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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Evidence Development & Coverage Advisory Committee

December 13, 2006

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

Panelists

Chairperson
Alan M. Garber, M.D., Ph.D.

Vice-Chair
Alexander H. Krist, M.D.

Voting Member/Patient Advocate
Nancy Davenport-Ennis, B.A.

Voting Members
Wade M. Aubry, M.D.
Marc L. Berger, M.D.
Mark D. Grant, M.D., M.P.H.
Mark A. Hlatky, M.D.
Nora A. Janjan, M.D., M.P.S.A.
Bernard Lo, M.D.
Sanford J. Schwartz, M.D.
Jeremy Sugarman, M.D., M.P.H., M.A.

HCFA Liaison
Steve E. Phurrough, M.D., M.P.A.

Panelists (Continued)

Consumer Representative
Linda A. Bergthold, Ph.D.

Industry Representative
Michael L. Ryan, Pharm.D.

Guest Expert Panelists
Barbara Alving, M.D.
Steven N. Goodman, M.D., M.H.S., Ph.D.
Cary Gross, M.D.
Steven A. Wartman, M.D., Ph.D.
Deborah Zarin, M.D.

Executive Secretaries
Janet Brock
Kimberly Long

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PANEL PROCEEDINGS

(The meeting was called to order at 8:00 a.m., Wednesday, December 13, 2006.)

MS. BROCK: Good morning, everyone, welcome committee members, chairperson, guests. I'm Janet Brock, and along with Kim Long and Michelle Atkinson, I am the executive secretary for the Medicare Evidence Development & Coverage Advisory Committee, also known as MedCAC. The committee is meeting today to consider proposed changes to the standards Medicare uses to determine coverage for clinical trials. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interest. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations also disclose any current or previous financial involvement in any clinical trial activity. This includes direct financial

investments, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.
I would also ask the presenters, please adhere to your time. We have numerous presenters to hear from today and a very tight agenda, and will not be able to allow extra time. There is a timer right up here. It will turn yellow as a two-minute warning and then it will turn red when it's finished.
Voting members present today are Alex Krist, Nancy Davenport-Ennis, Wade Aubry, Marc Berger, Mark Grant, Mark Hlatky, Nora Janjan, Bernard Lo, Sanford Schwartz, and Jeremy Sugarman.
The conflict information provided by the panelists has been reviewed by the agency and no one has been recused.
The entire panel, including nonvoting members, will participate in the voting. The results of the voting will be available on our web site following the meeting.
I ask all panelists to speak directly into the mikes. Unfortunately, you have to share.
And lastly, for those in the audience, there is no

eating or drinking allowed in the auditorium. I would now like to introduce Dr. Barry Straube.

DR. STRAUBE: Thanks very much, Janet. I am Barry Straube, the chief medical officer for CMS, and I want to welcome you all to this, in my mind, historic meeting of the MCAC and as we'll talk about, the MedCAC going forward. Before we get started, I do want to thank very much Alan Garber for having been the leader in terms of chairing MCAC meetings in the recent or more remote past; he has done a spectacular job. And I especially want to thank Dr. Steve Phurrough, who is the director of the Office of Clinical Standards and Quality. I would also like to recognize Sean Tunis, who is in the audience this morning, as well as Jeff Kang, who preceded Sean, for their help in developing and making this process an incredibly efficient and certainly integral parts of CMS. So I want to thank Alan, Steve, Sean, Jeff, who is not here, and everybody who has given their time into this particular meeting on Medicare services in clinical research studies.

Before we begin with that deliberation,

however, I would like to share with all of you some interesting news that we have here this morning. As you may know, this committee is chartered by the Secretary of Health and Human Services, Mike Leavitt, to advise Medicare on coverage issues by reviewing and evaluating medical literature and other pertinent data on the effectiveness and appropriateness of medical services and items that are covered or eligible for coverage under Medicare. The committee, which has been referred to as MCAC, meets several times a year here in Baltimore to discuss a range of crucial coverage decisions. In the past year the MCAC has advised us on techniques for managing type 1 and type 2 diabetes, things to look for when covering drugs off label for cancer treatment, diagnosing coronary artery disease, and spinal fusion surgery for treating low back pain. As the MCAC tackled some of these controversial subjects, it became an integral part of our coverage process here at CMS.

Now I'm pleased to share with you that Secretary Leavitt has reauthorized the committee through November of 2008. The Secretary has to reauthorize the committee to continue its

existence and he has done so, so we can all look forward to your wise counsel for at least the next few years. As part of this reauthorization, the Secretary has approved a name change, so as of a couple of weeks ago; the MCAC is now the MedCAC, which stands for the Medicare Evidence Development & Coverage Advisory Committee. In my mind and Dr. Phurrough's, and the rest of the team, it is more than just a name change to us here at CMS. We believe that it signals all those who are working with us to develop better evidence about the impact medical technology has on the health of the Medicare population.

This goes hand in hand with our coverage development initiative that we have been developing over the past several months and on which my staff have been working with stakeholders, including some of you in the audience today, to enable Medicare to keep up with the rapid advances in health technologies while ensuring that the care our beneficiaries receive is reasonable and necessary. Now providing evidence-based decisions to our providers and beneficiaries is a key strategy in our road map. So this committee today is part of the CMS quality

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agenda.
The focus on evidence in health care decision-making and care is a national initiative, as reflected in several meetings I participated within the past two weeks alone, and I represented the Agency at these meetings. The first was the Institute of Medicine evidence-based roundtable. Another was a recent meeting of the Health Industry Forum on comparative effectiveness. And the third, just, we met two days ago, was the IOM's forum on the science of healthcare quality improvement and implementation. CMS works closely with AHRQ on Medicare issues dealing with comparative effectiveness studies which are done on an ongoing basis, as well as evidence gathering and use on a daily basis. We at CMS intend to incorporate scientific evidence for decisions made by the Agency that affects quality and efficiency of care and avoidance of unnecessary complications and costs.
It seems most appropriate that this panel meeting centers on the Medicare clinical trial policy. For the CMS staff today, this has been an issue they have been examining for several years. It was actually a very pet project of, a

key focus of Mark McClellan when he was administrator, and continues to be with Leslie Norwalk, our acting administrator. This is where we're trying to understand better how to provide coverage so that Medicare reacts to clinical research studies in a way that protects the interests of our beneficiaries and fulfills our responsibilities under the Social Security Act. That said, I welcome you to this morning's historic deliberations and want to thank you for putting in the time and effort to do so. And now I will let Dr. Garber and Dr. Phurrough proceed with the convention of CMS's first MedCAC panel. Thank you very much.

DR. PHURROUGH: Thank you, Barry. I also want to welcome you, and I will spend a few minutes after Alan's comments and we introduce the panel talking about exactly what's happening today and the focus. It is as Barry said, something that we have been encouraged to do to relook at our policy, and we are interested in and excited about moving forward with that.

I want to especially thank the panel. We were able to bring people together today who have significant experience, knowledge and skills

in the creation and evaluation of clinical trials and various aspects of clinical trials, and we're excited about having you here today, and I appreciate the time and effort it takes for you to be part of that. I will now turn it over to Alan for his comments and we will have the panel introduce themselves.

DR. GARBER: Thank you, Steve. I'm Alan Garber, you want to add my welcome to those of Steve and Barry. I want to thank the panelists, first of all, for agreeing to consider these very important questions, and to the people who have come here to participate in today's meeting. We are addressing some extremely important questions and I know they are of interest to everyone in the room, and there is a set of specific questions about clinical trial policies that this meeting is devoted to. We're not going to cover every aspect of clinical trials policy, but some fairly specific issues as to what constitutes a good clinical trial. They are issues about reimbursement plans and so on and so forth that are outside today's agenda, not because they are unimportant, but will be questions for another day and probably for another group,

because this group is really concerned with coverage and evidence development issues. So, it will be most useful to all of us if any questions and comments from the audience, or from the panelists are directly on point of the questions that are the, that form the agenda for today. I realize that there is a tremendous amount of knowledge and wisdom in the room, and I hope we will be able to use that most effectively, and because of that, I hope we will as tightly as we can adhere to questions of direct relevance to the MedCAC questions that I believe all of you have received copies of.

We have a very crowded agenda today and a number of speakers are signed up and are scheduled. In order to give everyone a chance to be heard, we will be adhering very, very strictly to the allotted time, so if you have five minutes, you will have a little light that goes on when you have two minutes left that's amber, and then it will turn red, and we will typically cut you off mid-sentence if necessary once the light goes red. And I apologize for that, that's not to be taken personally, but is in the interest of fairness to the other speakers and also to the panel, which

will need to have time for their own deliberations. So please adhere very, very tightly to the allotted time that you have. There may be opportunities to offer further comments, particularly in response to panelists' questions, later on in the meeting.

Thank you again for coming here, and I will turn it over to Janet. Actually, I think we're ready to get underway, starting with the panelists' introductions, beginning with Dr. Krist.

DR. KRIST: My name is Dr. Alex Krist, a family physician at Virginia Commonwealth University, and I have no conflict of interest to disclose.

MS. DAVENPORT-ENNIS: I am Nancy Davenport-Ennis, my organization is the Patient Advocate Foundation. We deal in removing obstacles to health care for patients throughout the country, and I have no conflicts of interest for the discussion today.

DR. AUBRY: I'm Wade Aubry, I'm a senior advisor for the Health Technology Center in San Francisco, a nonprofit technology forecasting institute. I am also a part-time employee of

UCSF, which conducts clinical trials, and within Health Tech, the Health Technology Center is interested in helping to organize trials for studies of technologies in which there is an evidence gap. I have been on occasion in the past an advisor to the medical industry companies, usually with a group of medical directors talking about coverage and reimbursement issues. I have no conflicts.

DR. BERGER: I'm Marc Berger, vice president of outcomes research and management at Merck & Company, a pharmaceutical company that does conduct clinical trials.

DR. GRANT: I am Mark Grant, a senior scientist at the technology evaluation center for Blue Cross Blue Shield Association, and have no conflicts of interest to report.

DR. HLATKY: Mark Hlatky, from Stanford University, a cardiologist, and I have been involved in clinical trials that have been funded by NIH and others.

DR. JANJAN: Nora Janjan, a radiation oncologist at University of Texas in the M.D. Anderson Cancer Center. I have participated in several clinical trials sponsored by the

pharmaceutical industry and also served on a variety of advisory boards.
DR. LO: Bernard Lo from the University of California San Francisco. I have served on the data and safety monitoring board for a number of clinical trials, but have no conflicts.
DR. SCHWARTZ: Sandy Schwartz, University of Pennsylvania. I am an internist there. The university receives substantial revenues from clinical trials and related costs. I have participated in and been a principal investigator of several trials. I serve on several advisory boards for pharmaceutical companies and for payers in the United States making determinations or recommendations regarding evidence and sometimes coverage.
DR. SUGARMAN: I'm Jeremy Sugarman. Like some of the others, I work in an institution that conducts many clinical trials, and I have participated in both industry and federal clinical trials, and I have consulted with big pharmaceutical companies on bioethics.
DR. BERGTHOLD: I'm Linda Bergthold, an independent health care consultant and a Medicare beneficiary as of June. I'm the consumer rep on

this panel and I serve on various technology boards, and I have no financial conflicts of interest today.

DR. RYAN: I'm Mike Ryan, general manager of Amgen, which sponsors numerous clinical trials, and I am the industry representative on the panel.

DR. ALVING: Barbara Alving, acting director of the National Center for Research Resources at the National Institutes of Health, I'm the representative of NIH to CMS and I have no conflicts.

DR. GOODMAN: I'm Steve Goodman, epidemiologist and biostatistician at Johns Hopkins, and I have designed and analyzed many clinical trials.

DR. GROSS: I'm Cary Gross, an internist from Yale School of Medicine, and I have been a co-investigator on clinical studies in the past.

DR. WARTMAN: Steve Wartman, president of the Association of Academic Health Centers, and our association consists of organizations that conduct enormous amounts of clinical trials. I have no financial conflicts.

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DR. ZARIN: I'm Deborah Zarin and I work at the National Institutes of Health. I direct ClinicalTrials.gov, which is the world's largest international clinical trials registry.

DR. GARBER: And this is Alan Garber. Just as disclosure, I think all of us with university appointments have some stake in this issue, I think Stanford wishes they had more of a stake in clinical trials, but I have also had involvement with the VA and have consulted to various industry groups in the past, and also currently I have done so. So, I guess you could say that we all have some stake, even though I likewise don't have any financial interest that would affect my deliberations.

As promised, here are more comments from Dr. Phurrough.

DR. PHURROUGH: All right. I want to spend a few minutes talking about the particular issues today. The clinical trial policy is fairly nuanced, and we want to ensure that we're comfortable with exactly where we're going today. And I will just speak from here. There are some slides for people to peruse if they wish. For the presenters who are in the front row, we will ask

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you to present at the microphone in the center, and we'll pass along this nice little box that supposedly will advance your slides, we'll see whether it works, and it does. These are the three particular issues we're addressing within the clinical trial policy today. Our current policy was implemented in 2000 following a White House executive memo telling us to do that. Prior to that, the difficulty was that many of our contractors looked at patients being treated inside clinical trials as being experimental and all services provided to them within that trial being experimental and, therefore, not covered. We were then faced with the issue of beneficiaries inside a clinical trial to not have any services reimbursed, even though outside the trial they could have those services reimbursed. That was the goal of the executive memo that actually followed, and we have been asked to clarify those rulings. So since 2000, we have had in place a clinical trial policy. There are a number of inquiries and issues that have been addressed over the last six years, and that's the reason for this particular meeting today. As Alan mentioned, there are a number

of problems in the clinical trial policy centered mainly around reimbursement that are not on the table today. Those will be addressed as we move along in the NCD process, but they are not issues for this particular panel. Whether, how Medicare plans cover this and are reimbursed for this, Medicare secondary payer issues, part D issues, all those kinds of issues are issues that we are not going to be discussing today.

Let me talk just a bit about the first section of the clinical trial policy and the first section of our discussion today, and that's the standards that we want to apply to clinical trials. Currently, the current clinical trial policy has this formulation of what the policy says are three requirements of a qualified trial and seven highly desirable characteristics. Those three requirements are listed here, I will talk about those a bit more in a minute, but the first one is more of a standard and the second two having to do with the kind of trial and who can participate in the trial, and I will talk about those a bit more in a minute. They are in fact the current policy's self-definition of what a good trial is, and I think it's a pretty good list

of characteristics, and the question we're asking today is should those be modified. In our questions we have proposed some changes to both those sets of standards. First of all, the central set of standards, we think, can be handled in potentially one of three ways.
We can continue the current definition.
If you have looked at what we call the seven highly desirable, the policy currently calls seven highly desirable characteristics to broadly define what a good clinical trial is. We can continue that, we can go to a more narrative definition, or you could recommend that we adopt someone else's definition, another federal agency's or any others that you may be aware of.
In addition to the looking at the general definition of a good clinical trial, we believe that these Medicare-specific standards that are currently in the trial are not different than what a good clinical trial is, it's just that those standards are standards that we at Medicare want to ensure are met by clinical trials that we are funding services for. So we believe these to be a subset of what a good clinical trial is. Those that we specify do not need to be

word-for-word within that definition, but they need to be a subset of whatever definition that you propose for us. And there are several that we think need to be added to that particular list, and I will talk about those individually.

The general standards I just mentioned, there are a couple of definitions that we have proposed and provided to you that you may want to address if you think that's a good thing. I've listed one of those. There is a second one here. Again, feel free to dissect or delete these entirely. If you think a general definition such as this is a good thing and want to do something different, feel free to do that.

Just reshowing this list of seven highly desirable characteristics, we're asking what you believe should be standards for a good clinical trial. If you think that those are sufficient as defined by the first NCT, or there are other entities out there, as I mentioned, who have their standards, and you may want to point to those as being, CMS adopting those same definitions.

Let me talk a bit more about the Medicare-specific standards. The first one, the

first requirement just repeats law, it is not really a standard of the trial, we are going to, we can comment if we ought to remove that from law, but it will not be listed as a standard of a good clinical trial. The next two are standards for a trial.

The first one says it has to be, the trial has to be of therapeutic intent. The question we'll ask is do you think Medicare ought to continue that requirement. There has been some concern among the public about what therapeutic intent means, and so we are asking that you look at that definition and see if you agree with what we have proposed here as a definition of therapeutic intent.

The second one that we currently have and are proposing to continue is that this, because it's a trial of therapeutic intent, it needs to be not with healthy patients unless we're looking at particularly some diagnostic procedures. We are not proposing any changes to that, we're asking your input on that particular one.

Here are five -- we'll have a couple slides of five things that we think need to be

added to this particular list. We think the trials ought to be registries, so we are proposing that all trials that we provide coverage for must be in ClinicalTrials.gov, there are some coding issues, and essentially in the parenthetical there, it would require an NCT number on the claim for that trial to be covered.
We think that the trial results ought to be public regardless of the outcomes, regardless of whether the trial is completed or not completed. There's challenges in doing that. We would love for ClinicalTrials.gov to be able to do that, but at a minimum, because there aren't mechanisms currently, we want the protocol, or we are proposing that the protocol clearly indicate that the results of the trial will become public, even if the trial is ended for whatever reason.
The third issue, I will not spend a lot of time on this, but there was a concept that we developed a year and a half ago or two years ago that says that in some cases we may cover technologies only when patients are enrolled in clinical trials, we don't think the evidence is sufficient for us to provide coverage broadly. We want to add that into the clinical trial policy

and in those instances we may propose some more specific standards than what's the list of general standards that you assist us in developing. It would be unlikely, I would think that we would do that, but it may be for a particular technology that we want some other specific standards met by that particular trial. So that's the purpose of this particular bullet.

We have some concerns also about trials that do not necessarily address the populations that are affected by the technologies that are being evaluated in the trial, so we believe that it's important that protocols specifically address the various subpopulations affected by a particular technology that's under investigation and that the protocol discuss how you're handling that or not handling that within that particular trial. So if you're testing a hypertensive drug and we want the protocol to particularly specify the epidemiology of hypertension, populations involved in hypertension, and how your trial plans to ensure that you have adequately addressed that particular population in your trial. So that at the end of the day, we don't have a hypertensive drug trial that addresses white males, but that it

broadly addresses all those who have hypertension as a disease process.

The argument obviously could be, and the discussion that we've had is that if there is no subpopulation difference, then the trial can generalize information. But that, we're proposing that it specifically be addressed within the protocol.

The last one on the screen is similar, a bit more nuanced. It is very common that we get requests to cover technologies for our populations when the trials did not include our populations, so we want to specifically say if you're going to bring us a trial for coverage, and there may be trials that we are paying, reimbursing services under the clinical trial policy that may not be for coverage, there are a whole host of reasons they would necessarily need Medicare coverage, or coverage may already be in. But if it's for a technology that currently does not have coverage, then we expect you to be enrolling our patients in that trial unless you can clearly demonstrate in some manner and outline very clearly in your protocol that you don't need to do that. So if you have a convincing argument that a

pathophysiological intervention that works in a 45-year-old is going to work in a 65-year-old or a 70-year-old, then have at it.

We think that's a pretty difficult thing to do and so particularly for things that are not covered, if you're going to expect us to reimburse for it, the trial needs to have enough Medicare beneficiaries in that trial to arrive at specific clinical and statistical conclusions around our population. That's what number five is.

So those are the proposed specific standards. Now once we talk about standards, the second part of the clinical trials policy is to ensure that those standards are met before we start paying for services within that policy. The current process is challenging. For the Medicare-specific standards, we have not defined any system at all in the process. Our contractors in some cases have been involved in this, but there is no guidance to them that tells them how that should occur.

For the seven highly desirable characteristics, there are two current methods for being certified as meeting the standards. We do

not in the current policy on a trial-by-trial basis look at that trial to see if those standards are met. We have these two particular processes, one a naming process and one a self-certifying or deeming process. The current policy says that if you're funded by a specific federal agency, CDC, NIH, AHRQ, VA, DOD, and CMS or its predecessor HCFA, then we will consider you to have met those seven standards. If you are part of a study funded by one of those agencies, then we will consider you to have met those standards. If it's an IND, you will be, an IND-exempt trial, you are deemed to have met the standards. So those are the current mechanisms for the agency to assume that the standards have been met.

The current policy also has a self-certification process. The self-certifying process was to have a set of standards established that would be applied by the PIs of the investigations and then those PIs certifying to me, but that policy was never implemented, it currently is not used.

So that's the current policy.

For the proposed policies, we think the Medicare-specific standards are an internal issue.

We will need to devise internally a process and we will do that through our NCD and outline what we think is the appropriate mechanism to ensure that those standards are met.

For the general standards, we would ask you to recommend to us what the general definition should be. There needs to be some discussion of, is the current process adequate.

We think that the deeming status is appropriate currently. We think it should be expanded to include other federal agencies who are supporting trials now that are not on the current list, and we think those are appropriate.

We do have some concern that all we have said in the current policy is funded. We think we ought to expand the language to say reviewed and approved, as well as funded, just to make sure that those things occur.

We think that this deemed status should be continued for the first three, for those that are funded, or reviewed and approved by a federal agency, or done by cooperative groups, or IND studies.

We have some concerns about continuing to fund IND studies since their deemed status was

temporary until we developed a certification process, and since we never did that, it remained temporary. We have had some instances where there is coverage for some IND-exempt trial that we have concerns about, where the trial was not a very high quality trial.

IND-exempt trials are trials on drugs that have FDA approval for some indication and the trial is not to get additional labeling or additional approval, it's looking at other issues around the drugs, and it does require, the FDA regulations do require IRBs to approve the trial. However, we think that IND should meet the same criteria as any other trial within this policy and question whether it should be deemed just because they are IND-exempt, an issue that we'll have you discuss today.

We also are not particularly enamored with the self-certification process and have never implemented it. And we want to answer, we will have you discuss whether we should continue some kind of self-certification process or develop an alternative, because we do think that self-certification is not necessarily a great method of doing this.

We think that there is a need to expand to some other options of covering trials, and here are some options that are considered. This particular list is not particularly a list that we endorse. Unlike some of the others where we were endorsing, these are just some potential options where you may recommend to us that these are methods to approve clinical trials.

