted pursuant to appropriate study design, that results will be useful in

[18] Decision Memo for Clinical Trial Policy, July 9, 2007. CMS has concluded other NCD processes by issuing final decision memoranda that did not change existing coverage policy. See, e.g, Decision Memo for Radioimmunotherapy for Non-Hodgkin's Lymphoma, CAG-00163N, July 25, 2005.

improving healthcare delivery, and that study participants are adequately protected; surely, these elements mirror many of the requirements imposed by FDA for an IND trial. Accordingly, BIO urges CMS to maintain the deeming process for such trials. The self-certification process proposed by CMS only should be employed for studies that fall outside of "deemed' status.

III. Potential Legal Exposure

BIO is significantly concerned that the self-certification process outlined the Proposed Revised CRP would expose our members—the sponsors of important research on biotechnology treatments—to legal liability, even though such sponsors would be acting in good faith in self-certifying a research study. A process of self-certification—as opposed to being deemed or certified by a federal agency—would mean that sponsors would be determining on their own whether the 13 proposed standards are met. Because the standards are broadly written, each one is open to subjective interpretation. This would create uncertainty and place sponsors in the untenable position of not being absolutely certain that they are meeting these nebulous requirements. We are greatly concerned that even sponsors who are acting in good faith to comply with the standards potentially could be subject to False Claims Act liability should CMS interpret the standards differently after the fact. We urge CMS to better define the standards and provide guidance in writing regarding them and to ensure that enforcement actions only occur for those sponsors who knowingly fail to comply.

Additionally, BIO is concerned about situations in which, subsequent to a sponsor self-certifying, facts change such that the certification is no longer accurate. For example, there may be situations where a sponsor initially certifies that results of a study will be made public, and then the sponsor is later unable to publish the results. How will CMS address such situations? It would be helpful if CMS would address situations where there may be a change in the facts and circumstances addressed in a self-certification statement. Establishing a process to provide sponsors with the option of updating certification information would be useful for all parties in this regard. It would also be reasonable to provide a safe harbor for sponsors whose certification is accurate at that point in time, and where a new situation may not be within their control.

As a practical matter, study sponsors who self-certify that they meet the standards need assurance that CMS will evaluate adherence to the standards in a consistent manner. The standards can be subjective and open to various interpretations, so it is important that parity be maintained amongst study sponsors, for both federally and privately funded studies. To further this goal, it would be useful if CMS would make public the system that the agency will use to measure adherence to the standards. To assist study sponsors in meeting the standards, BIO recommends that CMS include in any Final CRP NCD the methodology that CMS will use to ensure compliance with the standards; the process that CMS will use to select which studies are scrutinized; specific measures that CMS will use to determine compliance with each standard; and a dispute resolution process.

IV. Certification Standards

In addition to our concerns regarding the legal implications of the self-certification process, BIO has concerns regarding the details of the certification process, as well as several of the standards. These concerns are described below. The more guidance provided by the Final Revised CRP regarding each standard, the more straightforward it will be for sponsors to certify that they are compliant.

A. Process Concerns

To obtain coverage of the usual patient care in a clinical trial, the Proposed Revised CRP would require the sponsor/principal investigator to certify to CMS that the standards in the policy "have been met."[19] Given that some of the standards are forward-looking, it would be impossible for a sponsor to certify that such standards "have been met." For example, the Proposed Revised CRP would require a sponsor to certify that study results "must be made public within 24 months of the end of data collection" and that if study results are to be published, a full report "must be made public no later than three years after the end of data collection." BIO does not believe CMS should require sponsors or principal investigators to certify that they have already complied with forward-looking standards. At most, the certification should address only standards that could have been met at the time the statement is submitted and request explanations of how the sponsor or principal investigator plans to satisfy any forward-looking standards.

[19] Section IV.F. of the Proposed Revised CRP.