The first one is FDA post-approval studies. That is becoming obviously a much more prominent part of FDA, we have encouraged that to occur in some instances by, through our NCD process, and we think we ought to, as one department, assist them in getting some of their post-approval studies done. So we are asking you to look at that.

As mentioned before, our CED process, coverage and evidence development process in some cases have required clinical trials. We are just formalizing that in this particular policy and this would say that if a trial was required through a national coverage determination, then it would be covered under the clinical trial policy.

We've had a lot of requests in the past that a federal agency be formed to sort of trial

by trial review these and say they do or do not meet the standards, so that's an option to discuss. One of the reasons we have some federal agency people here is to sort of talk the issue of is that a doable process. We have also been asked to put together a multi-stakeholder panel, not just federal agencies, but a broad panel that may include academia and industry to review trials and look at that, so that's another potential option that we'll have you discuss.

One option that has been addressed is that most federal agencies, as they go through their trial approval process, have some kind of checklist for their reviewers, and the reviewers have the protocol, they go through the checklist. Could we ask some federal agencies to add to the checklist a requirement to, here's what Medicare thinks a good trial is, does this trial meet those standards. So they would check that off even for those trials that may not be funded.

And then lastly is an option that says if the trial has been approved for funding by a federal agency but not funded, then that would meet the deemed status. That does have some appeal. There are some concerns that we have

heard from some of the reviewers who say because they know that all trials are not going to be funded, they may not necessarily be real stringent at the bottom end of the trials, and some of those trials that are on the bottom of the list that don't get funded, may in fact not be necessarily great trials. So those of you who have been involved in those processes as reviewers may want to speak to that particular issue. So these are some options for expanding the number of trials that are covered, and we're asking you to consider those, or propose others that you think may be appropriate.

Finally, we're just going to briefly talk about the various things that we pay for. In the current trial we talk about, the current trial talks about routine costs and what routine costs are covered. It is a bit confusing. It says that, as you see on this list, we cover things that are covered outside the trial except for the investigational item. And then in the next paragraph we say we cover conventional care. Well, if it's covered outside the trial and it's an investigational item, is that conventional care? So it is somewhat confusing, and we want to

clarify that in this particular process. We do not define administrative costs, we do not define what investigational costs are in the current policy, and so we want to do that in the new policy.

We are proposing that there be three services discussed, routine services, administrative services and investigational services. The routine services, we essentially are not proposing that there be any change in what the routine services are, it just be reworded such that it's more clear. We will continue to say that routine costs, routine services do not include the investigational services, they have to be for patient management.

There has been a number of concerns raised that we in Medicare are paying for lots of things in trials that aren't involved in patient management. They're just needed for data collection in the trial. We want to clarify in this that if you need to do a particular service in a trial, if you are doing extra services, you need a CT scan every other day, whatever that might be, we're not going to pay for every one of those unless it is actually used for patient

management within the trial. That's not different, we just want to clarify that. We also want to define administrative services so that it's clear what those are and that we do not pay for administrative services. And then we want to add a definition of investigational clinical services, and we are suggesting that there perhaps are three classes of investigational services that we may cover. One is if it's covered outside the trial, we will cover it inside the trial. We think that's a part of the current clinical trial that may not have been well thought out, so we think, you know, if we're paying for it outside the trial, why should we not pay for it inside the trial. Again, we're adding the CED language that codifies our guidance document in a policy that says if we require a trial to the CED, then we will pay for the investigational services within that trial. And then we want to talk about humanitarian use devices just a bit. FDA has a required and now regulatory categorization of devices known as humanitarian use devices. It essentially is a device that is only, would only affect less than 4,000 patients a year. It could

be a device that is used broadly for some other group or it could be a device that is not used at all, but if there is a particular indication that involves less than 4,000 people, then it's given this humanitarian use device categorization. It can then be given a humanitarian device exemption for marketing. That HDE status is similar to a 510(K) or a PMA approval; it means that you are free to market your device. There are some restrictions to that. It has to be approved by an IRB in your facility, there are some reporting requirements. There is no prohibition on it being used off-label if it -- as there are not prohibitions on any other technology approved by FDA and using it off-label. The HDE status is approved by FDA if there is evidence of safety and probable benefit. The definition of probable benefit is such that it doesn't require much evidence at all. There has to be some clinical trial that says yes, this may work in this particular population. This never meets our standards of reasonableness in a CMS coverage process, so we have no national decisions, no national policy on how we pay for HDEs. Some of our contractors have in limited

circumstances covered HDEs, but as we have looked at a couple of instances of those at the national level, that will never meet our evidentiary standards.

So a potential is for us to, in the new clinical trial policy, have a broad policy that says if you're an HUD with an HDE and you are the investigational item in a clinical trial, then we would cover that under the clinical trial policy.

There are two ways also that this can work. If the particular technology is noncovered by CMS, we would under the definition of investigational items not cover it in the particular clinical trial. Only if it was covered by Medicare under some other process would it be covered in the, the non-HDEs be covered.

So for the HDEs, you could recommend that even if it's noncovered nationally, it be covered in the clinical trial, or you could suggest to us if the Agency has gone through the process of covering this particular technology and decided that it's noncovered, it needs to be treated like any other noncovered technology and not be covered in the, under the clinical trial policy either, without changing the national

coverage determination. So this one is a bit more nuanced and we will look for you to advise us one way or the other on both of those particular issues.

So that is the clinical trial policy, the three sections of it, and our particular interest in the kinds of things that we want you to opine on today. We have provided some questions, I'll not display those, there is a set of questions in everyone's chair so that the audience has a copy of those. You've had those questions and we've had some discussions around those questions, so we will not go over those at this particular time. So with that, Alan, I turn it back over to you.

DR. GARBER: Thank you very much, Steve. Just a couple of things before we start with the scheduled speakers. Janet is going to be testing all of our equipment here to make sure that things are working. I can't see all the panelists very well, so if you have a question or want to make a comment, raise your hands high. I was going to suggest put your tent cards up but they're taped down. But anyway, if you're standing right behind your seat, I'll assume that

you really, really want to speak.
And let me first ask, are there any quick informational questions that you have for Steve before we start with the scheduled speakers?
Okay. Great. Well, we're off to an excellent start here.
The first speaker, and let me just ask, I think you all have the speaker list so you know what order you're in, so be prepared when you're next up, of course. And we'll start with Dr. James Dougherty of the Alliance of Dedicated Cancer Centers. Please introduce yourselves and state any conflicts.
DR. DOUGHERTY: I'm Dr. James Dougherty, representing as a consultant the Alliance of Dedicated Cancer Centers, which are ten nationally recognized comprehensive cancer centers. I have no conflicts, and stated as such. I'm a medical oncologist and the former deputy physician in chief at Memorial Sloan Kettering Cancer Center. Our comments basically really are majorly pointed to Question 2.A and to Question 3. In terms of comments for Question 2.A, the definition of therapeutic intent and the coverage of trials that enroll healthy patients,

the Alliance of Dedicated Cancer Centers recommends that CMS formally adopt its historic interpretation of the therapeutic intent requirement. While the NCD provides that a qualifying trial must have therapeutic intent, it does not provide specific standards by which to evaluate this intent. And as reflected in the MCAC worksheet, CMS is apparently considering a definition which provides that therapeutic intent must be a major objective of the study.

In light of this and in light of our experience through the Alliance of Dedicated Cancer Centers, some Medicare contractors construe therapeutic intent requirements differently. For example, one contractor apparently believes many Phase One trials should not be covered under the NCD because their intent is to determine safety and toxicity rather than to primarily assess the effect on patient outcome.

The Alliance strongly supports CMS's historic view that therapeutic intent need not be the primary purpose of a trial as long as it is a purpose of the trial, as demonstrated by appropriate outcome measurements. And in light of the apparent confusion on this issue among

contractors, we strongly urge MCAC to recommend that CMS clarify the NCD to reflect this reasonable interpretation. A contrary position would have the effect of carving out potential coverage of important clinical trials such as Phase One B trials, which do not generally have therapeutic intent as a primary objective, but in fact virtually all such trials do certainly have therapeutic intent as a secondary purpose. A more restrictive policy could in fact be a very crippling blow and disallow Medicare participation in some important aspects of cancer research.

A second issue addressed in Question 2.A relates to the current CMS policy of requiring covered trials of therapeutic intentions to enroll patients with diagnosed disease rather than healthy volunteers. The Alliance strongly urges CMS to consider expanding coverage for trials focusing on patients in the Medicare population who are currently healthy but are at high risk for developing disease, particularly cancer, such as patients at high risk for breast, prostate and colon cancer due to family history or the emerging presence of genetic marker research. These trials in our estimation have an incredibly

important therapeutic purpose, and the research conducted by the Alliance of Cancer Centers in this area already suggests that these treatments and these studies have enormous potential for reducing the incidence of cancer and improving outcomes of cancer-diagnosed patients.

In terms of remarks for Question Number 3, the definition of deemed trials, the MNCD currently defines deemed trials to include among others trials that are supported by centers across the groups that you've already outlined this morning. And once again, the Alliance strongly recommends that the language be specific and formally clarify that this in fact would also include trials conducted at National Cancer Institute comprehensive cancer centers.

In our review of the MCAC question worksheet, CMS appears to be considering a definition of a deemed trial as a study supported by centers or cooperative groups that are funded by a federal agency that has reviewed and approved the study. While the cancer centers are funded globally through federal agencies, primarily the NCI, at present agencies do not review and approve specific clinical trials, except to the extent

that they in fact fund the trial, or in fact fund the comprehensive cancer center's activities. So it's our request that, once again, CMS clarify the proposed definition of deemed trials to include all trials conducted at comprehensive National Cancer Institute cancer centers. Thank you.
DR. GARBER: Thank you, Dr. Dougherty.
Next up, Bryan Soronson from the AAMC.
MR. SORONSON: My name is Bryan Soronson, from the University of Maryland, not University of Washington as listed. My testimony today is presented on behalf of the Association of American Medical Colleges.
Question 1. AAMC strongly supports option 1.C. The FDA guidance on general considerations for clinical trials is the most authoritative source.
Question 2.A. As currently stated, the two criteria are confusing. The first bullet makes a definitive statement that a clinical trial must have therapeutic intent, while the second bullet implies that trials of diagnostic interventions may also be covered. AAMC suggests that in addition to paying for routine costs of trials of therapeutic intent, Medicare pay the

routine costs for beneficiaries participating in trials of diagnostic interventions. These trials are important because they lead to earlier detection of conditions which treatments are most likely to be beneficial. It is even possible that such trials would be covered by Medicare under the CED.

2.B, the proposed CMS definition of therapeutic intent forecloses the possibility of coverage of any Phase One studies. AAMC supports Medicare coverage for certain Phase One studies, particularly those of cancer treatments.

You also asked whether CMS should define therapeutic intent differently for studies evaluating diagnostic services. The evaluation of the diagnostic service does not have therapeutic intent, though as stated above, Medicare should cover routine costs of patients enrolled in these studies. CMS should make clear that these studies will be covered, provided that they meet the criteria set forth in Question 2.B.

In terms of standards, the AAMC has the following comments on each of the standards: We support requiring the registration of trials on the ClinicalTrials.gov web site. While we

strongly support requiring public release of study results, there currently exists no publicly supported and operated site through which such information could be reported. To impose such requirements now would be in our judgment premature. We support requiring an explicit discussion of consideration of relevant subpopulations in the study protocol.

Our major concern with the proposed standard four is that it attempts to limit Medicare coverage to those studies that are designated specifically to enroll a statistically valid Medicare population. Many significant pathologies that afflict Medicare beneficiaries have their onset long before individuals become eligible for Medicare and require treatments that extend throughout the individual's Medicare-eligible years. Typically these studies of these conditions seek to recruit a broad spectrum of population that may currently include but not be especially directed at Medicare-eligible participants. The knowledge gained from these studies may be of enormous benefit to Medicare enrollees, as well as to younger populations. It is a very shortsighted

view that does not serve the Medicare population well to exclude such studies from Medicare coverage. Moreover, to adopt those standards could well have the perverse consequence of deterring enrollment of Medicare beneficiaries in studies that may be of great benefit to them. The AAMC supports the use of any standard required through national coverage determination using CED, and we also request that CMS clarify whether the study meet all five standards to qualify for Medicare coverage. Question 3, AAMC supports all criteria listed. We ask that CMS clarify that meeting any one of the four criteria will qualify the study for deeming. Question 4, the AAMC supports allowing IND-exempt studies to be deemed if they meet any one of the four criteria listed in Question 2.B. Question 5, the AAMC supports the deeming of these studies only if they meet any one the four criteria listed in Question 3. Question 6, one, any study required through the national coverage determination using a CED is most desirable as opposed to the other three standards listed.

Question 7, the first criterion of routing clinical studies is that such items and services are available to Medicare beneficiaries outside of the study. Within the medical community, such items and services are commonly referred to as standard of care or conventional care. We recommend that CMS adopt these terms since they are already widely used and understood, and thus will provide greater clarity for those implementing the policies.

The second criterion is that the items and services are used for patient medical management within the study. The meaning of patient medical management is unclear. It would add clarity to revise the criterion as follows: Diagnostic tests that comply with requirement of 42 CFR Section 410.32(a).

The three remaining criteria are reasonable and should be adopted.

Question 8.

DR. GARBER: Thank you, Mr. Soronson. Sorry, but your time is up. Thank you very much.

MR. SORONSON: Thank you.

DR. GARBER: John Siracusa, from Biotechnology Industry Organization.

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DR. SIRACUSA: Good morning. My name is John Siracusa. I'm manager of health policy at the Biotechnology Industry Organization, representing biotechnology companies in the United States and around the world. Our testimony highlights several issues for the committee to consider.

First Bio strongly urges CMS to permanently extend deemed status to IND-exempt clinical trials. These trials are carefully regulated by the FDA and the exemption applies only when certain criteria are met. The FDA has also expressly encouraged the use of the IND-exempt process for qualifying trials, for example, in 2004 for oncology therapies. Clinical trials operating under the IND-exempt process 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 the FDA's urging.

Bio also believes it is critical that CMS expand its coverage policy to include all Phase One studies except for those conducted in healthy patients, and all Phase Two studies. The current coverage requirement that

clinical trials have therapeutic intent unfortunately leads to confusion and inconsistent coverage determinations at local contractors. Coverage for Phase One studies is frequently denied and under some narrow interpretations of the NCD, coverage is limited only to Phase Three 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.

Bio also opposes removal of the proposed self-certification process. We understand that an inter-agency panel met and developed criteria for the types of trials that should be covered under this process, and we encourage the Agency to release that panel's findings to the public and to propose an alternative qualifying process for those research studies that are not deemed to be qualified clinical trials.

Fourth, Bio urges CMS to take every effort to minimize the burden of data collection for patients, providers and trial sponsors. In

determining whether additional data selection is necessary for Medicare-covered trials, we urge CMS to carefully balance the value of the information gathered against the burden of collecting it, to ensure that research resources are used efficiently. We also urge CMS to pay particular attention to the cost imposed on beneficiaries and providers and urge the Agency to consider ways to compensate physicians more appropriately for the data collection activities they undertake, as well as services they provide related to evaluating patient eligibility and drug administration. Finally, Bio supports the goal of encouraging Medicare beneficiaries to participate in clinical trials. However, Bio is concerned that setting specific criteria, requiring certain levels of Medicare enrollees in a clinical trial could limit beneficiary access to clinical trials. Bio urges CMS to adopt a policy that recognizes the many impediments to enrolling Medicare beneficiaries in clinical trials, such as issues related to age, comorbidities and complications. It is critical that CMS not impose stringent criteria that in fact hinders beneficiary participation in clinical trials.

We also support the increased use of the NIH clinical registries, clinical trials registry as a means of educating Medicare beneficiaries about available clinical trials. In conclusion, Bio appreciates the opportunity to testify today, and we look forward to working with CMS to increase beneficiary access to good clinical trials.

DR. GARBER: Thank you very much.

Next, Dr. Maurie Markman from the National Comprehensive Cancer Network.

DR. MARKMAN: Good morning. I am Dr. Maurie Markman, vice president for clinical research at the University of Texas and the Anderson Cancer Center in Houston, Texas. Today I represent the National Comprehensive Cancer Network and its 20 member institutions. I've also been a consultant to and recipient of research grants from a number of pharmaceutical companies involved in the conduct of clinical cancer trials. I appreciate the opportunity to speak to the Medicare Evidence Development & Coverage Advisory Committee on NCCN's and its member institutions' behalf about the CMS clinical trial policy national coverage determination. NCCN

shares with our colleagues at CMS a commitment and dedication to conduct research that will enhance our base of scientific and clinical knowledge in a way that will improve the effectiveness, safety and efficacy of health care technologies applied in the diagnosis and treatment of illness and injury to Medicare beneficiaries. NCCN believes and asserts that for a significant number of Medicare beneficiaries, participation in relevant clinical trials is the best approach to managing disease. In cancer diagnosis and treatment, this is particularly true, given the seriousness and life-threatening nature of oncologic processes and disease.

NCCN agrees with substituting the title clinical research policy for the current title clinical trial policy. The advancement, capabilities and promise of science argue for a more expansive and integrated payment model to support research that will result in more effective health care technologies for Medicare beneficiaries. NCCN recommends that CMS adopt an expanded definition of clinical research, as noted in the Clinical Research Enhancement Act of 1997. NCCN also recommends that CMS accept a

basic concept of clinical research that formally acknowledges the dual intent of the treatment of disease and the evaluation of the interventions. NCCN member institutions view therapeutic intent as an inherent and critically important quality of the conduct of clinical research. Studies in Phase One to Phase Four most often state explicitly that therapeutic intent and potential benefit to be derived from participation in a study. However, the absence of explicit mention of therapeutic intent should not be taken as an indication of the absence of intent to treat. NCCN is in basic agreement with the current definition of an automatically qualified trial. However, NCCN recommends an extension of the definition to explicitly include the granting of automatic qualification for and reimbursement of clinical trials to those trials that are conducted by institutions, proctored groups and similar entities that are recognized by federal agencies as approved clinical trial programs. This term and concept was advanced by the Medicare Cancer and Clinical Trials Coverage Act of 1997. Approved clinical trial programs would include programs approved by the federal agencies that are

named in both the 1997 legislation and in the CMS clinical trial policy of 2000.

In cancer care, such extension of automatic qualified status is best exemplified by the NCI designations of comprehensive cancer centers and clinical cancer centers as major research organizations. These designated centers are recognized and funded by the NCI and undergo rigorous and ongoing evaluation according to NCI requirements.

In addition, orienting the CMS clinical trial policy to emphasize approved clinical research programs would be consistent with the efforts of CMS, NIH and the FDA to collaborate more effectively and to streamline processes.

NCCN recommends that CMS continue to define routine costs as they are defined in the CMS clinical trial policy of 2000. Coverage of medically necessary conventional care, administration of investigational items and services, monitoring of the effects of investigational items or services, and prevention, diagnosis and treatment of complications arising from participation in clinical research are necessary to provide continued access to clinical

research for Medicare beneficiaries. NCCN also recommends that the revised policy should clearly address the coverage of Phase One clinical trials. The current CMS clinical trial policy explicitly excludes coverage of Phase One studies or trials that solely test toxicity or disease pathophysiology. Phase One studies have a therapeutic intent as part of research into the development of new therapeutic interventions. Moreover, the development of new therapeutic interventions and the study of disease pathophysiology are both included in the definition of clinical research in the Clinical Research Enhancement Act of 1997.

DR. GARBER: Thank you, Dr. Markman.

DR. MARKMAN: Thank you.

DR. GARBER: Next will be Dr. Cynthia Boyd and Ryan Meade.

DR. BOYD: Thank you, good morning. My name is Dr. Cynthia Boyd, and I'm chief compliance officer for Rush University Medical Center, where I'm also associate vice president and director of medical staff operations. I am a member of the board of the Health Care Compliance Association and I have no conflicts to disclose today.

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As most of you likely know, a year ago last week Rush entered into a settlement agreement with the United States and certification of compliance agreement with HHS OIG to settle Medicare and Medicaid overpayments associated with billing for services during cancer clinical trials. Rush voluntarily disclosed this compliance issue, which at first blush in an internal investigation had nothing to do with the clinical trials NCD but was focused on Medicare billing for clinical trial services which had already been paid by the sponsors. It did not take us long, however, before the internal investigation needed to take a hard look at Rush's compliance with the clinical trials NCD. At that point a fairly straightforward though unfortunate compliance issue turned into an odyssey of confusion and interpretative struggle. This was not necessarily because of the goals or policy of the clinical trials NCD but because the language of Medicare and the language of medicine are wholly distinct. My presentation today is not meant to rehash the Rush settlement; the facts, circumstances and corrective action are well known in the academic community.

Rather, I wish to offer comments on the proposed revisions from the context of an institution that likely is the only academic health center in the country that has publicly settled a Medicare overpayment case with DOG and OIG that was solely based on the clinical trials NCD.

We will divide our comments into two. First, the context for how providers must comply with the clinical trials NCD. Secondly, comments on three specific proposals before the committee.

About complying with the clinical trials NCD, clarity is critical. Above all, we urge CMS and this committee to be clear in whatever rules are adopted in the revised clinical research policy, because the language of Medicare rules deeply affects operations at all academic health centers. Words and terminology should be defined as clear as possible to avoid misinterpretation by persons who must deal with these issues who are not familiar with the language and structure of Medicare. We strongly encourage CMS to adopt a definition section for its revised clinical research policy.

Succeeding in clinical trials billing

compliance is not easy following the clinical trials NCD. The protocol schedule even, the compensation arrangement of the clinical trials agreements are grants, and the added cost section of the informed consent must all work in harmony and be synchronized if a provider is to have any hope of billing directly. All three documents, protocol, contract, informed consent, are written by different people in different professional languages. One of our greatest challenges has been to translate all three of these documents into a common language, and also incorporate the language of Medicare.

I believe it is important that CMS and the committee understand the knowledge deficit of Medicare that the research community and physicians have in general. This is why clarity and a definitions section can be one of the most helpful revisions that CMS could offer.

Proposals before the committee. We wish to turn to three issues that the committee is considering today. If there is one thing to our comments on the proposals, it is this. We urge CMS to place the Medicare beneficiary first in its decisions. At this time I would like to introduce

Ryan Meade, who is legal counsel for Rush.
MR. MEADE: Thank you very much.
First, therapeutic intent. A proposal before the committee today seeks to clarify the definition of therapeutic intent by stating that, quote, a qualified study exhibit therapeutic intent when a major objective of the study seeks as its goal the diagnosis or treatment of disease, including the observation of benefit of the intervention under study.
We would like to suggest a modification to this definition to promote greater clarity. It is unclear whether a major objective means one of the primary objectives only, or means any of the articulated objectives in the protocol, whether it be a primary or secretary objective. We would propose the following definition, quote, a qualified study exhibits therapeutic intent when any of the objectives articulated in the study's protocol seeks as its goal the diagnosis or treatment of disease, including the observation of benefit of the intervention under study.
Second, deemed IND-exempt studies. The committee is considering today a proposal that would no longer make IND-exempt studies deemed

studies. We believe this would undermine medical research, particularly among junior faculty and other faculty members who may be underrepresented in obtaining clinical research sponsorship. Many investigator-initiated studies are IND-exempt. Additionally, many of these studies are not funded by industry or any other source.

If the IND-exempt studies are no longer considered deemed, then Medicare beneficiaries may lose out on having therapies reimbursed during clinical trials that would otherwise be reimbursed outside the investigator-initiated trial. This will deter seniors from enrolling in investigator-initiated studies and will deter publication of outcomes and data that could help improve the lives of Medicare beneficiaries.

Dr. Boyd will finish with the third.

DR. GARBER: Actually, I'll give you 15 seconds.

DR. BOYD: Okay. Third is the population-based studies. The committee is considering today in Question 2.B whether to require qualifying clinical trials to explicitly discuss how the enrollment process will ensure that sufficient Medicare populations are enrolled

in the trial.
We applaud CMS's attempt to address health care disparities. However, to address health care disparities by requiring quotas for clinical trials would be a mistake and would hinder and restrict access to clinical care. Enrollment should not be based on the patient's race, gender or age unless that is what the clinical trial is investigating. Enrollment should be based on the patient's disease.
DR. GARBER: Thank you very much. As the panelists undoubtedly know, there are statements by the scheduled speakers in the books that we were sent. Yours is dated June 27th as a working paper, so perhaps if there is something more recent that you wish to provide, you can give people the information later. Thank you.
Next will be Dr. Joseph Bailes.
DR. BAILES: Thank you and good morning. I'm Dr. Joseph Bailes and I represent the American Society of Clinical Oncology, or ASCO, and its 20,000 members. I have no conflicts of interest to report.
We're proud of the fact that ASCO played an integral role in the development of the

patient care coverage policy, patient care cost coverage policy in 2000, and we believe the CMS policy has worked well over the past six years. We appreciate the opportunity provided by the reconsideration to discuss what we believe are the relatively few and relatively narrow circumstances in which the policy is not working well. We would urge CMS and the committee not to make major changes that would restrict its application. In general we believe the policy, the beauty of the policy is that it is largely self-implementing. In other words, CMS defers to the processes of other agencies which are in the routine business of reviewing, approving, overseeing, and in some cases funding high quality clinical trials, i.e., the NIH, FDA, NCI, et cetera. With that background, I will briefly address the specific questions raised by CMS and the committee for consideration. On the first question regarding the definition of a good clinical trial, we believe the current definition is both thorough and functional and do not support revision of the definition, as we don't believe that it will add to transparency or efficiency.

On the second question concerning Medicare-specific standards, we support the continuing requirement of therapeutic intent, but we believe it should be presumed in the case of life-threatening diseases such as cancer, and Medicare should not specify that the protocol specify therapeutic intent, but should recognize that for cancer patients, for instance, without other good treatment objections, a Phase One trial represents a therapeutic option.

With respect to other elements of Question 2, whether CMS should impose additional Medicare standards, ASCO endorses the goals, but we do not believe that a prescriptive approach is appropriate at this time. As noted in our comments, we support clinical trial registration and reporting of results, but there are issues of ongoing legislation as well as private sector, and until these become clear, we do not believe trials should be disqualified from coverage solely for failure to meet these requirements.

We definitely support representation of subpopulations, but we believe current efforts are addressing the issue. The suggestion by CMS that a clinical trial might be disqualified from

coverage by virtue of inadequate enrollment of the subpopulations does not take into account the difficulties sometimes faced in recruiting sufficient numbers from these groups. Clearly it should be a goal but not a disqualifying factor. On Question 3, we recommend continuation of the current deemed categories. And we also believe in connection with the fourth question that IND-exempt trials should continue to be deemed, because individualized consideration of the numerous IND-exempt trials carried out in cancer alone would burden the system and we believe hamper patient care as well as research. Regarding 5, we believe that it's review and approval of a federal trial agency that determines the value of the trial and not just federal funding, so the standard should reflect in our view that broader approach. On Question 6, we support integration of the coverage with evidence development in the trials policy. We do not believe it to be useful or efficient to have a federal panel review trials other than those possibly for coverage with CED. Finally, the important issue of defining what services are routine, we have no

problem with the proposed CMS revisions to the definition. They do not address, in our view, the fundamental uncertainties as to what is routine in clinical practice. This is an issue and we've suggested that the process would benefit from a negotiation between the sponsor and investigators ahead of enrollment as to what is routine in the course of a trial. The result of that negotiation would be specification of exactly which costs are routine and which are not.

In the context of NIH-sponsored research, we encourage the Medicare clinical trial policy to cover all patient care costs according to the protocol, rather than attempting to specify which of those costs may not be routine and thus not covered by Medicare.

The clinical trial coverage policy in our view has been a great success, and we believe should continue mostly unchanged, with the exception of some of the few improvements we have suggested. Thank you.

DR. GARBER: Thank you very much.

Next, Dr. Samuel Jacobs.

DR. JACOBS: Good morning, ladies and gentlemen. My name is Dr. Samuel Jacobs, and I am

here on behalf of the University of Pittsburgh Medical Center and the University of Pittsburgh Cancer Institute. I am the principal investigator on a number of clinical trials funded by pharmaceutical companies.

Today I would like to focus on one of the challenges set forth to this board, to construct a clear definition of routine costs. In the previous national coverage decision, routine cost was defined and included in the coverage of standard care, the administration of an investigational item, and the care arising from the provision of an investigational item.

Currently CMS has proposed a change in the term from routine costs to routine clinical services. Along with the change in term, CMS has proposed an expanded set of statements to clarify services defined as routine costs. It is our belief that the problem is not with the definition of routine clinical services but with the concept. Definitions are inherently limiting, so if access to clinical trials is the goal, the logical solution is for CMS to cover standard care for clinical trial enrollees in the same manner as non-trial participants. If CMS would agree to

cover standard care for CMS beneficiaries regardless of clinical trial involvement, the administrative effort of constructing a definition of routine costs, as well as the effort of enforcing compliance with that definition, could be avoided.

It is our belief that for all studies, the cost of standard of care items should be covered in the same manner as patients not on a clinical trial, by Medicare and by associated payers.

We further believe that the physician can best define standard of care as it relates to a clinical trial at the point of service, just as they do when it comes to covering items and services for beneficiaries who are not enrolled in a clinical research study.

To be clear, research items in clinical trials are the responsibility of the trial sponsor, and standard care is the responsibility of the payer's insurer. The documentation, i.e. protocol, for a clinical trial will explain exactly what items are considered standard of care and which are solely for research.

We believe that our proposal is in

keeping with the three overarching goals of the proposed clinical research policy. First, allowing Medicare beneficiaries to participate in research studies. Second, encouraging research studies to add to the knowledge base on the effective use of items in the care of Medicare population. Third, allowing Medicare beneficiaries access to care which have not yet been approved, but are part of a qualified research trial. By covering standard of care equally between trial and non-trial participants, CMS would remove any disincentive to clinical trial participation and would equalize coverage for all Medicare beneficiaries.

This proposal does not require any change in coverage for CMS. Research-related costs beyond standard of care should be accounted for by the researcher and covered by the proponent of the trial.

To determine how the current policy can inadvertently affect Medicare beneficiaries' ability to participate in clinical trials, we would like to illustrate our understanding of qualifying clinical trial coverage for the Medicare managed care population. Please see the

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slides. Currently, Medicare managed care beneficiaries' coverage reverts to standard fee-for-service Medicare for routine care related to qualified clinical trial involvement. It is not logical to change coverage as a result of participation in a clinical trial. As seen on this table, the change is unnecessary when compared to standard care. The result is an increase in spending for the managed care beneficiary for items that would be covered had the patient chosen not to go on a clinical trial. The additional cost functions as a disincentive to clinical trial participation. This disincentive is in direct conflict with CMS' three overarching goals for clinical trial coverage I've just referred. Next slide. The financial coverage barrier translates to lack of access to clinical trials for approximately 14 percent, over six million people in the Medicare-eligible population nationwide. The result is that it's highly unlikely that a researcher will be able to enroll a fully informed patient with managed care plan into a clinical trial.

While 14 percent nationwide warrants consideration, the impact is even more significant when the focus is turned to major metropolitan areas. As shown in the table, Medicare managed care enrollment can represent as much as 40 percent of the Medicare-eligible population. Further compounding the situation is the fact that many of the nation's major research institutions are located in the above --

DR. GARBER: I'm sorry, Dr. Jacobs, but your time is up. Next speaker, Dr. Laman Gray.

DR. GRAY: My name is Dr. Laman Gray. I am a professor of surgery and director of the division of thoracic and cardiovascular surgery at the University of Louisville. I was also a principal investigator for the AbioCor total artificial replacement heart between 2001 and 2004, and at that time we performed seven of the 14 implants at Jewish Hospital in Louisville, and we were designated as a participating center for the post-approval study beginning next year. I have no conflicts of interest.

On behalf of the countless clinicians, scientists and engineers who've worked in the artificial heart program since its inception in

1964, I'm honored to, and deeply grateful that this device has received the market approval by the Food and Drug Administration, this under an HDE designation. To my knowledge, this is the only HDE exemption in the nation this year, and one of the very few not targeted to the pediatric population.

My comments are in support of expanding the clinical research policy to include important provisions in the HDEs. First and most importantly, I ask that the committee recommend that the HDE devices be covered items within the study that meets the requirements of the clinical research policy. HDEs by definition will benefit a limited population of less than 4,000 people annually in the U.S. In the case of the AbioCor, there are no other treatment options, including heart transplants or ventricular assist devices that are used in this group of patients.

It is important to note that the FDA does not consider the HDE devices to be investigational. They have met the standards set forth by Congress of safety and probable benefit. In the case of the AbioCor we acknowledged that more clinical data and patient information is

needed, but the clinical expertise, institutional commitment and resources necessary to provide the highest level of care in these patients is extraordinary.

Without financial support in the future, this program will not succeed. We are pleased that CMS has suggested a pathway which will allow for coverage of these very limited devices and ask that the committee recommend that a device with an HDE status be a covered item in any study under the clinical research policies.

Secondly, we would encourage the committee to recommend that a required and approved FDA post-approval study be a deemed clinical study. Not every HDE will come with a post-approval study. For those like the AbioCor that do have post-approval studies, the requirements are very thorough and scientific. For example, the AbioCor post-approval study for the first 25 patients to be performed includes more than 11 protocols, which include anticoagulation review by the IRB, quality of life measures, and an independent patient advocate.

The level of scientific oversight for a post-approval study with an HDE should have a

deemed status for the clinical research policy. And finally, we ask the committee to recommend that a deemed study is one that is approved by a federal agency but not necessarily funded by the agency. This will possibly broaden the scope of the clinical research studies, yet assuring the scientific and clinical design of the study receives federal direction and design. Again, I thank you for the time to consider the coverage of the HDE in the clinical policies.

DR. GARBER: Thank you. Next, Dr. Sam Silver. Okay, Bonnie Handke. Oh, is this Dr. Silver?

DR. SILVER: Good morning. My name is Sam Silver, and I am professor of internal medicine at the University of Michigan, and have no conflicts to report. I appreciate the opportunity to talk to this committee, and my comments today focus on a few issues of particular interest to many clinical researchers but not considered or fully addressed in other comments we've reviewed. We appreciate the Agency's efforts to clarify its current thinking through the recently released white paper.

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Recent OIG activity and ensuing discussions amongst researchers and health care providers reflect a disconnect between the original intent of President Clinton's executive memorandum on the one hand and its implementation and interpretation on the other. Original intent was to assure beneficiaries could participate in any clinical trial without risking coverage. In the executive memorandum they recognized that coverage of all clinical trials was critically important to those breakthroughs. The memorandum sought to assure Medicare beneficiaries could participate in any clinical trial without risking coverage, and it did not require that all covered trials have significant implications for the Medicare program.

If CMS is to fill its role as a public health agency, its policies must encourage and support the conduct of all scientifically and technically sound clinical studies, or at a minimum, must not discourage their conduct. At a time when researchers and research organizations are encountering increasing difficulty in recruiting volunteers to participate in clinical trials, it is particularly important not to

discourage participation based on ability to pay out of pocket. Discouraging clinical research by interpreting the NCD as to preclude coverage of scientifically and technically sound clinical studies based solely on funding source is contrary to CMS's pursuit of its public health mission as described by the Secretary in connection with the recent health information technology initiatives. Mere participation should not result in coverage exclusion. We wish to avoid policy revisions that may result in noncoverage of otherwise covered items and services provided in the course of many important trials, for example, an investigator-initiated pilot study designed to determine relative safety and efficacy of two approved or standard of care therapies such as, even though this would be a difficult study, a randomized study comparing radical prostatectomy versus definitive radiation therapy, a promising but unfunded Phase One study of off-label use of an approved chemotherapy agent such as a Phase One/Two study escalating the dose of an FDA-approved drug to high doses as part of a bone marrow transplant preparative regimen, revised NCDs should assure that participation in clinical

trial does not in and of itself result in noncoverage in these circumstances. Revised NCDs should permit coverage of otherwise nonstatutory prescribed indications and treatment, like alginate bone marrow transplantation for myeloma. If we are going to accumulate evidence for Medicare beneficiaries, specifically for the alginate BMT, there is a high priority NIH, NCI, BMT clinical trials network protocol which would otherwise exclude Medicare beneficiaries because alginate bone marrow transplant for myeloma is part of that study. Recent Agency guidance has suggested that a study comparing a gold standard surgical procedure against a newer, also covered standard of care, but less invasive procedure where a beneficiary's participation in the trial does not affect in any way the care he or she receives, would result in noncoverage of both the procedure itself and all related items and services. There is no difference between a trial of an investigational agent versus a trial of an approved agent used off-label that merits differential coverage. It is critical in any clarification of the NCD that the Agency fully

define what is a clinical trial addressed by the NCD and what categories of clinical research, if any, do not implicate the NCD at all, and therefore, do not have any impact on coverage of otherwise covered items and services.

There is an importance of self-certification or alternative mechanisms. Revisions to the NCD should include implementation of the self-certification process contemplated in the original NCD. We should permit coverage of items and services to which a beneficiary would normally be entitled absent participation in a trial, and risks of failing to implement this would exclude Medicare beneficiaries from more studies, contrary to the intent and more widespread use of retrospective data analysis versus a gold standard.

DR. GARBER: Thank you, Dr. Silver.

DR. SILVER: Thank you very much.

DR. GARBER: Next, Bonnie Handke.

MS. HANDKE: Good morning. My name is Bonnie Handke. I'm an employee of Medtronic, one of the world's leading medical technology companies specializing in implantable and interventional therapies that alleviate pain,

restore health and extend life. We are committed to the continual research and development necessary to provide high quality products and to support innovative therapies that improve health outcomes. We appreciate the opportunity to provide comments today.

My comments today will be focused on the provisions related to humanitarian use devices and humanitarian device exemptions, specifically Question 8.B. For the most part, coverage for HUDs are determined at the local contractor level on a case-by-case basis. Local contractors take into consideration individual beneficiary medical condition and history in a determination of whether or not the HUD is considered reasonable and necessary. It is important that this process be maintained for those HUDs that are not being very investigated as an objective within a study.

Additionally, we support CMS's recommendation to include in the definition of investigational clinical services those HUDs that have received HDE status and are the investigational item or service in a study that meets the requirements of this policy.

I have provided background material

regarding HUDs and HDEs in my comments submitted to the panel. In the interest of adhering to the allotted time, I trust that you have received and reviewed these comments.

An HUD is intended for unique, difficult-to-study populations where applying strict standards of evidence generation is not reasonable. Generating the data required to move from HDE to premarket approval status is a slow and difficult process due to the limited number of potential investigational sites and subjects. These devices are utilized in situations where all other reasonable treatment options have been exhausted.

In these cases where the benefit likely exceeds the risk, we understand that CMS will continue to follow the local coverage determination process for HUDs similar to the basic coverage approach used for all other FDA-approved products. Medicare payment policy for HUDs should continue to be consistent with the rules and guidance established by the FDA.

Medtronic believes that it is important to avoid creating any misunderstanding that coverage of all HDEs is restricted to those which are being

studied under an FDA-approved Category B IDE clinical trial, or other trial as described by the policy.

Specific to the clinical research policies, Medtronic urges the panel to recommend adoption of CMS's definition of investigational clinical services to include HUDs. Rather than singling HUDs out as a third condition, they could easily be included in the first. I have included suggested language revision in the written comments.

We also urge the panel to recommend that CMS add language to the policy that highlights the other coverage avenues for HUDs when they are not part of a study as described by the policy. HUDs with an HDE are not considered to be an investigational item from a regulatory perspective and should not be considered investigational from a coverage and payment perspective except in the circumstance of a trial.

Furthermore, beyond the clinical research policy, we believe that CMS should offer clarification to improve the local coverage process, and have also included language for your consideration. Thank you.

DR. GARBER: Thank you. Next, Scott Reid.

MR. REID: Hi there. My name is Scott Reid. I'm the director of health policy and payment for Boston Scientific. I just want to thank the panel very much for this opportunity to make a brief presentation. I have submitted a disclosure statement for the record, and these comments that I'm delivering today are made on behalf of Boston Scientific. Let's see. Moving right along here, I know that some of the presenters are kind of working through some of the questions that have been posed for this particular panel. The way I would like to structure my comments is really work toward some of the background and context as to why we are giving an answer, or recommended answer for Question 8.B, and so as a result, they will focus mostly on HDEs and some of the background and context for that.

As Dr. Phurrough noted earlier today in his comments, the HDE pathway or humanitarian use devices were developed by Congress, and the intent being to treat small patient populations who otherwise would have a very difficult time being

examined in a larger clinical trial. One of the recommendations that we'd like to make is that in cases where local carriers have developed coverage policies, that those would continue to stand and would not be impacted by this clinical research policy. We just want to make sure that to the extent that there's already access and local coverage, this clinical research policy would only be affecting those HDE technologies that are coming under those studies.

Also, another point that I wanted to emphasize, as Dr. Phurrough was bringing up to the group, certainly this clinical research policy is seeming to expand coverage for HDEs and that's very encouraging. We would also like to specifically point out that we would like this policy to apply also in cases where a national noncoverage decision does apply. Certainly, you know, the standards for reasonable and necessary in establishing a national coverage decision are much higher, but we would argue that for the HDE population, that even in cases of national noncoverage, that under this clinical research policy, a coverage pathway could be established.

And also as part of the record, just,

again, Congress about ten years ago created the HDE framework. Again, it's encouraged to stimulate research development for small patient populations. It's really a two-step process under which companies would seek to get HDE approval. First you have to go for the humanitarian use device designation, basically showing that there are no comparable devices and therapies out there, and that the treated population would be 4,000 patients or less on an annual basis. Then after that HUD designation is achieved, you actually have to apply for the HDE, and then once approved, that does provide a standard of safety and probable benefit, not safety and net effectiveness, as you would see with PMA approvals.

And I would, just looking at this box at the bottom of the page, I would probably amend that a little bit. FDA provides an approval path for treatments that improve health outcomes. I would revise that maybe to say the HDE provides an approval path that seeks to improve health outcomes, just by virtue of the fact that the probable benefit is there but not the actual effectiveness.

Again, just making reference to some of the statutory authority that would allow for coverage under the clinical research policy, we would encourage that this policy cover all HUD and associated services, that we believe that the qualified studies be automatically eligible. And again, just making the point that in those cases where national coverage does not apply, that local contractors are free to make decisions outside the context of this clinical research policy.

Now, one of the specific examples I would like to very quickly draw your attention to today is that this policy is needed now, because there are technologies out there that would potentially greatly benefit Medicare patients, and under the standard of reasonable and necessary that CMS must look to in developing a national coverage policy, if often means that certain technologies can't achieve that standard.

I'll make quick reference to technology that was, initiated coverage review at, the final decision came out in November of this year. This is for an intracranial angioplasty and stenting technology. It achieved HDE status and basically the request was that the HDE population be

covered. Because of the limited patient population and the limited but encouraging clinical trial data, CMS felt that it could not cover this technology on a national basis under the reasonable and necessary standard, and that basically hopefully means that under this clinical research policy, these types of very encouraging technologies for Medicare patients can be covered. So I think the way to put it in the box at the bottom, this clinical research policy would enable real world development, address unmet needs in the Medicare population that certainly would be consistent with the HDE program's intent that Congress laid out about ten years ago to make treatments for small populations. And also, I would argue that it's very consistent with the CED, the coverage with evidence development program intent.

And just the last slide, as it gets to Question 8.B, we would really, we agree with the proposed policy. We would just make a couple of recommendations as it relates to question three, or the item number three of Question 8.B. we would just say HDE approval status rather than HDE status, just making reference to the fact that FDA

has approved this technology. And I know that for the purposes of this definition, investigational really is referring to the item or service under review. However, if we could just call it the item or service in study, that would be our proposal, as often private payers look to those pronouncements and these policies as trying to justify why something is investigational and therefore not covered. So basically with those very modest changes, we would submit those answers for the record, and also just include a quote from the FDA web site, which shows that FDA does not consider use of HUD items as investigational. So that in closing, I thank you very much.

DR. GARBER: Thank you. Dr. Marc Whitacre.

DR. WHITACRE: I have a Power Point presentation.

MS. BROCK: It's coming up.