The Proposed Revised CRP requires that certification be provided by the "sponsor/principal investigator;" however, the term "sponsor" is not defined. Although "sponsor" likely includes the entity designated to FDA as the sponsor of an IND trial, it is unclear whether a company supporting investigators conducting an IND-exempt trial would be considered to be a sponsor (such a company may also employ a contract research organization [CRO] which may assume primary responsibility for the conduct of the trial and the associated regulatory responsibilities), or how an investigator-initiated trial would be addressed. Even in an IND setting where a company is the sponsor per FDA regulations, the standards set forth by CMS are unclear. For example, the certification would require that the "sponsor" be "capable of executing [the study] successfully." However, the general practice is that company-sponsors do not themselves execute clinical trials, but instead engage clinical institutions and investigators to execute them. Unless the term "execute" is intended to refer to the FDA-sponsor's regulatory obligations, e.g., compliance with FDA requirements for a sponsor's study obligations, which includes a process for delegating the "sponsor's" obligations, it would not be feasible for many company-sponsored IND trials to be certified by the company-sponsor. Accordingly, we ask that CMS specify that the principal investigator be responsible for submitting the self-certification in this circumstance.

A company sponsoring a trial is not in a position to ensure that the investigators will actually carry out all of the specified standards, yet the company's certification could result in liability if the standards are not met. Examples of standards that depend on the investigators' conduct and are therefore beyond a sponsor's control include the requirements that the study comply with human subject protection requirements and be conducted according to appropriate standards of scientific integrity. In addition, the sponsor's ability to publish the study results depends on the investigators' cooperation. Sponsors should not be expected to certify to the compliance of other parties.

BIO also recommends that CMS use the definitions for investigator, sponsor and sponsor-investigator found in 21 CFR § 312.3. These definitions are also referenced on the ClinicalTrials.gov website. Sponsors and investigators who perform studies that are under the purview of FDA should not have to contend with multiple definitions in order to comply with the CRP.

B. CMS Challenges to the Self-Certification

The Proposed Revised CRP states that coverage will be denied if the CMS Chief Medical Officer finds that the study "does not meet the criteria outlined in this policy or the study jeopardizes the health or safety of Medicare beneficiaries."20 The policy does not specify when this finding could be made. BIO is concerned that CMS may intend for coverage to be denied during the course of a study or even retroactively after completion of a study. If this is CMS' intent, sponsors who self-certify compliance could be exposed to liability with respect to services furnished prior to the time that the Chief Medical Officer issues such a finding. In light of these potential consequences, BIO proposes that a process be established by which parties can challenge or appeal an adverse finding by the Chief Medical Officer.

Additionally, we note that during the Special Open Door Forum, Dr. Phurrough discussed very generally potential monitoring by CMS to determine compliance with the self-certification standards. BIO requests that such procedures be incorporated into this policy, to provide sponsors and providers with clear notification and knowledge of what such monitoring would entail.

C. Unclear Standards

A number of the proposed standards lack clarity, and the need for clarity is especially important because of the liability that might result from an incorrect self-certification. BIO requests that CMS expand upon and further explain the certification standards, to further assist sponsors in meeting these standards, and to provide uniformity and consistency in implementation of this policy. Examples of the need for clarification include:

- "The research study is well-supported . . ." It seems incongruous that a study of an experimental procedure must be "well-supported by available scientific and medical information . . ." While the rationale for a study endpoint or hypothesis being tested would likely be supported by medical/scientific information, there may not be sufficient prior research in an innovative area for a study to be "well-supported."
- "The research study does not unjustifiably duplicate existing studies." Research often seeks to confirm prior study results. Would such confirmatory studies be excluded from coverage? In order to gain an

20 Proposed NCD Manual 310.1.

understanding of how a particular new drug performs in different populations, studies can be duplicated across various geographical areas. Would this be considered duplicative? Also, a particular sponsor may not be aware of a duplicate study being performed by another sponsor, particularly if the other sponsor has not certified, and the study is not listed by CMS. Would this be considered duplication? Would certifying to this standard necessitate documentation through a literature review? Even a literature review would not provide comprehensive information regarding studies that are underway.