DR. WHITACRE: The only old conflict that I have to disclose is 15 years ago I received the free use of a laser from Coherent Medical as payback for helping to develop that laser. The majority of my comments today will focus on some problems to be avoided in future Medicare studies

and recommendations on how to produce information from these studies that is clinically useful and interpretable by patients, physicians and health care administrators.

It's necessary to consider the purpose of different forms of treatment. Preventative treatment. Prevention of bad outcomes is one of the pillars of religion. It's deeply rooted in human behavior and is easily harnessed and exploited. There is an infinity of diseases to be prevented. Everyone is a candidate for preventative treatment, and preventative treatment is a great opportunity for physicians and vendors.

Careful thought should be given before directing resources to improve testing of common diseases. Consider the following hypothetical. What if a perfect test for detecting breast cancer existed? Nearly half the female beneficiaries would be found to have breast cancer. Corrective and palliative treatments are more likely to be effective per individual. Medical effectiveness should not be defined solely on the basis of a statistical test. The presence of a statistically significant difference has supplanted the judgment of agencies and most doctors and patients, and the

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reasons are listed and I'm sure they're very familiar to most in the audience. More importantly, statistics is an indiscriminate tool, and subgroup and multivariant analysis are the principal instruments of these statistical errors. An important implication for this Agency is that statistics believe that bigger is better. There is almost no practical limit to the lower size of statistically significant differences. Larger and larger efforts and sums of money are required to look for smaller and smaller differences. A huge study should not be required to prove a major medical advance. A statistically significant difference has nothing to do with patient benefit. Medically effective treatments exist that benefit only two percent of patients and treatments exist that benefit 98 percent of patients. The term "medically effective" provides little or no information that can be used to make an intelligent decision about what, if any, treatment should be pursued by a patient or doctor. There are also numerous problems in research study design and actually execution, truncated data, not accounting for the placebo

effect, not reporting important effects of treatment, not reporting all the data, distorting the data, omitting the control group, and having low expectations. One way of having a device or drug trial succeed is to set its endpoint at a low enough value that the patient may not notice a noticeable improvement on the quality of life, though there is a statistically significant difference in the outcome.

Available studies suggest that patients or doctors do not make medical decisions rationally considering the best available information. Pascal's wager type logic strongly discourages rational discussion of the risks and benefits of medical testing and procedures, and creates an artificially high demand for both.

Research should be done into how to modify patient and physician behavior so a more rational assessment of medical needs and desires can be made. Outcomes should be reported to clinically relevant endpoints, not surrogate markers. The effect of length and lead time bias and stage migration should be considered. Length and lead time biases and stage migration create the illusion of progress.

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A dichotomy between the optimal individual and group decision should be discussed. Consider a lottery that sells 500,000 tickets for a dollar with a one in 500,000 chance for a $1 million win. Cost analysis would say the lottery ticket should be purchased. However, the remaining people who had the inconvenience and risks of actually purchasing the ticket have not experienced any gain, but some have lost money and some may have lost their lives.

Other suggestions would be to ban magnified Y axes in publications. Subgroup and multivariant analysis should be avoided as these are akin to reshuffling a deck of cards until you get the desired hand. Results should be presented not just as relative risk reduction, but also as number needed to treat and absolute risk reduction. The number needed to treat is an important marker of medical, ethical and economic issues. Suppose the number needed to treat is 50. For an individual patient, there's a 98 percent chance that refusing treatment will be the correct decision. Few decisions in life can be made with a 98 percent probability of being correct.

DR. GARBER: Thank you, Dr. Whitacre.

Sorry, your time is up.
That concludes the prepared presentations, and now I would like to call on the people who signed up as open public speakers. You will have three minutes each to speak. The first person who signed up is Pat Barnett, and next will be Gwen Mays.
MS. BARNETT: Good morning. I'm Pat Barnett, senior director of government health policy for ITEK Pharmaceuticals. Thank you so much for the time.
There are three issues I just wanted to bring up; these are not necessarily related to the questions you're dealing with today, but may look into the overall concept of coverage development or just the gathering of evidence in the future.
One is, I'm not clear in what you're looking at today how CMS will reconcile the clinical trial discussion you're having today with the CED NCD policy. There are some differences there and I'm not sure how those will be resolved in the future, which is a question for my company.
Is there an opportunity to introduce comparative effectiveness, including safety issues, into trials supported by CMS? Gayle

Morinsky recently raised that as an issue and I think that may be an important thing to consider as you're looking at CMS money on some of these trials, because it provides a valuable tool for determining optimal patient care.

Third, we're requesting that CMS would require codes for all drugs and services provided to Medicare patients, whether or not these are paid for by CMS or given to patients under an ABN or at no charge. The reason for that is the new chronic care warehouse, which was created under MMA, is a valuable source for longitudinal studies and evaluation of effectiveness and safety of a number of treatments over time, but without specific codes for all therapies and treatments given to patients, there may be some important data which is missing from the database, which could be used.

Thank you so much for your time.

DR. GARBER: Thank you. Gwen Mays, and she will be followed by Merrill Goozner.

MS. MAYS: Thank you and good morning. My name is Gwen Mays, and I am director of government relations and reimbursement for AbioMed. We are a cardiac assist device company

based outside of Boston, and we are the manufacturer of the AbioCor total replacement heart which, as you heard earlier from Dr. Gray, is we believe the only HDE approved by FDA this year.

I'd like to just add to the comments you've heard earlier for inclusion of HDE in your revised clinical research policy, and I'd like to point to the question specifically about whether coverage should be included if there is a national noncoverage decision. And I would just ask you to consider putting this a little bit in context. To the understanding of AbioMed and hopefully Boston Scientific, as well as Dr. Phurrough's shop, we have been advised that this situation really only applies to two devices, and I'd like to address the AbioCor artificial heart. The national noncoverage decision for the artificial heart was established in 1986. 20 years ago it was advised to us as clarification that HCFA at the time would not pay for artificial hearts as part of their policy they were developing for human heart transplant. The decision was not based upon any evidentiary standard other than two patients, Barney Clark and

Bill Schroeder, names many of you may recognize. In other words, the national coverage policy that was determined at that time was not based upon the evidentiary standard that is used today. So we find ourselves in somewhat of a difficult situation. CMS, and Dr. Phurrough earlier stated that the attempt is to provide a pathway for HUDs and HDEs under your revised clinical policy. Without being able to go forward with coverage under this policy we're in somewhat of an awkward box, in that we're held to a 20-year-old national noncoverage decision that doesn't apply to our technology today. So I would ask for your consideration, although I agree and most times would argue that public policy is not set on anecdotal or one-case scenarios, we find that we're in a situation that we would definitely like to bring this technology thoroughly to market after well over 40 years of clinical development and research. Thank you for your time.

DR. GARBER: Thank you. Merrill Goozner.

MR. GOOZNER: Thank you for allowing me to comment this morning. I'm Merrill Goozner, the

director of the integrity in science project at the Center for Science in the Public Interest. My group works along with other consumer groups to promote transparency in scientific research. My testimony this morning has the support of the Consumers Union and the Center for Medical Consumers.

We've been working for legislation that requires all clinical trials to be registered with public registries like ClinicalTrials.gov, including trials sponsored by the private sector. We strongly endorse the standard cited in Question 2.B that a trial must be registered on the ClinicalTrials.gov web site as a prerequisite for payment for related medical costs; that it must specify both the method and timing of public release of trial results regardless of the outcome or completion of the trial; that it must be relevant to subpopulations; and that the trial should be relevant to Medicare populations.

Since there is some question as to the sufficiency of the information currently listed on the ClinicalTrials.gov web site, we would also recommend including one additional criterion. It should state that payment for routine care will be

contingent on external qualified researchers, especially government researchers like those at the FDA, having access to the raw data from the trial, whether posted or not. This requirement is necessary so that research is conducting meta-analyses where reanalysis studies have access to all the data they need. We believe recurrent experiences with data hiding by private industry, such as happened recently with Bayer and Tracewald at the FDA, warrants this additional criteria. We believe the public's right to know the outcomes of research supported with public funds outweighs any proprietary information claims by the private sector.

We also have some concerns about the issues raised in Question 4 for the advisory committee which involves IND-exempt studies. Our concern is that by allowing IND-exempt studies to qualify for Medicare payment of routine clinical costs, taxpayers and Medicare could end up subsidizing trials sponsored by the private sector whose primary end is to help the marketing of a particular drug or medical device. These are sometimes known as seeding trials. A cursory reading of the academic

literature shows that there are many such seeding trials that would meet the current CMS criteria that the staff has proposed for covering IND-exempt studies. They have therapeutic intent, they won't be advertised, they have institutional review board approval. It is our belief that even if such trials meet these criteria, their real intent is to encourage doctors to prescribe the drugs being tested instead of alternatives, which are often better understood or are cheaper because they're available as generics.

We don't believe Medicare, given its fiduciary responsibility, should be subsidizing that kind of trial. It provides no significant new information about a drug's use and it did nothing to inform the public about the potential risks of the drug. I am sensitive to the arguments made here this morning that it's possible for IND-exempt studies to have value in exploring new off-label uses of drugs, especially in cancer therapeutics, but in opening the door to these uses, CMS should not simultaneously open a loophole for less honorable uses of this exemption, and I think you should take that into account as you draw up the criteria.

We believe that if the public knew the stakes, it would not support a yes answer to Question 4 unless some additional protections were built in to insure that public funds are not used to subsidize industry seeding trials. Thank you.
DR. GARBER: Thank you very much. Is there anyone else who wishes to speak in the open public speaker time? That's all the people who signed up, but perhaps some of you didn't get a chance. Nobody?
Then let me ask the pleasure of the committee. We could take a break now for about 10 to 15 minutes and then resume. Let me warn you that it will take you probably five minutes alone once you decide to come back here to get in your seats and get going. According to my watch, it's now 9:56, so let's resume at 10:10.
(Recess.)
DR. GARBER: Okay. We are now going to have some time for questions to the presenters. I see that most of the presenters are here and hopefully the rest will filter back in. Before we open it up to the questions, let me just thank the presenters. I think that your presentations were very much on target for the topic today, and I

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think that I speak for the committee in saying that it's very useful in helping us shape our thinking about the questions that are before us. So, let me just open up now for the committee any questions for the presenters. Let me add, by the way, that what we've done in previous meetings because it has been helpful is to actually ask questions of the presenters in the context of our discussion of the voting questions, and you may wish to defer questions as long as the presenters will be available for much of the remainder of the meeting. I hope that that's the case, because usually things will come up in the course of our deliberations. So if you will stick around, that may be the best way for us to be able to put questions to you. Any questions right now? Deborah.

DR. ZARIN: I have a question for the several people who talked about cancer clinical trial centers and I guess my question is, if you're an NCI-funded cancer center, what exactly is the oversight of the clinical trials that are done there? For example, is there a general granting mechanism and then a review when it's up for renewal, or is there any prospective review of

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the actual protocol of trials that are done at the cancer centers.

DR. MARKMAN: There are a number of processes. First of all, there is a formal requirement to be an NCI-designated cancer center. There has to be a formal mechanism whereby all clinical trials are reviewed for scientific merit. So it's actually a requirement of an NCI-designated core grant, that there is a formal scientific review. Now I want to emphasize, that's independent of an IRB review. There's obviously an IRB but there's a scientific review. That process is also formally evaluated by the NCI's process of reviewing through external, when you have the grant and you have renewal of the grant, there's a very formal mechanism of review in the process, looking at the minutes, looking for the quality, looking, for example, if the trials were closed if they didn't accrue properly. So there are very formal requirements that are built in to the NCI designation itself, so I think that's a very important part of that in addition to which, there is formal auditing and monitoring that goes along with the trial as well, that are not just at the

every four or five-year time frames where the trials are investigated.
So for example, if you're doing a trial that is coordinated by TCAF, which is part of the NCI, they will formally come in on a yearly basis and review your trials, so that's all built into the mechanism of being an NCI center. Does that answer your question?
DR. ZARIN: It answers it very well. I have one more question, though. You can also do, at the NCI cancer centers, I think you do non-NCI-funded studies as well.
DR. MARKMAN: Right.
DR. ZARIN: Are those reviewed, is the review process for those overseen by NCI the same way you just described?
DR. MARKMAN: Yes. In other words, there is a requirement, the requirement of the scientific review is of your entire clinical trials portfolio, it's not just of the NCI studies. In fact, they would expect you to be even more rigorous over those studies simply because the NCI-funded studies in fact already have a review, for example, by the NCI mechanism itself. But the studies that are not

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NCI-designated, they want that further review of the justification for doing each trial, are they investigator-initiated, are they pharmaceutical company-supported, what is the review, what is the auditing and monitoring that goes into this.

DR. ZARIN: Thank you, and that's very helpful.

DR. GARBER: Dr. Silver, did you want to address that?

DR. SILVER: Yes, but in addition to cancer centers, of which I'm a member at the University of Michigan, there's also CRCs which at least at this time have similar review mechanisms, whether they're -- but that kind of differentiates investigators from cardiology that don't have the aegis of an overall encompassing center grant. So it really puts investigators into two categories, those that have this kind of deemed status because of the regulated authority of the cancer center, and those investigators that don't have that umbrella.

DR. GARBER: Thank you. Cary, did you have one?

DR. GROSS: Actually, that answered by question.

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DR. GARBER: Okay. Yes?
DR. JACOBS: There's also a data safety monitoring plan that not only defines the up-front protocol review process at the beginning, but also continued data monitoring on a very routine basis.
SPEAKER: And you also have an effective monitoring board that reviews the ongoing process within the cancer centers.
DR. GARBER: Yes, Nancy.
MS. DAVENPORT-ENNIS: I have a question that I would like to address to Dr. Bailes, and there may be others who testified earlier that would also want to address this question. But could you speak with the panel about the typical patient that would be considered for an IND-exempt trial, and the frequency that those trials are used with patients in the oncology community?
DR. BAILES: They are used with some frequency in the cancer world, but often, they are more often probably, individuals who qualify for these are more often at institutions, and Maurie may want to talk about how Anderson does it, because they have a pretty good process, and I think that may answer your question better than I could.

MS. DAVENPORT-ENNIS: Thank you.
DR. MARKMAN: The concept of IND-exempt is obviously a complicated one. The FDA has very clearly set out specific criteria as to when a drug or a drug regimen is IND-exempt, and an IND-exempt study may in fact be a study that is sponsored by a pharmaceutical company, but it may very well also be a study that is simply done, as we would call an investigator-initiated study at an institution. So the FDA's requirements include safety and added risk of whatever you're doing, and for example, a new combination. They are concerned about the question of potentially changing a label. But there's a series of criteria that the FDA set out and if all of these are satisfied, the study will be IND-exempt. I think the important point from my perspective is that IND-exempt is a very specific criteria that relates to FDA criteria. Something could be a therapeutic trial, a very reasonable therapeutic trial that is IND-exempt, or it may not be IND-exempt, because the FDA's criteria, again, relate primarily to the safety and the question of does a company want to change the label. If there's no intent to change the label

and the FDA says it doesn't appear that you're going to add excessive safety, the FDA will say it's IND-exempt. But that's a different question than whether there is therapeutic intent and whether someone should pay for it. So that's how I would respond.

I think it's really a very different question. IND-exempt is a criteria that relates to the FDA and very specific criteria of the FDA, but it's a different question of are you doing something that has therapeutic intent.

SPEAKER: These are therapeutic intent trials.

DR. MARKMAN: Right. But again, you can absolutely have therapeutic intent as IND-exempt or non-IND-exempt. These are FDA criteria.

MS. DAVENPORT-ENNIS: I think as a follow-on to that question, then my real question in the matter is typically patients that are going to be engaged in an IND-exempt trial, are they moving to IND-exempt trials often because there is simply lack of other better alternatives for their therapy?

DR. MARKMAN: Again, IND-required or

IND-exempt doesn't relate to the question of is there therapeutic intent, is it better. It is simply these I think five or six criteria of the FDA that relate to safety in a drug or combination of drugs that have already received FDA approval for some indication. So clearly if there's a drug that has not received FDA approval, it is not IND-exempt, it's under an IND.

But the FDA has said if you're using commercially available drugs, you may have to still do it under an IND if there is an added risk or you're getting it by an unusual route or you're doing an unusual combination. But again, from a patient's perspective and the benefit they may achieve from that is a separate question. Again, it's a very specific item, six criteria set up by the FDA that do relate to the fact that if there is an intent to change the label, marketing label, then of course it has to be done on an IND. But even if you don't intend to change the label but yet you feel that, you know what, there may be really added toxicity here, then they want you to do it under an IND. So it's a safety issue, not a therapeutic intent issue.

MS. DAVENPORT-ENNIS: I want to thank

you for the clarification for the committee.
DR. GARBER: Mike, I think you were next, and then Cary.
DR. RYAN: So is it safe to say, then, that an IND-exempt trial is a lower risk trial, but not necessarily a lower science trial?
DR. BOYD: If I could just speak a little bit about that, IND-exempt trials allows investigators who otherwise do not have a funding source but really have an idea, something they've observed in perhaps clinical practice with their patients. It allows them the opportunity to use drugs that are already FDA-approved but not approved perhaps for what they want to use for that trial. So it's an off-label use of an FDA-approved drug and perhaps you're looking at toxicity, therapeutic intent, efficacy. And so these are typically younger investigators, investigators who are just starting out who, the furthest thing from their mind is relabeling a drug, but looking to see what's going to benefit their patient population.
So it allows, number one, medical research to be furthered in a way, but it also allows investigators to truly use what they have

observed in practice to see if they can now apply this, and many times you may come up with a drug that may be less toxic to the patient than the current FDA-approved drug that is being used. And this is commonly seen with anticancer therapy. So it's, certainly there is the concern, and I understand that PIs may be entering into these IND-exempt status so they can do this for drug companies, but I would encourage the committee to think about this as a practicing, from a practicing physician's or PI's perspective where they have observed a population of patients with particular illnesses and perhaps seen bad effects from drugs that we are using, and now looking at the off-label use of these drugs to improve the care and the health of patients. It also is a way to enroll seniors into these trials where otherwise you may not have had that opportunity. And again, these are IRB-approved studies as well.

DR. GARBER: Next, Cary.

DR. GROSS: One of the concerns that seems to be expressed during the comments this morning is that there is substantial variability in the scientific value within the non-IND

studies. So, what would you propose to help evaluate which ones are these exciting new investigator-initiated studies that can compare to widely used treatments and the results would affect care, versus ones that have, you know, been described as seeding trials, or other such studies?

DR. BOYD: I share the concern that I think the way particularly academic health centers are set up, it yields to people functioning in silos and perhaps doing things in a way that there is not sometimes the oversight that needs to be there. So I applaud the committee approaching this from that perspective. I think that having, I think getting rid of that deemed status, though, would be throwing the baby out with the bath water. So where I don't have the answer of how that study would be vetted to ensure that it is being used, you know, quote-unquote, as a good clinical trial, I think it would hamper research to get rid of it altogether.

So perhaps the IRB's function would change a bit in terms of what they look at with that, perhaps having, you know, this interagency panel that would vet this, having the FDA, CMS and

perhaps the NIH look at this from another perspective. But I think the idea itself of having our own investigators be the source of new ideas, to cut that off would be, or could be, harmful.

DR. GARBER: We want to move on to the other questions now.

DR. BAILES: These all have the same scientific review in IRB approval. As Maurie pointed out, this is an FDA distinction, it's not a therapeutic distinction, in the cancer world anyway.

DR. GARBER: Dr. Silver, quick.

DR. SILVER: Yeah, just a very quick comment. I think this is really independent of the goodness of the trial. You have junior investigators frequently with excellent ideas about using a drug that's already FDA-approved for another indication. There are some brilliant ideas that go on and I think that there are real possibilities. I wouldn't equate IND-exempt trials as some kind of a second status as opposed to an IND trial of a B-2 drug, you know, so I don't think you necessarily have -- you know, you can rank the goodness of science based upon an

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IND-exempt trial.
DR. GARBER: Thank you. I have down Wade, then Linda, then Steve, then Deborah, and Marc. Wade?
DR. AUBRY: I have a question for Dr. Phurrough. Is that appropriate here?
(Laughter.)
My question has to do with prevention trials. There was some testimony about prevention trials, particularly the use of biomarkers or genetic markers and studying that, and whether that might qualify under a clinical research policy. So my question is, under the current clinical trials policy, are there any examples of prevention trials or is that statutorily not allowed? And would that apply also for genetic markers or other types of biomarkers which a trial might be designed that has a therapeutic intent for that cancer, for example?
DR. PHURROUGH: To answer the question, it has several answers. Has CMS covered costs inside preventive trials, yes. We would not necessarily have covered the preventive service itself unless that was covered outside the trial. Does our current policy preclude the

coverage of preventive trials? That's a separate question from whether we've applied the coverage policy correctly or not, in some cases perhaps not. It would be difficult to argue that our current definition includes preventive trials. So if in fact the committee thinks that there is benefit to covering preventive trials, then our definitions may need to change to clearly elucidate whether we do or do not cover those trials.

The question of the costs covered inside the trial, again, a separate question, depending on whether they are authorized by Congress or other regulatory processes.

DR. GARBER: Steve, when you say the current policy does not cover preventive trials, are you referring specifically to primary prevention or all preventive trials?

DR. PHURROUGH: Well, I was speaking mainly of primary prevention at the time. I guess secondary, tertiary prevention, you could in most cases determine it has therapeutic intent.

DR. AUBRY: My question was primarily directed towards primary prevention.

DR. GARBER: Okay, thank you. Next,

Linda.

DR. BERGTHOLD: I want to ask a question of one or two folks who presented. Almost every one of the testimonies argued against having any sort of a quota for enrolling more Medicare beneficiaries in trials, and in fact that's not the intent of this language. There's no quota in this language. But it is a troublesome issue that because this is a voluntary thing, if you look back, what, ten years, there hasn't been much increase in enrollment of Medicare beneficiaries. Putting aside the complaint, I guess you could call it a complaint, that it's hard to do that, it's difficult, do any of the presenters have ideas for how, you know, how CMS or anything that we do here today could encourage -- I've heard a couple of things, I'd just like to know if there's somebody that has something specific that would explain how to encourage enrollment of more Medicare beneficiaries in these trials.