- "The research study design is appropriate to answer the research question being asked in the study." Who decides what is appropriate? This standard is very subjective and would be improved if a new clause were added clarifying that the study design is appropriate *based on the scientific literature available at that time*.
- "The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards." The purpose of this standard is unclear. Research protocols do not typically address all of the issues raised in the Medicare proposed standards. It seems unnecessary for CMS to require a change in the drafting of protocols when sponsors could employ other written methods to specifically attest to meeting the Medicare standards for the purposes of the CRP. Therefore, BIO recommends that CMS delete this standard as redundant.
- "The clinical research study is not designed to exclusively test toxicity or disease pathophysiology." This standard is very confusing, as it further states that "studies of all medical technologies measuring therapeutic outcomes" as one of the objectives meet this standard only if they relate to life-threatening conditions. In order to clarify this standard, as well as the standard that would require that the principal purpose of the research study be to "test whether a particular intervention potentially improves the participants' health outcomes," BIO suggests the following modification: "For a research study that is not a Phase I study, the principal purpose of the research study is to test whether a particular intervention potentially improves or maintains the participants' health outcomes or to compare the outcomes of interventions evaluated in the study. For a Phase I clinical study, the study is not designed exclusively to test toxicity or disease pathophysiology in healthy individuals; this criterion will be met if the study measures at least one therapeutic outcome as a primary or secondary end-

point, and the disease or condition being studied is life-threatening as defined in 21 C.F.R. § 312.81(a)."

- "A full report of the outcomes must be made public no later than three (3) years after the end of data collection." Does the requirement for publication of study results have to appear in the protocol itself, even though publication and data release are not usually addressed in a protocol? Do studies that are being conducted to support FDA approval need to be published before FDA has acted on the application? This standard not only would be difficult or impossible to certify to in advance, but could result in compliance problems if study results are not accepted for publication, or otherwise not publishable, perhaps because of a failure to recruit enough subjects, or other implementation issues. Does the requirement to make results public require formal publication in a journal? Would placing study outcomes on a sponsor's or other website meet this standard?
- "The research study protocol must explicitly discuss subpopulations. . . ." This standard is particularly burdensome, especially for small trials Does the requirement that the protocol "discuss subpopulations" require the study to be powered to reach findings as to those subpopulations? If so, does that as a practical matter deny coverage for small studies and studies in which subject recruitment fails to meet subpopulation objectives? Alternatively, will it be sufficient to explain that the trial is not designed to assess treatment in specific subpopulations?
- "The research study protocol explicitly discusses how the results are or are not generalizable to the Medicare population." We note that the Proposed Revised CRP states that "CMS standards are aimed to ensure that the research will generate evidence that can be used for determining Medicare coverage." Does the requirement that the protocol discuss "how the results are or are not expected to be generalizable to the Medicare population" allow coverage of a study in which the results will not be so generalizable? This would only be feasible if the proposed research study were designed to address this population and size the study to make meaningful conclusions about the potential impact of a new drug on the Medicare population. It is not practical to expect all trials to accommodate this issue.

D. Applicability of Local Coverage Determinations (LCDs)

The Proposed CRP would clarify that items and services provided within clinical research studies are subject to Medicare contractors' local policies, "including LCDs and claim adjudication." However, BIO is concerned that this policy would affect coverage for large, multi-site clinical research studies that are conducted across several local contractor jurisdictions. Requiring sponsors of approved clinical research studies to seek coverage from individual local contractors is inefficient and may result in varying coverage decisions, which poses challenges for research studies occurring in multiple sites. CMS should clarify how the proposed language regarding LCDs will affect the conduct of such trials, and in applying this policy, aim to reduce the uncertainty for patients and providers in obtaining Medicare coverage for approved clinical research studies. Specifically, BIO recommends that CMS revise the definition of "usual patient care" to clarify that "…investigational clinical services would be covered *for any Medicare beneficiary* outside of the clinical research…" This revision would provide multi-site trials with consistent standards across trial sites by clarifying that when an item is covered by many local contractors, the item would be covered when provided in a qualifying trial.

E. Coverage for Complications

The Proposed Revised CRP states, "Medicare covers reasonable and necessary items and services used to prevent, diagnose, and treat complications arising from participation in these research studies." BIO agrees that Medicare should cover these items and services, and to ensure that this policy is applied consistently across the country, we ask CMS to issue clear instructions to its contractors to cover care related to complications. Although the current clinical trial policy includes similar language, some providers and Medicare contractors have misinterpreted this provision to mean that Medicare will not cover care related to complications and they require sponsors to pay for that care. We ask CMS to include in the final policy the statement made during the Open Door Forum that treatment for adverse events in clinical trials would be covered for patients in the trial to the same extent as if the event occurred due to care provided outside of the research study. We also ask CMS to continue to cover items and services needed to prevent, diagnose, or treat for complications arising from participation in all clinical trials, not just trials meeting CMS' standards.