DR. BOYD: I think approaching this from -- I see two areas that CMS is trying to address with this. Number one, getting beneficiaries, more beneficiaries to participate,

meaning the elderly, than have done so before, and then getting certain subpopulations to participate. I think that this is a policy issue and I believe that health care disparities are an important issue that needs to be addressed. I think by putting it in the realm, however, of clinical trials would be a mistake, because I think you cannot discriminate patients based on their disease. So if you're going to wait to get a certain subpopulation in your clinical trial and you live in Rhode Island or you live in Texas or Illinois or whatever, you're not going to get that subpopulation, but you're going to have patients who have disease that you can treat at that point. I think the issue of health care disparities needs to be addressed at a different level.

I think the prevention issue is a big, big piece of that, because I think the diseases that you see beneficiaries who are treated, particularly in cancer trials or maybe with hypertension and the associated diseases have their basis in prevention. And I think if we looked, if policy starts to look at ways to include subpopulations earlier in preventing some of those illnesses, that helps.

I also think health care disparities is a multifactorial issue. I don't think using the clinical trials realm is going to help solve that, I think it will hinder research. I think if you start saying who is going to be in a trial, you don't know who's going to enroll in a clinical trial when you open a study. Sometimes it takes a couple years to get patients in that, and if there's going to be a further hoop of what the demographic of that subject or patient will be, I think it will really hamper both the population, the elderly population who would be able to participate, but it will also discourage people from doing research.

DR. BERGTHOLD: You know, everybody had a lot of good reasons why it's hard. Can anybody give me any suggestions for how it could be more productive? Because what you just said is it's difficult, and yes, we know that.

DR. BOYD: I guess the only thing would be if there were trials specifically designated to look at a subpopulation. So if a trial were created to say we are going to look at Hispanics or Latinos with complications from diabetes or, you know, people with the diseases that typically

afflict these subpopulations and designate those as those studies, that would be a way to address it.

DR. GARBER: Dr. Jacobs.

DR. JACOBS: I want to be very provincial for a minute. Western Pennsylvania has a 40 percent incidence of Medicare HMO patients. My colleagues tell me they can't enroll those patients because they're disincentivized because of the costs that they need to cover the trial.

DR. GARBER: Okay. Let's see. Next is Steve.

DR. GOODMAN: I have a question for the folks from Rush, who might have to stand up again. You alluded to the need for clarity and the problems at Rush, and I'm one of those who don't know what all those problems were. I would be interested in knowing separate from the issue of the difficulty of separating out, the billing procedures basically, I would be interested in knowing, and forgive me if you highlighted it in your presentation, I don't think I saw it, a very precise wording of the current policy which led to big problems, and big problems separate from just the issue of your billing system, but actually as

you alluded to, you know, caused big problems, because reasonable people can interpret it several ways.

DR. BOYD: Well, probably one of the biggest was the term routine costs. Investigators interpret routine costs of this is what I routinely do and how I routinely practice. And so what was the difficulty there was bringing that under the context of what Medicare meant by that and what physicians or clinicians felt that meant. As you know, that then breaks out into what is covered outside of clinical trials, covered inside of clinical trials, and part of what we went through with that were off-label use of certain drugs that perhaps were covered outside of trial but then inside the trial, it was not. We have received clarity on that.

What is, typically the term that's used is, we stay away from standard of care because that has more a med mal flavor to it, and call it conventional care. Well, as you know, and thankfully, the NCCN for cancer studies has a very good algorithm for most of the diseases out there. But what starts to happen is who defines what is conventional care. So working through what was

routine costs, probably the biggest hurdle was all other Medicare rules apply.
Once you get into the realm of the NCD, all other Medicare rules apply, which means the reasonable and necessary. Physicians have no real clue of what this means because they feel if the patient is in front of them and they're sick, or they need to order a test, it's reasonable and necessary.
So some of the things we worked through as an institution was, number one, helping to define the language, and then understanding the structure of Medicare, looking at the statutes, looking at the NCDs and noncoverage pieces. People would go on the web site and read things and think it would apply to them. So that was the biggest one, routine costs.
DR. GOODMAN: Was there, separate from the issue of reimbursement, was there confusion about which studies qualified overall? I would like to know specifically if there was a different interpretation of whether this was a coverable study under the policy or a noncoverable study.
DR. BOYD: Yes. We had, and we're an institution, we do mainly Phase Three clinical

trials, but probably the one where we had the issue come up was a Phase One trial and therapeutic intent. And had we not known to do this, we probably would have gone on with it, but we contacted our local Medicare director, and it was denied because it was felt not to have therapeutic intent.

DR. GARBER: Okay. Deborah, Marc, and then Cary.

DR. ZARIN: I wanted to go back to the issue of deemed and nondeemed studies. When the original panel had met, the idea of deeming them was to see whether there was a process already in place that would essentially guarantee, or with a great degree of certainty to Medicare, that those seven highly desirable characteristics of the study existed. So you have characteristics about methodologic quality, whether it's not unnecessarily duplicative, et cetera, whether it has ethics review. And so the deemed categories were those where we knew there was a federal program in place either from a funding agency like NIH or the VA, or in the case of an IND study, although they're not always prospectively reviewed, there's always the potential for FDA

staff to review them after the fact.
With IND-exempt, the point was that nobody prospectively that we knew about reviewed them for scientific quality. You did know that, if they were done at an institution that received federal funding, it would have IRB approval, but you didn't know if it was reviewed for scientific quality.
So my question is, are there other categories or sort of other processes out there that aren't currently listed under the deemed categories that exist that Medicare could piggyback onto? In other words, procedures out there that are just like was just described in the cancer centers, where there is a process for open transparent scientific review that we didn't already know about that could be added to the deemed process.
DR. GARBER: I'll take that as a no, at least outside cancer. I think cancer is well represented here and the other fields not quite so much.
DR. GOODMAN: There are those studies that go through GCRCs, general clinical research centers, now to be all converted to CTSAs, do go

through this process. It may or may not be at quite the same level as the cancer centers, but they are pretty similar. That doesn't cover nearly all, but it is another process within many institutions whereby studies are reviewed.

DR. ZARIN: Right.

DR. GARBER: Okay, Marc. Or Bernie, did you want to join on this?

DR. LO: I'm sort of torn between when you want to have discussion and knowing you want to ask questions.

DR. GARBER: On this topic, yeah.

DR. LO: Because I think we have to be mindful that these GCRCs are being phased out, and under the CTSA plans, there isn't necessarily that same dedicated scientific review that the GCRC has.

DR. GARBER: Yeah, it's not uniform across the institutions for the CTSA. Marc.

DR. BERGER: So, I want to return to what was raised peripherally a couple times about the roles of the IRB. So with an IND study, yes, the FDA may review it after the fact and sometimes they may not review it at all. And so I'm a bit confused about the deemed status. I understand

the process, why you want to make it as rapid as possible and not put barriers in place. The one place where I know a protocol is always reviewed before it actually gets implemented is the IRB, and I always thought the IRB had, beyond even protection, it also was supposed to be looking at whether the scientific merits of the study were worth any risks of exposure to patients. So I guess the question I have, and I guess it's in response to Deborah's question, can we not ask of IRBs to begin to perform that function.

Now at large medical centers, the IRBs do this kind of function. I'm not sure that every -- I know there's been a controversy whether IRBs do uniformly a good job about what they're doing, but it seems to me a subset of IRBs can do this kind of function, and I'm curious to know whether people would think that would be a good idea, to require an IRB review be done by an IRB that could look at this and say this is a reasonable kind of thing to be done and the scientific merit is there, and whether or not therapeutic intent is the right criteria or not, but it does meet the criteria of what a good

clinical trial should be that providing good scientific data, providing appropriate guidance in terms of protection of human subjects, and is going to move us forward in terms of improving our clinical understanding.

DR. GARBER: I think most of our institutions are not interested in redefining IRBs to make the job even tougher than they already are, and they have a hard enough time recruiting people for IRBs. But they do not do an NIH style review in general. Deborah, did you want to address this point?

DR. ZARIN: I was just going to say, I agree with what Marc said, but when we raised it with the IRB community we get basically Alan's response, which is that we're underfunded, we don't have the wherewithal to do a real scientific review. When we've even suggested asking IRBs to ensure that trials are registered, we get pushback saying that's more work than they can handle.

DR. GARBER: Yeah. I think for most of our institutions, they can't handle their current workload. Cary.

DR. GROSS: I have a question about the intent of this policy, which is the increased

access to clinical trials for Medicare beneficiaries. And in the interest of time, I would like a response just in a show of hands. For all of our presenters today, how many of you have hard data from your own institutions or the organizations that you represent that after this new trial policy was implemented in 2000, there was an increase in enrollment of Medicare beneficiaries?

(Show of hands.)

DR. GARBER: Steve.

DR. WARTMAN: Let me just pick up on that question in a little bit broader context. For those of you who represent organ institutions or represent institutions that do clinical trials, would you characterize the number of clinical trials as staying about the same in the last few years projected for the future, decreasing or increasing?

(Discussion off microphone.)

DR. GARBER: So is that a consensus, that it's increasing in cancer?

DR. BERGER: There's been a general increase in cancer studies anyway, so is that related to the changed policy or is it just

tangentially related to the research?
DR. GARBER: Go ahead, Dr. Markman.
DR. MARKMAN: I'm obviously not here representing the National Cancer Institute, but some of these questions related to Medicare beneficiaries, the NCI-designated cancer centers have an obligation to enroll populations, including the elderly and Medicare populations. It is a requirement, and we in fact have to report what we are doing, and not only the Medicare population, but obviously there are ethnic minorities in our area.
So we have to report what we're doing and if we're not meeting the demographics in our area, we have to describe what we're going to do to improve it. Now that's not on a specific trial, but that is a mandate of our center for our NCI approval, that we in fact meet the demographics in our area. So it goes along with the statement of what are the requirements of NCI designation, they include this, they include the scientific review of all trials. So this is built in to being an NCI-designated cancer center.
DR. GARBER: Okay. Mark, this will be the last question and then we'll move on, and you

can ask questions in the context of our discussion of the voting questions. Mark.
DR. HLATKY: This was just a comment.
If the issue was the impact of the prior regulations, at least one of the commenters in the written materials pointed to a study, specific study that was done that looked at this at least in cancer in terms of representation of older patients, and claimed that there was actual data to show that it improved, if that is the thrust of the question. I don't know if other areas have looked at that, but the claim was that it had a positive impact.
DR. GARBER: Yeah. Let me just add that with respect to the Rush experience, which I also know almost nothing about, I think it highlights the importance for CMS to have a policy that's very clear and well understood, and other speakers have addressed this as well. Let me just point out that that's the intent of this meeting, is to confer a greater degree of clarity on CMS's policy. And obviously when you have in broad terms payment for routine costs incurred as part of clinical trials, to operationalize that is quite difficult, and we may never get to the level

of detail that we need to interpret at the local level. We're trying to, I think, hit an intermediate level here where we do at least establish the principle, the application in somewhat broad terms, but not so broad that they're meaningless to people who have to make decisions. Steve?
DR. PHURROUGH: I would also like to just clarify, part of the difficulties we have, and the panel needs to be cognizant of it, I think Dr. Boyd made a quite lucid comment in her first presentation that terminology of medicine and CMS aren't necessarily maybe dissonant, in fact maybe discordant, and that's true. We write policy based on a whole host of issues, mainly what Congress tells us to do or what the administrations tell us to do, and so our policies are based upon some specific languages that we may not have the ability to change to meet current practices. So we pay for routine costs because the White House told us to pay for routine costs. So that's a definition that's unlikely to change significantly, or that's a term that may not change significantly.
We separate routine costs from

investigational costs because there's a clear Agency past history of, we don't pay for anything that's investigational. So we need to define those differently so that we don't get taken to court because we changed precedent without doing rulemaking, and we're attempting to do this as not rulemaking that we're doing.

So even though it may not be clear, there is typically some lucid reason for doing what we're doing. Whether it's logical or not may be a different matter. So as we have these discussions, I will interject those times where we may say well, yeah, let's pay for conventional care. Well, conventional care isn't a Medicare term. Routine costs, routine services is a Medicare term, so we want to define that so it meets the needs but doesn't have us wind up in front of the Ninth Circuit or the D.C. Circuit, neither of which are necessarily places that we like to be.

DR. GARBER: Your federal government at work.

(Laughter.)

Now is the time for the charge to the committee, and the charge to the committee is to

get out your questions, the worksheet questions. So we will be working off the written questions, not on screen or anything. If there is anyone in the audience who doesn't have a copy, I'd suggest that you go right outside the room and get one at the table outside. And we will be going through the questions one by one.

We have tried to refine the questions a few times to make them as clear-cut as possible. There is nothing like an MCAC or MedCAC meeting to reveal new ambiguities that we hadn't previously suspected, and that's also part of the public comment process, although most of what we've heard is not about ambiguity in the language but about its implication, but that's fair game for discussion, of course, as well.

So we'll be going through the questions one by one, and again, let me remind you that you can ask the presenters for points of clarification. I should ask also, is there anyone in the office from FDA who would be prepared to answer questions about how the FDA interprets some of these terms?

(No response.)

Okay. Well, that's unfortunate, but we

will proceed regardless.
So first, Question 1.A, using a general definition of attributes that comprise a good clinical study, CMS provides the following general definitions of clinical studies for discussion. One of them is from FDA guidance published in the Federal Register, the other is from an epidemiology textbook. I won't reread this now, but you might take a couple moments to review.
So option 1.A is, we can use one of these general definitions and you could, about attributes comprising a good clinical study.
Option 1.B is to use the existing highly desirable characteristics that CMS has operated under. And option 1.C is to use something like endorsing an external -- an external description listed here only as an example is the FDA guidance, which is also under 1.A, but 1.A is only the excerpt from the FDA guidance. Bernie.
DR. LO: I wanted to raise a question and concern about the current CMS definition, particularly the last two lines which refer to ethical principles that have their origin in the Declaration of Helsinki must be followed. I didn't know if this was intended or not, but the

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latest comments to the Declaration of Helsinki put two requirements on clinical trials that may or may not be what CMS intended.
One is a set of restrictions of placebo controlled clinical trials, which actually are at variance and contradictory to FDA requirements for placebo controlled trials for things like depression and peptic ulcer disease.
The second is a requirement that at the conclusion of a trial, the sponsor under the Helsinki, whatever it is, number 30, paragraph number 30 requires the sponsor to make available after the trial the agent that was found to be effective in the trial, regardless of whether it's actually approved for use in the jurisdiction.
So you know, the Declaration of Helsinki is often referred to as sort of embodying good ethical principles, but carries some implications that have regulatory significance.
So I'm wondering, why not just adopt either the common rule or the FDA standards for informed consent and IRB review, which really are the heart of what are generally considered to be ethical principles, and not try and bring in all the other things from the Declaration of Helsinki.

DR. GARBER: Mark.
DR. HLATKY: I think that one thing that came out to me in reading these options is there's an issue as to whether we're talking about clinical research, good clinical research, or clinical trials, which I consider to be a subset of clinical research. And I am a little confused as to what our charge is in terms of looking at that, because I think that one could definitely do good clinical research that was not necessarily a trial in that sense of it. Nor even do all clinical trials use investigational agents, so if investigational agent means the thing that's under investigation, that's different than meaning, you know, that something is investigational in the sense that it's not proven or not used in other venues. So I found some of the language to be, in the written options that currently exist, to be a little difficult.
DR. GARBER: Let's ask Steve to address that, and then Jeremy and then Marc.
DR. PHURROUGH: On the first question, yes, we're talking about a broad definition of research versus narrow definition of trial. And the issue of using the term investigational is one

that we struggle with and can't get away from. Unfortunately we have within the Agency a long history of saying we don't pay for anything that's investigational, and that's used in a sense that's different than used in perhaps the research community where anything that you do in a trial is investigational, even though the item or services within that trial may in fact have routine use, conventional care uses.

So we can't get away from having to separate, use the term investigational and define it as the particular services that's under study in this particular trial, versus everything that's within the trial. So that's the distinction we're trying to make. And yes, it's confusing, and we're certainly looking for some assistance in how to do that, but we can't use the term investigational as is typically used in the research community. We have to limit it or then we don't pay for anything, so we need to very clearly limit what the term investigational means.

DR. HLATKY: Well, this very first option, though, says investigational product or procedure, and that's, I guess that language is another example of the language meaning different

things to different people.
DR. GARBER: But Mark, that may be a reason why you wouldn't want to use this particular definition.
DR. BERGER: That's because it's an FDA definition, so we've got to realize where it's coming from. The FDA is concerned about investigational products, but if you remove the word investigational, that might be a more general definition around clinical research, although it's not my favorite definition either.
DR. GARBER: Yeah. If I might paraphrase what Mark Hlatky said, I think it might serve us well to distinguish between the study drug or the study test, and investigational, which has a specific meaning in the FDA context, just to avoid that particular source of ambiguity, so that's the only one. I have -- Sandy, is this directly on this point? I have Jeremy, that's been waiting for a while, and Mark Grant, Mike, okay, and then Deborah.
DR. SUGARMAN: I wanted to pick up on Bernie's concerns with respect to not only the contradictory and controversial nature of the Declaration of Helsinki with respect to placebo

controls and reasonable availability, but also if we link the definition to a document or a declaration that's changeable by another body at any time, it could be problematic because that's what's happened with the declaration over time, it's been revised several times with shifting norms that we want to avoid.

DR. GARBER: Okay. Mark Grant.

DR. GRANT: I was going to echo Mark Hlatky's comments, but also had difficulty in trying to sort of conceptualize the interface between these definitions and the CED and the use of registries, and how we call registries good clinical research, or we deem them as such. All the definitions and even clinical trials imply, in fact, there is some comparison in measured effectiveness. I don't quite understand how that all fits in with the CED and the coverage with research participation, and using registries.

DR. PHURROUGH: In our most recent discussion of what coverage evidence development is, we separated it into two categories. The only category that's applicable to the clinical trial policy is the second category which talks about participation in some type of study, versus just

collection of a database. We have some concern in the use of the term registry in that many clinical trials utilize databases to collect information which could be classified as a registry in the broad term of a registry, but are not because they're collecting data.

So this does not include, the use of CED under this policy would not include any concept where we're just collecting point of service kind of data. We're talking about the second part of CED, which says participation in a study.

DR. GARBER: Okay. Next, Mike Ryan.

DR. RYAN: It would seem to me that when we're looking at this, there's two criteria that we should apply. One, whether or not the definition is broad enough to encompass a variety of research. The second one is whether or not it's clear enough to allow the investigators to really determine whether the trial meets the standards.

When I apply those two criteria to the three definitions, I find the first definition, which is clinical trial investigation, far too narrow. When I apply it to 1.B, I find many of

the terms here justifiably duplicate, design is appropriate, credible organization to not be clear enough. And so the only definition here that I find meets both of those criteria really is the Rothman definition, which in my mind comes from a fairly well respected source, it is broad enough to encompass what we need to do, and at the same time is simple and clear.

DR. GARBER: Sandy.

DR. SCHWARTZ: My question has to do with the same thing and trying to, I don't think -- I'm a little concerned about trying to come up with a definition that I think will probably take us all month to do and not get to any of the other questions. But I think if we could maybe focus on some of the key principles that need to be included, and I'm struggling with what are the implications of these different definitions in terms of everything else that we're going to be talking about.

The first definition, and either one of the first definitions is a broader definition of clinical research, and Steve, this hits on the question you were answering before, whereas 1.B states everything in terms of health outcomes. It

means that clinical research is being defined as something that directly affects health outcomes. And I think that's a fundamental issue that we need to address as a committee, what is the breadth of how we're going to define research for the purposes of these suggestions for this meeting.

DR. GARBER: Deborah.

DR. ZARIN: I would propose that we go with a brief definition that would include the following points. Something about having an explicit written protocol of a study that looks at the health effects of a diagnostic or a therapeutic intervention, and that it uses methodology appropriate to the scientific question, something along that level of detail. And then look at the seven highly desirable characteristics as sort of what they are, highly desirable characteristics of good quality beyond that.

But the explicit protocol I think is important, because I think one of the earlier concerns about this policy originally was that there was concern that it could be deemed to provide coverage of things that Medicare wouldn't

otherwise cover by essentially pretending to be research by, you know, collecting one or two data items in a casual way, saying it's a research study, and then getting Medicare coverage for something that otherwise wouldn't be covered. So I think that having an explicit written protocol helps with that.

DR. GARBER: If that's something -- I'm just wondering whether we should encourage Deborah to actually write that up into some specific language. Is there an interest in pursuing her suggestion? She has three things plus the -- the three things were explicit protocol, looking at health outcomes, and it employs appropriate methodology, as sort of I think explanatory points being the existing CMS definitions.

DR. AUBRY: I would be in favor of looking at that.

DR. JANJAN: I think one issue that needs to be considered is that we can't look at the definition in a vacuum because when you get to Question 2 where we talk about study registry and clinical trials, and the issue of duplicative studies, does that mean in the future if there is a trial already listed on the registry, that CMS

might not pay for a study that may be similar performed at another institution. So it's got some implication as to the definition that we're approving here.

DR. GARBER: Well, one thing, if we have Deborah write this into specific language, then we would discuss the second question before we return to vote on that. That would be my proposal just as a procedural approach. Yes.

DR. LO: I wanted to ask a procedural question. I'm really allergic to having committees trying to draft language, because it usually takes too long. I wanted to ask Steve, is what you're looking for really our sense of what points ought to be considered, or do you really want us to sort of pick language? I'm just afraid we'll get bogged down.

DR. PHURROUGH: We're not necessarily interested in transcription of specific things. If you give us a definition in broad terms, we'll put the language together. For instance, if Deborah's concept enamors each of you, then we can try and put that in some broad terms and flash that up on the board and see if that makes sense, but we would do some modifications to make it fit

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our language.
DR. GARBER: Barbara, I think you had your hand up first, and then --
DR. ALVING: It just goes on down the line.
DR. GARBER: I would like to say that I agree that maybe we should just look at 1.A, 1.B, 1.C, and see which one most approximates what we think would work best, and then could incorporate some of Deborah's comments into that. In terms of an NIH perspective where we're very interested in working in a very integrated fashion with CMS, then we would hope that if we do have good clinical trial results, then CMS has to move forward with coverage decisions. We felt that 1.B, again, going along with the seven characteristics, really was a very appropriate definition to get us started, so we really didn't see any overwhelming need to change what CMS has already been working with this particular --
DR. GARBER: So what you're proposing, if I interpret correctly, would be Deborah's proposal could be an amended version of the, I guess what is the existing CMS, okay. Mark, go

ahead.
DR. BERGER: Words are important here.
We recently issued a draft guidance on registries looking at comparative effectiveness through AHRQ, and the word registry can be used in about three different contexts. A registry could be just what you're talking about, a collection of massive data. Doing a registry could actually be the collection of the data. And a registry can actually be a study which is an observational study which is intended to ask some, impute some cause and effect, even though it's a weaker design compared to randomization.
And so just using that word alone here is confusing, and so in the context of CMS's coverage of evidence development, the registry is actually the third definition, which has to do with trying to design a prospective cohort study to allow us to be able to impute some safety and effectiveness of some technology which is different, and that really sits well within the context of what clinical research is. It's not a randomized clinical trial, but it is clinical research.
So I really urge that we do have

definitions here around what clinical research is, and there are standard definitions for this, and then talk about what clinical trials are eligible underneath that, because there are all kinds of different designs that might be eligible. The more explicit we make this, I think the better our conversation will be. And I think that's what a lot of us are struggling with, in terms of thinking about what you're trying to get at. Having said that, I will argue that although the FDA definitions are wonderful definitions, they are looking at a very narrow slice of clinical research. So using FDA definitions is the wrong idea, because that's where you get involved with investigational drugs and always looking at things which are not being used. I would think that CMS wants to encourage comparative effectiveness studies where you're taking things which have nothing to do with the FDA definitions, which may not even be a specific drug, but it may be a system of care, in order to evaluate different systems of care, which is more effective or which is more, you know, efficient, in order to be able to better design in the future that will make the Medicare benefit not only more

effective, but more efficient.
So in that kind of health services research which fits under the definition of good clinical research, doesn't get discussed at all within the context of FDA definitions. So I'm trying to urge us to move more toward the general epidemiological approach to thinking about clinical research in very broad terms, and then more specifically look underneath that in terms of what are the specific designs we're talking about and have those definitions spelled out, not necessarily as part of the guidance, but you might have it as a glossary, so everybody knows, when we're using these words, what exactly do we mean.
DR. GARBER: Okay, thank you. Now it's going to be Steve Goodman, Cary, Steve Wartman, then Nancy.
DR. GOODMAN: Well, I'm glad that comment was just made because mine built on it. I think what the problem is that we have language here that contemplates many issues, and we want to separate them. And the language is driving how we talk about the issues, but here are the issues as I see them. One is the scope of what CMS actually wants to cover or encourage, that's the first

thing. And all of these, by the way, are implicit in the current language, so we encounter them sequentially in this 1.B. Then is, is it an idea worth studying? Then is, can a study design actually address that idea or answer it. And then is, can the people, institutions or systems properly execute that design. Then is, are the patients properly protected and legal requirements met. And finally, will it produce generalizable knowledge, that is, will it be, and actually I don't know if you have it here, will it actually be published or will it be public, so does it have actually any social benefit. So each one of these addresses each step in that process.

I would argue that the issue of is it a good clinical study is a much more narrow question than is it a study that fulfills all these requirements and will serve a social good and will serve CMS's purposes, and legally mandated purposes. So we have to be very, very clear about each one of those things and how they are operationally.

I would say to follow on Jeremy's point about linking the ethical principles to an external document, I would say that's true of all

these things. I would say linking what you consider to be a coverable or good study or relevant study addressing all these things, it has to be internal to CMS. Because your requirements, the issues we're talking about today are unique to the language, the statutory language and the mission of this Agency, which is different than all the other definitions out there, including the Rothman definition, which is not a definition of a good clinical study, it's just a definition of what clinical research is, which goes into, which would only feed into the very first of the things that I said, what's the scope here. Let's start with the scope and then let's outline how we craft language to meet that scope.

So I think you're stuck having to create a definition for yourself. So we have to work on 1.B, because otherwise, you'll always be based on shifting sand. Craft it for the purposes and missions of CMS, which I think will be very, very similar to what you have with maybe a little bit more precision and maybe an overlying conceptual framework, instead of trying to infer that from the language, and borrow language where appropriate from some of the other guidelines so

there isn't an unnecessary duplication. So I think we can look to the FDA for that language that's actually appropriate, and it's nice to make consistency where consistency serves an overall purpose.

And the last thing I will say is that it's also important, you have to decide whether these, you want all of these to be operational, and I think this was already said. So in the area of, when we say is the study, is the idea worth study, and one of the criteria there is does it unjustifiably duplicate existing studies. While that is a desirable characteristic, do we care that there actually are no structures in place to guarantee that? And in fact, IRBs don't guarantee it, nobody guarantees that.

So it is a characteristic of a good study, but there is almost no way you can ascertain it. Now if you happen to show that it's duplicative, you can then rule that study out of hand if it's a seeding study and you can identify it as such. Or you could keep it there just for that purpose, but in general we have no extant procedures, particularly for non-IND studies, and I agree with all the comments that were made

before, to guarantee that that's true, because the IRBs don't do scientific, or adequate scientific review.

DR. GARBER: Cary.

DR. GROSS: Just very briefly, I wanted to build upon Deborah's comments. I think it's really important to clarify whether we are also talking about primary and secondary prevention trials. We often are speaking, if you look at the language, these documents are just dripping with therapeutic trials, and I'm hoping the committee is also endorsing the idea of primary and secondary prevention, and if that's the case, then whatever definitions we come up with, we need to be sure that throughout the documents and the questions that they reflect that.

DR. GARBER: Steve.

DR. WARTMAN: I'd like to agree with Bernie's thoughts about a committee trying to do some wordsmithing in this kind of environment and come up with some type of definition, that can maybe muddle things more than clarify things. I think what we want to try to do in the interest of CMS and in the interest of patients is have harmonization amongst definitions that are out

there currently, whether it be the FDA as a reasonable body to begin to look at, or other ones as well.

So I'm concerned that if we get too prescriptive in the definitional process as a committee now, we may be defeating our own purpose in terms of the business of real good quality studies. So I would urge that we think a little bit about looking at existing standards that are out there that are well accepted, like the FDA, that include a lot of the elements that frankly we do like, there may be a few that are missing that we would have to add, but that we strive more toward harmonization rather than toward unique definitional.

DR. GARBER: Okay. Nancy, then Sandy, and then Mark Hlatky, and then I would like to move on to a vote.

MS. DAVENPORT-ENNIS: Alan, thank you for the opportunity to comment. I think from the patient perspective I would like to remind the committee that the discussion that we're having today is certainly not going to have an impact only within the Medicare population, but indeed it is going to have an impact for every person in

America who at some point in their life might need the benefit of a clinical trial.

I think the second thing that I'd like to point out to the committee is that fundamentally our nation remains somewhat stagnant in the ability to accrue patients to clinical trials and to increase enrollment and participation by people in America in clinical trials, that being said against a fabric of a universal definition that is currently embraced across the provider community, a definition that has been embraced universally across the payer community.

Based on those three observations, it would be my recommendation that we consider looking at the question as it was posed to us. We have been provided with three options to respond to, and as much as we looked at 1.A to see, and as an English major wordsmithing is something I quite enjoy doing; however, when others have it right and this application is working well, we have a moral obligation to every American, all 300 million of them, that indeed we look at option 1.B, which allows us to use the existing highly desirable characteristics to define a good

clinical study. And I think as we look at the seven highly desirable characteristics, what we will see is the universality that allows clinical trials to move into areas that are new and evolving within the framework of a traditional definition that is being used across all the stakeholder groups in the discussion of clinical trials.

So thank you for the opportunity to share the observation, Alan, that our decisions today are universal and will have universal impact, and that, indeed, perhaps option 1.B may be a serious consideration for the committee.

DR. GARBER: Sandy?

DR. SCHWARTZ: As I said before, I don't think we should try to write this now because it will take forever, but I think option 1.B is where I would work from. But I do have, I don't know if it's a problem, but I think we need to be aware of the implication, and the way I read option 1.B in my experience is, I read these a lot more flexibly than the people who ultimately implement them do, is that this would be, and I think people should know this because there's been some discussion about whether Phase One and Two

studies should be included. I would interpret it as that Phase One and Phase Two studies would be excluded, because this says a good clinical study includes the following, aptitude and principal purpose of the study is to test whether the intervention potentially improves the patient health outcomes, and that is not really an objective of a Phase One or Phase Two. So if that's an important issue, then we probably ought to have a little bit of discussion about whether that's a goal or not, unless you're going to get back to that later.

DR. RYAN: As a clarifying question, who would make the judgments on those, and who would make the judgments about what is unjustifiably duplicative, or who would make the judgments about whether a design is appropriate or it's a credible organization? If this is the definition, who, ultimately, just from a clarifying point of view, makes those judgments?

DR. PHURROUGH: Let me talk to that a bit and it, again, is part of the challenge of being a government employee. Both to comment and explain what we do --

DR. SCHWARTZ: Think of the big bucks

they pay you.
DR. PHURROUGH: That's right. In general when Medicare says we're going to pay for something, we put out general guidance and we expect people to follow it, and we don't check to see whether they follow it or not. At least on a pre-payment review, we rarely check to see whether people follow it or not, we just assume that they're doing what the rules tell them to do, and they generally do.
Well, post-payment review occurs in various methods, contractors may do it, OIG may do it, Department of Justice may do it, there are various ways that that occurs. And the fact that we paid for something up front doesn't prevent us from determining that someone didn't follow the rules that we outline and therefore we're going to penalize them in some way, either by taking money back, fining them or sending them to jail, or whatever it is that the penalty may be.
And this policy isn't much different than that. Here are the rules. If you want to get paid for treating a beneficiary within a clinical trial, the expectation is that you're going to follow these rules. Now in the policy we

attempted to be, in this policy, unlike some other payment issues, we attempted to be a bit more definitive by saying okay, here are our rules. We don't have any methods of ensuring that people are following those rules, but there are other processes in place out there that essentially are evaluating the same kinds of issues. NIH is looking to see if trials are being done correctly and CDC is looking for trials they fund, and VA and DOD and so forth. So we're going to assume that if these other entities have paid for trials, that that means that they have insured that they are meeting the general standards of a good trial, and so we don't in those particular instances need to individually check trials to see if each of these seven characteristics have been met. What we're looking for now is something that's not too dissimilar from that, some general definitions that we will put out to the public that says if you're going to file a claim for a Medicare beneficiary in a trial that you're running, here are the standards that you need to meet. And if we continue the deemed process or some other processes, if your trial has gone through this process, then we'll assume that you

have met these standards.
DR. GARBER: Let me just add that we're going to touch upon this again in the discussion of some of the other questions. Question 6 in particular bears on this. We do not have to resolve exactly who's going to interpret this definition in order to settle on a definition, although that's obviously an important question. Very quickly now, we have eight questions, and if you actually count all the subquestions, we have ten-plus questions to get through today. So Mark Hlatky, Deborah Zarin, and Wade, and then we're cutting it off. Mark.
DR. HLATKY: For Question 1, since CMS is not a research organization, I would tend to want to see us adopt a definition that's fairly general and perhaps put together by more of the NIH rather than by the FDA, because it includes a broader array of clinical research than the clinical work simply considered by FDA. And the thing I guess I'm worried about is by adopting a definition that sounds good and then we find that certain kinds of studies are ruled out of hand from coverage, like a prevention trial for Alzheimer's or some other kind of thing, they say

well, it doesn't meet the definition, by the way, that we wrote. So I would like to see us adopt a broad definition for this and then have a process that decides whether that specific trial could be covered.

DR. GARBER: Okay. Wade.

DR. AUBRY: I just want to say that I favor 1.B for many of the same reasons that have been mentioned already. I also like Deborah's addendum or proposed addendum, but I think that two of them that focused on outcomes and the methodologic soundness, I think are already encompassed in the current seven attributes. But what's not covered is an explicit protocol, so I would favor option 1.B with a minor modification to say under bullet two, the study is, the study has an explicit protocol and is well supported by available scientific and medical, et cetera.

DR. GARBER: Okay. Deborah, and then I'll give Steve Goodman 30 seconds.

DR. ZARIN: I was just going to pick up on what Steve Phurrough said. I think that in a way the seven highly desirable characteristics are almost like a preamble, which is sort of similar to what I said. This is what we mean by clinical

research, you know, three bullet points. If you're doing clinical research and you've been funded by one of the following eight groups, or you're operating a cancer center, or whatever we decide, then you're assumed to meet the qualities that we care about and we're going to cover you. And then sort of the operational issues about the principles only matter if we're going to want to have a non-deemed procedure. In other words, I assume no one is going to look a year later at an NIH-funded study and say this is unjustifiably duplicative and so we're going to remove coverage, right? I mean, the operative decision is that it was an NIH-funded study and therefore, it's covered. Am I correct, Steve? I mean, if it's a Medicare covered service or something like that?

DR. PHURROUGH: In general, yes. You know, you can't ever in government say never, but the purpose of being deemed was that yes, you've met the seven highly desirable. Deemed doesn't necessarily mean that you've met the first, the Medicare-specific.

DR. ZARIN: Right, but the seven highly desirable then I would almost have like a preamble statement of principles, as opposed to part of the

definition of what we're going to cover.
DR. GARBER: Steve.
DR. GOODMAN: I'll try to take less than 30 seconds. I just wonder whether we're trying to read scope into this definition of good clinical trial, and maybe it should be preceded by saying for those, you know, we explicitly approve, you know, well conducted Phase One -- if it's not included, if it's not intended to exclude Phase One studies, it should say this includes Phase One studies, primary prevention trials, diagnostic trials, it has a list of studies so there is no ambiguity. And then there's a definition of what's a good trial. If you want to exclude those trials, then you should say it, but to try and weave this into a definition of what's a good clinical trial seems to invite all the confusion we've had here.
DR. SCHWARTZ: And that's what I carried away from reading the whole booklet, and then I came to what everybody is, with as much clarity as possible, because when you get into the field there is, the goal or objective of this whole process is to, I would say not encourage Medicare beneficiaries to get into clinical

trials, but to remove barriers to their entry, and the lack of clarity seems to be an almost universally perceived barrier.

DR. GARBER: Thank you. Now Janet is going to explain the voting procedure.

MS. BROCK: Just very quickly. We have a lot of questions to get through, so we're going to try to streamline this. What we have given you in your packet is a score sheet that has your name on it. We ask the panelists that you use this score sheet to record your votes. When Alan introduces a vote, say for Question 1, we will go down the panel starting with Dr. Krist, and you will state your vote for the record. If you have additional recommendations, you can add them to your score sheet, you may read them to the audience if you please. At the end of all of the voting, myself and my colleagues will take your score sheets from you so that we can tally them and show them to the audience via a spreadsheet on the screen behind me, and we will also have them available for others via the web site tomorrow morning.

I think those are the only things you need to know, other than we have lots of yes and

no questions, and obviously you're just going to say yes or no. For those questions for which we're using a scale, you have handy dandy little cards that you can hold up to designate the number that you've chosen.

DR. GARBER: So just another quick procedural question. What I would like to propose is that we break for lunch immediately upon concluding this vote, get back here within one half hour, earlier is better, so that we can move right on to Question 2. Alex, are you ready?

DR. KRIST: Yes. I vote for 1.B with the modifications for clarity that we discussed.

MS. DAVENPORT-ENNIS: And I vote for 1.B with the modifications of clarity, being certain that if we are going to identify Phase One and observational studies and other studies that have been cited, that we are certain that we do not exclude others.

DR. AUBRY: 1.B, for the reasons I previously stated.

DR. BERGER: 1.B, with the modifications to allow other study designs as discussed.

DR. GRANT: 1.B, with being explicit as

to the study designs being included.
DR. HLATKY: I'm more for 1.C, which would include an NIH definition of good clinical research.
DR. JANJAN: 1.B with the clarifications indicated.
DR. LO: 1.B with modifications and clarifications.
DR. SCHWARTZ: 1.B with modifications and clarifications, but also to the degree possible when the staff looks at this, to try to deal with the issue Steve raised about trying to harmonize these things as much as possible.
DR. SUGARMAN: 1.B with the suggestions for clarity and the included studies and types of studies.
DR. BERGTHOLD: Do I get to vote?
DR. GARBER: Yes.
DR. BERGTHOLD: Oh, great, 1.B.
DR. RYAN: 1.A(2), the Rothman definition.
DR. ALVING: 1.B.
DR. GOODMAN: 1.B with the specification of trial designs and the harmonization where possible with other language.

DR. GROSS: 1.B, actually the same thing, with modifications regarding clarity for trial design as well as the intent of the studies, including primary and secondary prevention.

DR. WARTMAN: Interesting. 1.C with some of the comments people made with 1.B.

DR. ZARIN: 1.B, with some of the comments people made with 1.C.

DR. GARBER: Well, I think I'll call that consensus of a kind. Okay, I'll see you back here around five after.

(Luncheon recess.)

DR. GARBER: Now we are at Question 2, or Questions 2 through 8, I should say.

DR. PHURROUGH: I would like to just make a comment about Question 2 and therapeutic intent, that may not have been clear from my earlier comments. When this trial policy was put together six years ago, you have to remember that it was in the context of a longstanding policy that we never paid for clinical trials. So there was a concern not only within HCFA at the time, but within the Department, that we're going to be opening flood gates for huge costs by paying now for services in clinical trials.

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Well, obviously we weren't. We were paying for most of this stuff anyway, so rather than paying for it outside the trial, we pay for it inside the trial. So one of the purposes of this therapeutic intent was to narrow the focus so that costs would not be excessive. You could certainly recommend that we throw therapeutic intent out the window, it's not something that necessarily needs to remain, it's there. If you think that's a good thing for Medicare to do, you can recommend that, or if you want to recommend some other requirements, you can do that. Or you can in fact delete these two, you could recommend that we just delete these two. So those are all options. Don't think you need to continue with this definition if you don't think you should.

DR. GARBER: Yes, Barbara?

DR. ALVING: You could also, if you leave therapeutic intent in, just, again, have in that glossary what that covers at a really broad definition of therapeutic intent.

DR. PHURROUGH: It's just difficult to put in the definition of therapeutic intent primary prevention and all that.

DR. ALVING: No, I agree. That's why I

think you need a separate glossary for all of this. Otherwise, you're wordsmithing a paragraph to death.

DR. GARBER: Well, these actually directly touch on our next voting question much more than Question 1. I can't see. Is that Mark Hlatky?

DR. HLATKY: Yes. Am I too early to say something about that?

DR. GARBER: No, we're on Question 2 now. We're going to deal with Question 2.A and 2.B separately. 2.A is, should we keep the two current standards in the bulleted points. So if everybody would raise their hands who wants to be recognized? Cary, Alex and Marc.

DR. HLATKY: I think the issue, again, is reducing confusion and making it clear that the intent is to cover or not, and I am troubled by the word therapeutic intent, which is quite vague. I might regard a prevention study as having therapeutic intent because the goal is to prevent disease, or extremely early treatment, or other kinds of studies that maybe are doing screening of, a better screening trial for colorectal cancer or something. All of those things seem to me to

be something that ought to be within the framework here, and I would be very worried that the language here excludes them.

And I was persuaded by the comments about Phase One trials, especially in clinical cancer areas where I think there really is the idea of giving a sick person an active agent. So I would like to broaden or at least put in some definitions underneath this that said, you know, we intend to say that these kinds of trials like Phase One cancer trials or diagnostic trials or prevention trials are included in this, or we've determined that they have therapeutic intent within the sense of this definition.

DR. GARBER: So, let me just tell you whose names I've got down. I've got Cary, then Alex, then Marc Berger, Jeremy, then Steve Goodman, then Wade. Okay? Cary.

DR. GROSS: I would propose definitely scratching the phrase therapeutic intent, I just think it's very unclear and there's no reason to use those words, and then define them to say oh, by the way, we don't mean therapy. So just use different language that's clear and concise.

Secondly, why are -- it sounds like

this is an area open for discussion -- why are we not including Phase One trials, and if we are, how can we make that clear in this section as well? And specifically what I'm addressing with the Phase One is the point one, where it specifically excludes them. So, can we just say we recommend to get rid of that first clause in point one because we want a Phase One to be included as well?

DR. PHURROUGH: You can certainly make that representation, yes. Phase Ones were excluded because we did not want at the time to be subjecting Medicare beneficiaries to safety-only trials. We wanted safety to be defined on some other patient population other than ours.

DR. GROSS: So that's something that's on the board, okay.

DR. PHURROUGH: Is that an appropriate intent in 2006 as it was in 2000 is open for your recommendations.

DR. GARBER: Alex.

DR. KRIST: I had concerns with both of the bullets, the therapeutic intent, as well as we've been talking about I think a different phrase. I was thinking of things like possibility

of improving health outcomes, we could do another phrase, that's still vague as it is, but it needs to be clarified.

And then the second one I have problems with is with the second bullet, the diagnosed disease. I mean, we have been talking about prevention some, and there's a whole spectrum. We have high-risk patients, that's one category. There's a lot of these pre-disease categories, pre-diabetes, pre-hypertension, that would exclude those groups. And then there's the healthy population that we just want to prevent. I think these should be included, and we shouldn't be actively excluding those groups of individuals as well, so that other two-sentence part of that phrase I think needs to be excluded.

DR. GARBER: Marc Berger.

DR. BERGER: I think that there should be clarity and not confusion. If we accept that we're modifying the definition for clinical trials as we did in Question 1, there is absolutely no need for anything in Question 2, that should be completely scratched. All they do is make confusion and obfuscate, and don't add anything at all in terms of the clarity that people need to

have to understand what is appropriately done in terms of clinical research as guidance.

DR. GARBER: Jeremy.

DR. SUGARMAN: I have problems with both definitions but wanted to speak to this therapeutic intent issue. I think there's, it seems like most people are troubled by it, and I think that's good. One of the main reasons to exclude it is the primary intent of any clinical research study is the creation of generalizable knowledge or for answering a research question, it is not primary therapeutic intent. And I think what it does is it forces the individuals who are charged with overseeing this research such as IRBs to think about research in a different way. And it also asks the participants in the research project to perhaps set out what we call therapeutic misconception, in which they erroneously believe that the extra procedures and aspects of research design are there for their benefit when in fact they're not. So it undermines the possibility of informed consent. So for those reasons, I think the therapeutic intent needs to go. I would say that research on therapies is fine, and then amending it for these

other types of research, but again, I think it needs to go.