V. Lack of Legal Authority

Finally, we want to reiterate the primary points discussed in the White Paper regarding CMS' legal authority. The White Paper addressed the interpretation of the April 10, 2007 proposed CRP, stating that: (1) CMS lacks the legal authority under the SSA to withdraw coverage for routine care items and services furnished in trials that do not meet CMS' standards, and (2) such a withdrawal of coverage would be contrary to existing laws and policies that support coverage of items and services in a clinical trial that would otherwise be covered as reasonable and necessary. We continue to believe that these legal and procedural flaws exist in the July 19 Proposed Revised CRP.

The Proposed Revised CRP would result in different legal and practical implications for two categories of clinical trials: (1) those that do not meet all of the 13 proposed standards for clinical research studies, resulting in a complete denial of coverage for Medicare beneficiaries in those trials, and (2) those that could potentially meet the 13 proposed standards, but where self-certification would be too burdensome or have legal implications that make it unfeasible for a sponsor, effectively resulting in a denial of coverage for participating Medicare beneficiaries.

For clinical research that cannot meet the 13 proposed standards, there would be a complete elimination of coverage of items and services that are accepted as standard of care. As discussed, Medicare beneficiaries have a statutory right to coverage of reasonable and necessary health care items and services for the diagnosis or treatment of illness or injury or replacement of a malformed body member.[21] There is no legal authority under the SSA to deny coverage of these usual patient care items and services solely because the patient is receiving them as a clinical trial participant—Medicare is required to cover these items or services whether inside or outside of a trial, provided the statutory criteria are met. Further, there is no legal distinction between a trial that can meet certain factual criteria and one that cannot—in terms of eligibility for Medicare coverage. While the proposed standards may serve other goals of CMS—such as promoting the public availability of clinical research results or development of subpopulation analysis—there simply is no basis for using such standards as a means of denying coverage to

[21] Social Security Act (SSA), §§ 1812(a), 1832(a) and 1862(a).

a participant in a trial. The appropriate and critical question should be whether the items and services are reasonable and necessary in diagnosing or treating the Medicare patient—not whether the particular study design lends itself to meeting the standards proposed by CMS.

CMS states in the Proposed Revised NCD that such standards are necessary to "ensure that items and services furnished to Medicare beneficiaries in clinical research are reasonable and necessary."[22] We believe that an item or service treated as reasonable and necessary when provided to a patient outside of a trial would be no less so in the context of a trial. Further, there is no support for treating a participant in a trial that certifies that it meets the proposed standards more favorably in terms of Medicare reimbursement than a participant in a trial that does not certify compliance.

For clinical trials that could potentially meet the 13 proposed standards, the lack of adequate guidance of how precisely to meet the standards could result in an inability of some sponsors to certify, which would be equivalent to a denial of coverage. Similarly, for some sponsors, the legal implications of self-certifying may discourage sponsors from self-certifying, which again would deny coverage to a Medicare participant in a clinical trial.

These outcomes do not serve CMS' stated goal of establishing a policy that would protect the interests of Medicare patients who participate in clinical trials, as many will be denied coverage. Further, many potential Medicare beneficiaries likely will not choose to participate in clinical trials if CMS finalizes its proposal to permit Medicare coverage only in self-certified trials. Such a result would hinder CMS' stated goal of supporting research that will provide information on this patient population.

Addressing these critical legal issues is another reason why the clinical research policy is not appropriate for a NCD and should be promulgated as a NPRM instead. BIO firmly believes that CMS should issue a proposed rule if it wants to establish new conditions of coverage for items and services that already have been determined to be reasonable and necessary in the past.

[22] Section IV.C. of the Proposed Revised CRP.

We very much appreciate this opportunity to comment and look forward to working with CMS to encourage increased Medicare beneficiary access to and participation in clinical trials. We urge the agency to withdraw this NCD immediately and to issue a NPRM for the agency's clinical research policy instead. If you have any questions regarding our comments, please contact Sandra Dennis at 202-962-6673 or John Siracusa at 202-312-9281. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

Sandra J.P. Dennis
Deputy General Counsel for Health Care Regulatory Affairs

/s/

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