For the second bullet, the idea of healthy patients, I don't know if one's a patient when one's healthy, and so I think it would be healthy persons, again, to sort of highlight that.

DR. GARBER: Okay. Bernie.

DR. LO: I agree with the previous concerns, but I want to say a little more about Phase One, because it strikes me that there are lots of different types of Phase Ones. In the classic sort of dose findings, toxicity findings studies I think are different than other types of studies, for example, Phase One studies that use a combination of FDA-approved agents to review the histology, with a much higher response rate. Gene transfers, you see a very different kind of patient than cancer trials. A lot of Phase One gene transfer studies really are assessing whether the process delivers the agent to the right tissues, and there is not really any sense that they're going to assess any clinical outcomes. So I guess the question I want to ask is, do you think it's appropriate for Medicare patients to be administered a new cytotoxic agent,

first of all, which starts well below the expected MTD, and with no prior studies in elderly persons? To go back to, Steve, what you were saying earlier about concerns about Medicare safety, it strikes me, I would like some clarification as to what you think or what the rest of the panel thinks should be our stance on those types of studies, which are different than other Phase Ones.

DR. GARBER: Yeah, I think that's probably something we should have a general discussion about. Steve Goodman.

DR. GOODMAN: Well, that was exactly what I was going to speak to. I think, I don't know whether this is sort of a statutory question or the way we think the world should be. I think for many patients, the Phase One trial is in fact in a sense the standard of care. I mean, it is the best thing that that patient could be offered at that time, because everything else is pretty hopeless. That may be relatively hopeless too, but it offers some hope.

And the second thing I would say is that even though the primary goal is to assess safety and toxicity, we don't put poisons into

people if there's no hope of benefit. The reason to poison them is because we're hoping that the cancer is poisoned more than the patient. So there's obviously an implicit therapeutic intent behind it; otherwise, we would not give this agent to them at all. So what it really is trying to do is finding an optimal risk-benefit point, and what we tend to do in cancer, and arguably there are other ways to do it, is we tend to focus on the safety issue first. And then we go to, we pick a point of toxicity that we think, that we think is just the exact point where there's an optimal toxicity/prospective benefit balance. That said, the response rate in many of these is quite low. So if we're going to define it on the basis of the potential for the design or the setting to produce a response, that gets us into very, very murky waters. But I do think that these days for many, many patients and not for all, we could parse this very, very thinly, a Phase One design, even though people do sometimes get treated with very often either inactive agents or subtherapeutic levels, the ultimate goal of the entire process, and certainly of administering the drug to the patient, is to find a dose that will

provide some benefit at acceptable toxicity. And as I said, it's often the logical therapeutic option to offer even though, as Jeremy says, the primary goal is to produce generalizable knowledge and not necessarily to treat that patient. So for those reasons, I think that Phase One designs should in general be, you know, included, although pharmacokinetic, pharmacodynamic studies on, you know, quote-unquote, healthy patients may fall in a gray area.

DR. GARBER: Wade.

DR. AUBRY: I for one, maybe I'll take a little, slightly different view. I don't really have as much of a problem with the term therapeutic intent as others, because I think CMS is not the NIH. Its primary business is not research, but rather it's to provide finance for illness or injury, you know, the basic statutory basis for Medicare coverage. And so I think therapeutic intent is a reasonable option. I also believe that there may be some early stage trials in which a therapeutic outcome is part of the design and may be appropriate to be considered. But I think probably we're spending

too much time on Phase One trials. I think the emphasis should be on later stage trials, later phase trials rather than spending so much time on Phase One, and I, just for a second, Bernie Lo's comments that there may be Phase One trials that really wouldn't be appropriate at all for coverage.

One other point is that I think what we mean by therapeutic intent is also diagnosis, so maybe we should say that. In the second bullet you could say, for example, trials of diagnostic interventions may have therapeutic intent, because they are used to make a therapeutic decision, and may enroll healthy, it may enroll healthy patients in order to have a proper control group. So you could add a phrase in to basically say when we're talking about diagnosis, it could also mean that that has therapeutic intent.

And I reference as a previous study the Stanford medical necessity study which used the term health intervention in its standard model definition of medical necessity, and that was basically a more general term to include both diagnosis and therapy.

DR. GARBER: Thanks. Steve Wartman.

DR. WARTMAN: I find this very enlightening and agree with a lot of what I heard just now. I support the point of view that says that depending on what we do with the previous question in terms of clarification, clarity, definitional scope and so forth, it could conceivably render Question 2.A somewhat moot. And we would have to ask ourselves the question in that case, what does this restriction on therapeutic intent really accomplish in that context. It may not accomplish a lot if that first definition is handled appropriately. Be that as it may, I think that when the term, and in some of those things I read about, therapeutic intent being a major objective, major objective is very, very vague terminology that I've seen. Primary, secondary, tertiary objective, et cetera, et cetera, we'd have to consider all that we mean by that. I do think, though, that the discussion of Phase One, if we can come out of today with some rational position on Phase One, it would be a great help, because that's where a lot of confusion is in the community right now. We may all have different philosophical views of that; my

own is that it's part of a process that goes on through many phases, and a necessary first step in many of the things that we do. Some people may differ on that point of view, and I think Bernie's comment in that regard is very appropriate. But I think at the end of the day, we would do everyone a service if we could come to some concluding recommendation about that.

DR. GARBER: Okay. I've got Nora, then Deborah, then Barbara.

DR. JANJAN: Thank you. Two points. Number one, with regard to Phase One trials, since 25 percent of Medicare's budget as I understand from some sources is spent in the last six months of life, I don't think this is a small issue about having patients make themselves available to Phase One trials when no other drugs, no other options are available. I would rather see a patient have the option to get on a Phase One trial rather than to get therapeutics that have very limited benefit to them after failing several other regimens. So I think it's important that we clarify the Phase One trial.

But I agree with Marc Berger, less is more. I don't think we need this. We have the

definition expanded in Question 1 and I don't know what this accomplishes.

DR. GARBER: Steve, did you want to respond to that?

DR. PHURROUGH: Let me just comment a bit about where I think the Agency and the department may be. My impression is we are not going to get tremendous support at the department level for expanding to Phase One trials whose only goal is the goal that many of you said we should be looking at, sort of, you know, the toxicity, pathophysiology kinds of discussions where we're not looking at any potential for response. Now we've talked a lot and heard mostly from cancer folks, but, you know, obviously there's a whole host of drugs out there that have nothing to do with cancer. I know that's a problem for you, but there are drugs out there that have nothing to do with cancer, and we have to look at those trials also.

And so I think, not that I'm advocating that we continue the definition or the restriction on therapeutic intent, but I do think that we are going to have to have some limitation on studies where there isn't any plan at all to see whether

there is going to be a response. So potentially that may be, and if we do that, that's going to be separate from the definition in Question 1. So obviously Question 1 does include trials that, good trials that look at toxicity and pathophysiology. So a potential recommendation would be that we just keep the first sentence of the first definition, which says must not be designed exclusively to test toxicity or disease pathophysiology, leave it at that and move on. So that's an option that may resolve or meet all of your concerns.

DR. GARBER: All right. Deborah is next.

DR. ZARIN: I think I agree totally with Steve. I was going to say that if you look at Phase One trials in ClinicalTrials.gov now you have a lot, for example, for restless leg syndrome, or for erectile dysfunction, or you have first in human studies, you have things like TGN 1412. I don't imagine that that is something you want to really encourage happening in the Medicare population, with the possible exception of when people have, you know, illnesses where this is the most rational approach for them. So I think that

I would avoid Phase One studies for now. I just think it's not appropriate at this point.

DR. GARBER: Barbara.

DR. ALVING: I'm looking for a middle ground here. I would say that perhaps you could also say that in general CMS will not consider Phase One drugs, or make some sort of, allow CMS to have a little bit of wiggle room for specific situations. And I think whatever decision we make does have intended and unintended consequences. You could say that by doing Phase One studies in the Medicare population, you're really thinking about them up front. Right now it's like okay, we're not going to touch them, they are older, have comorbidities, but we all know this is a rapidly growing population, and many of them are in excellent health and will force us to really think about the special physiology of aging. So that's another way to look at it, but I would allow CMS wiggle room so that it's not excluded, it potentially could, but it's not in its primary mission.

DR. GARBER: Deborah, is this a point of information about this?

DR. ZARIN: Yeah, I just wanted to

clarify that if Medicare doesn't cover a Phase One study doesn't mean it's not going to occur. I think, I hate to say this to you, Alan, but isn't part of this an economic shifting of costs? I mean, someone funds Phase One studies now, and this proposal could either shift some of those costs to Medicare, perhaps away from industry, or shift them back to industry, I'm not sure. But I don't think it's probably correct to say that if Medicare doesn't cover it, it wouldn't occur.

DR. GARBER: Well, virtually any policy Medicare issues changes costs. That's one reason there are so many people in this room. I don't mean to be presumptuous, of course.

(Laughter.)

Sandy.

DR. SCHWARTZ: I think what I was going to say has largely been covered.

DR. GARBER: Steve Goodman.

DR. GOODMAN: I just want to ask a question. I don't know whether the tenor of the discussion is going toward or away from Phase One trials. At our cancer center they currently, at least my understanding is and I was told this morning, that they are covered. So if we start

saying that they won't be covered, this would be a disaster there. So I think it's interpreted very differently and perhaps inconsistently, but this would involve a cutting back at least at some of the cancer centers.

But I just want to ask the question to Steve Phurrough. He said what happens if we just end it at the first sentence. So here's the typical situation. The Phase One trials, the primary goal is to establish safety, some toxicity level, but almost all of them do look to see if any patients respond. So if that's the secondary objective, does that qualify? Because it's not exclusively, even though that's not the primary endpoint, would that qualify in that setting where they are in fact going to look and see if there's any response to the drug?

DR. PHURROUGH: That's not a significant change from what we have now. Our current definition does not specify to what degree therapeutic intent must be within the trial. Part of this discussion was, at least in our original formulation, was to more clearly define when therapeutic intent is met. Based on the discussion, because that, because therapeutic

intent may well eliminate other types of study designs ignoring Phase One. I know we focused a lot on Phase Ones, but ignoring Phase One, and it may challenge the diagnostic testing, it may challenge preventive testing, let's just remove that and then let's try to come up with something that would prevent those types of Phase Ones that we don't want to cover. And then, because currently there is in general the assumption that many Phase Ones, if not most Phase Ones, currently aren't covered in the clinical trial policy.

DR. SCHWARTZ: Are or are not?

DR. PHURROUGH: Are not, under the current policy.

DR. GARBER: Mark Hlatky, then Jeremy.

DR. HLATKY: I would certainly like to see somewhere in the language even if we do what you said, to make explicit the discussions that we've had that we consider Phase One clinical trials in cancer to be distinct from other ones. And I think there's a lot of differences between them and other trials, and I think we can get away from a lot of concerns --

SPEAKER: Why do you think there's differences?

DR. HLATKY: I think the biggest difference is that a lot of other Phase One studies are done in normal volunteers that are healthy, they are pharmacokinetic studies, whereas chemotherapeutic agents are tested mostly in patients who have advanced disease, because of the recognized toxicity, and I think that's the biggest difference, is that we're talking about, you know, really different kinds of --

SPEAKER: How about in heart failure?

DR. KRIST: Or you could just say a life-threatening condition.

SPEAKER: Or whatever, Alzheimer's disease.

DR. GARBER: Jeremy.

DR. HLATKY: I guess I'm trying to say that I would be concerned that just striking the sentence to say not toxicity would still leave us with the cancer trials that I personally am convinced are very reasonable things to have covered.

DR. SUGARMAN: A potential way around this is to simply delete the "it must have therapeutic intent" and maintain the first and third sentences of that first bullet. And the

reason for that is that the oncology Phase One trials are distinctly different from most other Phase Ones because they do involve patients with disease, where it would be unethical to test a dose with known toxicity and mechanism of activity in a healthy volunteer. And we don't know, we can't anticipate what those other conditions might be, but it's conceivable that there are other conditions that will mimic those considerations that oncology currently holds tightly to, and doesn't force us to say that overall this is going to lead to therapeutic intent, when we know from the analysis of those data that there's a four percent, looking at what happens in Phase One trials, of classic oncology trials, a four percent chance of any therapeutic benefit whatsoever in a Phase One. We don't have to play that game, and still get around trying to meet all the goals.

DR. GARBER: Mark Grant.

DR. GRANT: I personally don't have any problems with the terminology, as vague as it may seem, of therapeutic intent. I think its implications are pretty clear. And also, I think the focus here on cancer is -- there's a whole spectrum of disease which afflicts older folks,

Alzheimer's disease, there's all sorts of functional impairments that are really critically important, and I think we need to really consider those things at the same time, and I would be disinclined to single out cancer addressed as a special cause.

DR. GARBER: Okay. Alex, and then I'd like us to vote. It sounds like, we don't expect complete consensus here, but as we go through, explain which way you want to go on keeping the language, and then in brief terms any modifications you make, and that's been implicit in several of your comments, but not all of you would make the same modifications, so if you could say a little bit about that, that would be great. Alex.

DR. KRIST: I was just going to respond to Jeremy's comment about just eliminating "it must have therapeutic intent" in that sentence only, and then you still have the following sentence that you have to have folks with diagnosed disease, and you're ignoring the folks who are high risk in prevention and predisease, and those subgroups as well. So that would be the problem with just taking that one sentence out of

there.
DR. GARBER: Okay. So, Alex, why don't you go ahead and tell us how you vote. Question 2.A, should these two current standards remain in the revised policy, and modifications.
DR. KRIST: Well, I guess I would vote, given the discussion, would be to say no, but to keep the first sentence of the first bullet.
DR. GARBER: Nancy.
MS. DAVENPORT-ENNIS: And I think from our position that we would be saying, I think we can say yes. However, I think there are two modifications that we have to include, Phase One clinical trials for chronic, debilitating and life-threatening illnesses, and that we need to also amend in the second bullet, may enroll healthy patients, because indeed, that would mean that observational studies and perhaps even prevention studies, you would not be able to get to the population that those studies are indeed designed to serve.
DR. GARBER: Wade.
DR. AUBRY: I vote yes for the reasons that I've stated before, and I would add the modification or the clarification that would

define a diagnostic intervention having therapeutic intent in order to be covered under this.

DR. GARBER: Marc.

DR. BERGER: No, I vote no. I think they should be eliminated. I think they add confusion. If you do want to keep the first sentence about restraining restrictions on studies exclusively designed to test toxicity, that would be fine.

DR. GRANT: I vote yes and I would include language that reflects that some of the Phase One or earlier trials in fact do have promise to improve health outcomes.

DR. HLATKY: I would vote no, because I think under the proper definition for clinical research, that we've already taken care of this, so we don't need these two additions.

DR. JANJAN: I vote no for the same reason.

DR. LO: I would vote no, but I would include the exclusion of exclusively to test the toxicity or pathophysiology, and explicitly include diagnostic studies and prevention trials which may in fact include healthy people at high

risk.
DR. SCHWARTZ: So you would exclude toxicity and --
DR. LO: No. I would exclude studies that exclusively test toxicity or pathophysiology.
DR. SCHWARTZ: And I feel the same way. I just want to register that I think the issue with Phase One needs to be further considered because, even among the panel, there's a lot of confusion to what a Phase One trial does. You know, it's not a compassionate care kind of thing, and I agree largely with Wade that, you know, there is some point at which Medicare is not a research organization. And I think they have to balance the needs, you know, the goals of the program with the needs of the patient. So yes, but a little less supportive of the open door policy to Phase One.
DR. SUGARMAN: I vote no with the way that I'm interpreting how the votes are going, because people who are voting yes are voting to make changes and people voting no are suggesting changes. So I'm voting no just because it seemed like the right thing to do. But I want to delete therapeutic intent language from any definitions

that are used, and I'm fine with keeping the first sentence in the first bullet, and I also would suggest changing healthy patients to healthy persons.

DR. SCHWARTZ: I just want to clarify. I voted no.

DR. BERGTHOLD: And how would you expect a Medicare beneficiary to understand this? I want to vote with Wade, so whatever he said. And I would actually like to suggest his other addition, which is that we include trials of health interventions instead of therapeutic interventions, because if we're going to delete it in the first bullet, it should be clarified in the second.

DR. RYAN: I agree with the previous statements that the new definition of the proper study covers this, and therefore I vote no, there's no need for these definitions any longer. I would ask also that we need to include language that allows for payment of Phase One studies where therapeutic outcomes are evaluated.

DR. ALVING: And I vote no, and I would say we need just plain language about Phase One so that CMS on its web site or under FAQ could really

discuss Phase One and its overall policy and consideration, and I would do the same for prevention trials.

DR. GOODMAN: I second that. I'd say exactly the same thing that Barbara said.

DR. GROSS: I vote no also, and the only provision is, again, to include a specific description of Phase One studies would be reimbursed if they are applicable to patients with chronic, debilitating or life-threatening illnesses.

DR. WARTMAN: I also vote no, provided that we solved the definitional issues in Question 1, resolve the Phase One study issue, and I also like the Phurrough modification.

DR. ZARIN: I've lost track of whether I'm voting yes or no, but I think that we should keep the first sentence, as Steve suggested, but I would propose changing it to say the study must not be designed primarily to test toxicity or disease pathophysiology. It's extremely easy to just add a secondary outcome measure of clinical effectiveness, and suddenly no study is exclusively designed to test disease physiology or pathophysiology. Also, I'm just a little worried

about incentivizing industry to move Phase One studies from healthy volunteers to Medicare beneficiaries with illnesses when it -- I would just raise that as a possible unintended consequence.

DR. GARBER: Okay. Thank you, everyone, that's our vote. We really have I think something like 12 more, or actually more than that, probably about 16 more questions to get through, if you count properly. So I'm going to suggest for Question 2.B, if we could just get hand raises about which of these you want. There are five items under Question 2.B, and why don't you raise your hands if you want to have further discussion. Some of these are straightforward, some maybe won't be, some may be more controversial. So we're going to go one by one first, and just raise your hand if you want to have further discussions. Steve?

DR. WARTMAN: Just a point of clarification, and that has to do with the timing of the registration on the web site. The question doesn't specify what the timing is, it just says a study must be registered. I think I read somewhere else that they said at the time of

enrollment of the first patient, or perhaps when there's funding. Could we seek some clarification on that point?

DR. PHURROUGH: For Medicare, the only concern we have is when we get a claim, so at the time the claim is submitted on that claim, we would require the NCT number.

DR. WARTMAN: I guess I'm raising that point to talk about the business of doing these kind of studies and posting something on a web site before it's come to fruition, i.e., they're funded or recognized, or whatever. Somebody comes up with a brilliant idea that nobody else has thought of, and they put it on the web site and then, you know, whatever might happen. So I'm just concerned about some type of modifying language, that we have a better idea of when -- I support the concept but I'd like to get a better timing issue down.

DR. GARBER: You know -- yeah, Deborah, did you want to address that?

DR. ZARIN: Well, I was just going to make the point that major journal editors require registration prior to enrollment of the first subject. So to the extent that Medicare cares

about getting generalizable knowledge that might lead to a journal publication, you might consider hooking onto the ICMJE, the International Committee of Medical Journal Editors, which is also consistent with the WHO standards on that issue.

DR. GARBER: Yeah. And I think in the written materials we have, that was cited, so that's what I think the tenor is. So raise your hands only if you want to have further discussion of these. So first, Question 1.

(Show of hands.)

DR. GARBER: Okay. A couple people want that. Question 2.

(Show of hands.)

DR. GARBER: Question 3.

(Show of hands.)

DR. GARBER: Mark, you're the one that's going to miss the flight, but okay. Question 4.

(No response.)

DR. GARBER: Question 5.

(Show of hands.)

DR. ALVING: Clarification of what that actually means.

DR. PHURROUGH: That means that if we, in a national coverage determination where we're evaluating a specific technology, we could decide that we would only cover that technology in a clinical trial and here are specific standards we want that trial to meet. So we may apply some additional standards over and above what's in the clinical trial policy under CED. For instance, we may specifically say you have to enroll left-handed redheads, for whatever reason, I don't know, but it would be specific to that technology.

DR. ALVING: Maybe one more sentence to actually explain that would be good in there.

DR. GARBER: Okay, thank you.

Question 1, discussion. Mark, and then Mike.

DR. HLATKY: This is really kind of a minor point, but it seems to me that we want a -- I'm highly in favor of trial registration, I just thought this was too specific, with all due respect to Deborah, but I mean, there are other things that might come about, and maybe this isn't going to be the one that's going to be there forever. I think we ought to say that we ought to register trials, this is one of the acceptable ones and, you know, leave some wiggle room for

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later on.
DR. SCHWARTZ: Well, do you want to say -- can I go out of order?
DR. GARBER: Sure.
DR. SCHWARTZ: If what you're saying, Mark, is maybe we don't want to link to something, maybe we don't want to specify where it has to be --
DR. HLATKY: Yeah, exactly.
DR. SCHWARTZ: But I think it should be in one place, so CMS and the intermediaries don't have to look all over the place to try to find things. I think there ought to be one standardized database.
DR. GARBER: Deborah, did you want to address that, with all due respect to Mark?
DR. ZARIN: With all due respect to Mark, ClinicalTrials.gov is run by HHS, which I guess also runs CMS. It's one of five that are approved by the ICMJE. The next -- ClinicalTrials.gov currently has 36,000 studies, the next largest one has 5,000 studies. I think this is the show in town.
DR. GARBER: Yes, Mark, I actually have to say that if your goal is to make sure that you

have a viable clinical trials web site, or viable clinical trials registry, you don't let any clinical trials registry suffice. I mean, this is one way to promote the one that HHS sponsors. Mike had his hand up.

DR. RYAN: I think that while the industry certainly supports voluntary registration of trials, I think what we're asking for is to see some balance between disclosure and protection of confidentiality and proprietary information. When you do early trials such as this, there is the potential in registering those trials that you could reveal competitive information. So I think what we're looking for is that the requirement should be put in place, but Phase One trials should be excluded.

DR. SCHWARTZ: Or in those cases where trials don't get funded.

DR. GARBER: If you say yes to this, it means both. Phase One studies that a sponsor chooses not to list would not get covered. Steve Goodman.

DR. GOODMAN: This is really a question that maybe Deborah, in terms of clinical trials, there doesn't seem to be much debate about this.

But we've talked about a much broader range of research studies here, or diagnostic tests. Are we going to say that every small study initiated by, you know, an investigator in his own clinic has to be registered at ClinicalTrials.gov within the very broad range of studies we've talked about?

DR. ZARIN: I think that that's the point. The alternative that has been argued would be called secret human experimentation.

(Laughter.)

I mean, one of the purposes of trial registration is to ensure transparency, public disclosure that the research is going on, and accountability later when you either look for results and don't find them, or do find them. So that's the idea, I would argue, if Medicare is going to spend public money to fund a trial, then the public, to say nothing of the individual participants, have a right to be aware that the trial is going on.

DR. GOODMAN: So you would include diagnostic test studies.

DR. ZARIN: Oh, absolutely. In fact, the journal editors include those, so you can no

longer get a study published in an ICMJE-compliant journal unless you've registered that study.

DR. GARBER: Mark Grant.

DR. GRANT: Just a quick comment or two. I think registration really affords the opportunity to understand the quantity of unpublished data that's out there, which currently is incredibly difficult to ascertain for particular treatments.

DR. GARBER: Okay. So, let me just ask a procedural question of Kim and Steve. For these questions, can the panel just raise their hands to indicate their votes?

DR. PHURROUGH: Sure.

DR. GARBER: Okay. So we're just going to do voting by hand. We're going to do these one by one. Yeah, you still have to record it and turn it in at the end of the day.

DR. SCHWARTZ: Have we discussed everything?

DR. GARBER: No. We're going to first vote on number one, if we're done with discussion, and then we'll go to number two, so you don't have to retain it all, okay? So we're voting on number one, the study must be registered on the

ClinicalTrials.gov web site. Who votes yes? Raise your hands high, please.

(Show of hands.)

DR. GARBER: Who votes no?

(Show of hands.)

DR. GARBER: Okay. Now we'll open discussions for the second one, the study protocol must specify method and timing of public release of results regardless of outcome or completion of trial. Deborah.

DR. ZARIN: I guess the question is who sees the protocol, sort of what's the concept here, because CMS doesn't get the protocol. Do they mean that they want on the registry something about timing and release? It could be written in a protocol that no one will see. I'm wondering what the idea was there.

DR. PHURROUGH: Because these are Medicare-specific criteria, not the general criteria, we will be developing a more explicit method for doing this, the current other clinical policy, the IDE policy has contractors reviewing protocols, and so my suspicion is we may have something similar. A contractor may say hey, you're asking me to pay for this, let me look at

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the protocol to make sure that you have met these four or five specific things, not the general things that we decided in Question 1, but these specific things.

DR. ZARIN: So in a way by having this, you're responding to something I asked before, which is that implicitly there's a requirement that the investigator have a written protocol on file somewhere?

DR. PHURROUGH: Yeah.

DR. ZARIN: I mean, that may be worth saying explicitly in the beginning.

DR. GARBER: Steve Wartman, did you have your hand up?

DR. WARTMAN: I also share some of Deborah's concern. I think this is a difficult and somewhat expensive requirement, it may be impossible to enforce, and I think it gets CMS into issues that may be a little bit beyond the scope of what CMS wants to get into, issues of intellectual property, issues of contracting. You know, I just wonder if this recommendation belongs here.

DR. GARBER: Well, you know, maybe -- oh, go ahead. Nora, and then Sandy, and then

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Jeremy.
DR. JANJAN: My question about this was regarding the timing of public release of results. The question then is, if you have an ongoing trial and, you know, you have patient number 22 out of 50, is it even appropriate to -- we do annual reviews and periodic reviews of protocols and determine whether or not to continue trials, but do you want a public release of that? Because the first five patients may have a great result and everybody is clamoring to get in on it. I'm very, I just don't understand what the timing of the public release of the results refers to.
DR. PHURROUGH: Well, the intent was to say you've got to explicitly define in your protocol what your plan is to release the information, not the date, but we plan to release within 12 months of the end of the trial and the analytic process the results. So that there isn't, well, if there's no timing there, they could plan to release it in 2086.
DR. JANJAN: I understand that. That makes it more clear, I have no problems, but I was just wondering, do you want annual reviews on the web site?

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DR. PHURROUGH: That would be great, but no.

DR. GARBER: Next, Sandy, and then Jeremy.

DR. SCHWARTZ: I think this has the same intent, I feel strongly it's got the same intent as the first one. The rationale behind this, as I understand it, is that Medicare wants to facilitate research so that we can get more knowledge of, to facilitate scientific knowledge, and it's a public good, and if people want the public to fund the research, then their information should be available.

DR. GARBER: Yeah. Let me just interject that I think the intent of both of these, as you say, Sandy, is really to avoid biased reporting of results, and that all has to do with prespecification, endpoints, decision rules for stopping a trial, stopping accrual of patients and so on and so forth. That's what I believe these are getting at, to put as much specification on that as possible. Jeremy, you were next.

DR. SUGARMAN: My point has been made.

DR. GARBER: Then Bernie.

DR. LO: I agree with what Sandy said about the importance of this for transparency. To respond to an earlier point about how difficult this would be to enforce, yes, that's true, but there are a lot of things you put in regulations so that if something comes up later, you can go back and look. It doesn't have to be enforced prospectively. It might have a very salutary effect on IRB's and scientific study review sections to add this to the list of things they're going to look at in a protocol to see if it's there. So I would strongly urge that we keep this to sort of signal that dissemination of results without bias is essential.

DR. GARBER: Barbara.

DR. ALVING: And this is being done in NIH-funded trials and being asked for again as part of its public funds for public knowledge.

DR. GARBER: Okay. Mark Grant.

DR. GRANT: Just a quick comment. We could possibly be more specific about results. There are, you know, a multitude of results from any clinical trial. Are we talking about primary outcomes, are we not, or major primary outcomes?

DR. GARBER: It should be the

prespecified outcomes.
DR. SCHWARTZ: So all prespecified outcomes, primary and secondary.
DR. GARBER: Yeah. Mark.
DR. HLATKY: I think although the intent of this is laudable, I'm worried about it, I must say, because of issues that people might say that -- I mean, I think this really belongs in someone else's bailiwick like the NIH's, in terms of saying, you know, we're going to set policies about what the date of release are, is for our study. And the other thing to say is that you can have a plan and it may turn out that in the end, you know, your trial results don't get written up or journals don't take them, or whatever happens. I'm a little concerned, you don't know in advance what's going to happen. You can have a plan, but to say that I have a plan is different from saying that it's actually going to, the results are going to be warranted to be out there. I guess I'm not terribly comfortable with this one.
DR. GARBER: Cary.
DR. GROSS: This is a terribly important issue, and first of all, I don't think it could be in NIH's bailiwick, because there are

many trials that are not NIH-funded, so it wouldn't be feasible to say that NIH has to manage them.

With regard to having a plan for dissemination, I'm concerned about the language. It says here, as the analyses are completed, so we need I think a little more leeway, something more specific, in a timely manner within two years after the study's finally completed analyses, or something.

And with regard to the mechanism through which dissemination could occur, it could be either through publication or some other means, so it doesn't have to be contingent upon publication.

DR. GARBER: Okay. Mike, and then let's vote.

DR. RYAN: Just a point of clarification. If you have a plan that's in place and you meet this requirement, and then on the retrospective review that plan is not executed because you can't get --

(Discussion off microphone.)

DR. PHURROUGH: I'm sorry. If the plan is there, all this requires is the plan, that's

correct. It does not require the plan to be implemented.

DR. SCHWARTZ: I think that's important for a couple of practical reasons. In other words, Michael may sponsor me to do a trial and then I don't get around to publishing the results, you know, maybe it's a multicenter trial. So you don't always have control over what actually gets done or what gets published.

DR. GARBER: Yeah. This language doesn't require control. It's just requiring it be prespecified. Okay. So let's vote now. Everybody who agrees with number two, raise your hand yes.

(Show of hands.)

DR. GARBER: Okay. Disagree?

(Show of hands.)

DR. GARBER: Number three, the study must have explicitly discussed consideration of relevant subpopulations as defined by age, gender, race/ethnicity or other factors in the study protocol. Sandy.

DR. SCHWARTZ: I would not have that here. I don't think it fits with the rest. I think it's an important issue, that that should go

into Question 1 where we talk about what makes a good clinical trial. So to me, here we're talking more about transparency/disclosure types of issues, and this is really a methodological type of issue.
DR. GARBER: Any other discussions of this point? Steve.
DR. WARTMAN: I would seek some clarification on what the word explicitly discuss means. You know, that could be several pages or an in-depth whatever, or it could be a little box that somebody checks off.
DR. PHURROUGH: I'm not sure we could get it any more specific.
DR. GARBER: Did you have in mind something like the human subject section of the NIH proposal where they have instructions?
DR. PHURROUGH: We had in mind what is required by NIH currently, where they have the same -- essentially this is taken right from NIH requirements.
DR. GARBER: That's about as specific as you can get, I think. Nancy.
MS. DAVENPORT-ENNIS: Just a quick observation, and that would be while I think all

of us would agree that we want to see trials that are inclusive, so that we can begin to accrue data of how drugs are responding in different subjects, that if we indeed voted yes in this category, perhaps it would need to be a conditional yes, that only if the trial is not mandating specific numbers of entities from each of these categories that are identified here. Because that would become a restrictive tool rather than a tool of access.

DR. GARBER: Well, I understand that you explicitly rejected imposing quotas; is that correct, Steve, that it has to be discussed based on the --

DR. PHURROUGH: This is not imposing any quotas in this section.

DR. GARBER: Wade, did you have something?

DR. AUBRY: I was going to say, that was my reading of it.

DR. GARBER: Okay. Everybody in favor of number three, raise your hand for yes.

(Show of hands.)

DR. GARBER: Okay. The nos.

(Show of hands.)

DR. GARBER: Thank you. Number four, if the study results are to be used to inform Medicare coverage policy, the study must contain an explicit discussion of how the enrollment process will ensure that sufficient Medicare populations are included to clinically and statistically determine that Medicare populations benefit from the intervention? I think we'll just go down, starting with Wade, just down the table.

DR. AUBRY: I think this one is problematic. I think because of the testimony that we've heard, that basically that it's difficult to ensure. I think that's the problem word. I think that it's reasonable to say that there should be a goal, there should be an attempt to enroll numbers of patients in the Medicare population, but it shouldn't be an absolute requirement, or a requirement that this be ensured.

DR. BERGER: I'm picking up on Sandy's comment, because I think both questions three and four actually are asking methodologic questions rather than questions about access or disclosure. And in fact, you know, if it doesn't do this, then Medicare has the option not to do anything to

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cover it, so just talking about this here is irrelevant.
The question here is if you decide, if you write a good protocol, then you're going to address this issue appropriately when you say how generalizable are your findings for the population. If they're going to then bring it to you to use it for a coverage decision, it's up to them to decide if they brought you good evidence. If they didn't, hey, that's their burden.
DR. GRANT: I have a little difficulty with the phrasing regarding to, if the study results are used to inform, and so it sort of implies that there are two different kinds of studies, studies that will inform Medicare policies and studies that won't. And I would tend to agree that anything that would potentially restrict enrollment, this may be a deterrent in some respects. Maybe Steve could answer that.
DR. PHURROUGH: There are in fact studies that inform Medicare coverage policies and studies that don't. Many studies are around things that we already cover, so it would be unusual for us to change that, unless they are challenging the particular efficacy of that

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particular technology. The goal here is, and I certainly admit that it may not be clear what the goal is here, or not written well. The goal is to say, well, the goal is to encourage the completion of trials that will allow us to make coverage determinations, rather than our being forced to make coverage determinations with evidence that doesn't include Medicare beneficiaries, which is commonly what we get.

The difficulty is it's very difficult in many cases to say no. We do say no. These people don't like it when we say no, even when the average age is 45. So the goal here is to stimulate that to occur. And we tried to word it similar to the first one, although we probably didn't get there. We're not saying that you must enroll enough Medicare-aged beneficiaries so that the study is statistically powered to answer the question around that subpopulation, though that's not a bad idea. I think the goal here is to say that you have discussed, if you want this to be used to inform Medicare coverage policy, how your results will be able to be generalized to that population. And you may be able to say there is

no difference in a 45-year-old and a 70-year-old, and I'll just enroll 45-year-olds, and here's the reason why you can generalize that information to the 75-year-olds, and that may be sufficient.

DR. GARBER: Steve, you know, I have a little trouble with your explanation about studies that wouldn't be used to inform Medicare coverage policy. Remember, we're talking about before the trial is completed and you're saying there are -- you would have to say there are some studies that would be qualified under these rules to be, have the routine costs paid for by Medicare that would not inform Medicare coverage policy. And I just have a hard time understanding what those studies might be.

For example, if it's something that's already covered and you have a study that shows that that intervention is clearly harmful, I would consider that to be very relevant to Medicare coverage policy. And if it just confirms Medicare coverage policy, that also to my mind means it informs Medicare coverage policy. So I find that restrictive to say if it's to be used to inform Medicare coverage policy, it's a little hard to understand, given that we're not talking about

things like pure toxicity or dose escalation studies, and maybe I shouldn't take that as a given. But so what, if the intent here is really to say that this study should enable you to draw conclusions about whether something works in the Medicare population, I have no trouble, but I'm not sure that that's what this wording means.

DR. SCHWARTZ: Alan, the thing that strikes me here is -- well, I agree with you. I would delete that introductory phrase, if the results are to be used to inform Medicare coverage policy, that that clearly is true to the degree that there are more Medicare beneficiaries, it makes it easier in other MedCAC meetings to make decisions.

But I wonder if the real issue here is, and I think, Steve, if this is what you're trying to get at, we're all bothered by studies that arbitrarily exclude people because of age and nothing else. You know, they enroll people, and they exclude everybody over 65 and there's no rationale for that. And I just wonder if, you know, if that's the situation, if that's what we should say, you know, age alone should not be an exclusion criteria for these studies and if they

are, they need to be justified, for example.
DR. GARBER: Bernie.
DR. LO: I agree that the way this is worded, I don't think really gets at the goal. And it introduces, as we heard in the opening testimony, a lot of concerns and confusion. So first, I think the issue is not that you ensure that people are enrolled, but you have in the protocol some plans to enroll enough Medicare participants so you can make some sort of valid imprints about the risks and benefits about the intervention, the study intervention for Medicare populations. So I would take out any language that talks about ensuring and really talk about having an analytic plan to draw some conclusions and having a plan to enroll sufficient numbers of patients to enable you to draw those inferences.
DR. PHURROUGH: That's certainly what we're trying to say, even though we didn't say it very well.
DR. GARBER: We're going down the table and then back to Nancy and Mark Hlatky. Linda.
DR. BERGTHOLD: Well, I have some suggested language here. Taking out the first phrase, it would read, the study must contain an

explicit discussion of efforts that have been made to ensure that either sufficient Medicare populations are enrolled in order to generalize to the Medicare population, or how results can be generalized without, something like that. In other words, the point of this would be the study really should show what you have done to either enroll patients, or show that the study is relevant to Medicare without a statistically significant Medicare population. And the reason I think it's important to have this in here is we have not gotten very far with voluntary guidelines, and I would like to see something really explicit that forces the issue. So if somebody else has some other language that can make it clearer, I just think we need to have it.

DR. GARBER: Okay. Continuing down there with Mike.

DR. RYAN: What I'm hearing is the intent of this is to try to make sure that the studies are designed in a way that results can be generalized to the Medicare population. As Dr. Boyd pointed out, from Rush earlier, when you design these trials, you design them for the disease state, and you may design it for a disease

state for which only five or ten percent, for example, of that disease state happen to be greater than the age of 65. If you now want to say treatment is more generalizable for that, you power the study for the disease data at hand. What this would require people to do is to power studies for the subpopulation that was involved, which will mean much larger studies, much greater expense, much longer periods of time to do the research. And so, you know, that's not how clinical research is done, it's done around the disease state, not around the subpopulations.
DR. GARBER: Barbara, did you want to?
Okay. Steve Goodman.
DR. GOODMAN: Yeah. I don't understand why this is here at all. I mean, this seems to relate to criteria for Medicare coverage decisions, not whether you would fund the expenses of somebody who is enrolled in a trial. If five percent of a trial is over 65 and it's a trial that would produce disease-specific or treatment-specific knowledge generally, then they should be paid for.
It's not clear that you -- we haven't at all talked about how the results of the trial,

whether it be the Phase One trial, have to specifically, feed into the coverage -- how that can be contingent on the later coverage decision. I guess I don't understand this. I mean, if you're writing guidance for companies or for how, you know, what sort of evidence would most likely lead to approval or coverage for the indication, not paying for the clinical trial costs, then this would be highly relevant. So I don't really understand it from that perspective. The other is, even though Steve said that it doesn't have to be statistically powered, we have the word here, statistically determined. That's very loaded language. If we don't mean it, then you shouldn't say it. In fact, it is almost impossible, given both the realities, and also it doesn't make sense scientifically most of the time that we should power the trials to be able to make that distinction. I don't know what it means, statistically determined, short of getting the numbers to either decide in that population alone if it's effective or is there an interaction between other populations.

So I think, you know, in the end, generalizability is based on many things, of which

statistical significance all by itself usually plays only a small role, and we could look at the similarities of disease process in the clinical profile in the different populations, and we're always generalizing beyond where the studies are. So I think it's unclear what role this plays here and we absolutely have to take out, you know, statistically determined. If it's going to remain, you have to keep in words like discuss, you know, issues of generalizability.

DR. GARBER: Well, I haven't heard any strong support for the existing language, but let me just say that my understandings of Linda's modification of the language addresses your point, Steve, by first of all saying that it need not necessarily be powered independently as a clinical trial to say does this work in the Medicare population with conventional levels of statistical significance. But there has to be some argument, some good rationale for how this trial will enable CMS to draw conclusions about whether it works in the Medicare population.

DR. SCHWARTZ: I disagree.

DR. GARBER: No, no. Let me just --

I'm talking about my interpretation of what she

said. We're going to discuss in a moment whether that's right or whether that should be the language. So I think the question is, does it have to be a trial that included very, very few elderly people, or there could be a rationale offered as to why this might otherwise apply to the Medicare population in order to qualify for Medicare reimbursement.

DR. GOODMAN: That's still only for Medicare-aged enrollees in that trial. They're not funding the trial. They're only paying the costs for that very small subset.

DR. GARBER: That's correct.

DR. GOODMAN: So there's not that much at stake.

DR. GARBER: Exactly, because very few people's costs are at stake. Okay. Why don't we keep going down, and then we're coming back this way. So next, Alex.

DR. KRIST: I was just going to say, if the intent is to just understand the generalizability, number four could just be changed to, the study must contain an explicit discussion on how the results generalize to the Medicare population. And the discussion could be,

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we're not going to have sufficient power to generalize to the Medicare population, or we don't need to because this population does generalize. And if the intent is to just get people to think about that, then they would just have to discuss it.

DR. GARBER: Okay. Nancy, and then Mark Hlatky.

MS. DAVENPORT-ENNIS: Well, thank you for the opportunity to comment. As I read the language, I'm concerned, as many of my colleagues on this panel are, and so I will try to be repetitive quickly, Alan.

Number one, I certainly have great concern when I see that the study results are to be used to inform Medicare coverage policy, because that would say to me there is going to have to be some form of concrete information delivered from that trial to Medicare that would indeed give them enough information to make a coverage decision.

I'm concerned with words such as ensure and sufficient because they're global, and who's defining what is sufficient. And the issue of statistically determined is of great concern.

I'm further concerned that no matter what clinical trial we may want to look at in the United States today, we're probably going to see not necessarily the largest percentage of participants are going to be Medicare. So how will this play into the ultimate ability of an investigator to close the trial if they fail to attract? And I'm always looking at a process of, is there a way that CMS could incentivize providers and investigators to get more patients into these trials, and upon doing that, there would be an incentive for that process. And from that incentive process, we would be able to report back what the results are to CMS, and that that would be a voluntary process that would not endanger the termination and completion of the trial.

DR. GARBER: Thank you. Mark Hlatky was next.

DR. HLATKY: I agree with most of what was said already. The only thing I would say when I think about this is there may be a superbly designed study that is only going to enroll a few people in the Medicare age group, and I think the sense of what we're trying to do today is to

remove barriers to them being in those trials. And so there may be only a few patients who are going to get into the trial, and I don't think we want to say you can't enroll only a few, you either have to enroll none or enough to make a generalizable conclusion about that subgroup. I think that this potentially could be read that way and is problematic for that reason.

DR. GARBER: Bernie, then Sandy, and then Barbara.

DR. LO: Well, as I have been trying to revise this, I have crossed out every single word in four except for discussion, Medicare and benefit.

(Laughter.)

But I guess we need to go back and ask, what's the purpose of this coverage policy? Is it that we think that it's good per se for Medicare beneficiaries to be enrolled in a clinical trial, or is it that we think we need more information about interventions, their risks and benefits in the Medicare population. And I guess my concern is that I think we're confusing the notion that it might be a good thing for some Medicare beneficiaries to be in a clinical trial even if

they're the only one, or one of two, and there's going to be no inferences made.
But I guess that's, to me, a compassionate use argument. It's not, doesn't go to the point of we're trying to get information about what works and what doesn't in this population. And it strikes me if you don't have a plan for how the enrollment in your trial of Medicare beneficiaries is going to help address the question of what works and what doesn't, then it shouldn't be covered here. Maybe it should be covered some other way for humanitarian exception, but it really doesn't further the goal of trying to figure out what works and what doesn't.
DR. GARBER: Sandy.
DR. SCHWARTZ: Yeah, and I disagree here. I'm really where Mike and Steve and Mark and Nancy were, for a couple of reasons. One is, I think in addition to the two things you just said, Bernie, I think there's a third thing, Medicare's got an interest in advancing knowledge of disease in general, which does affect many Medicare beneficiaries in addition to other people. And I mean, while this is a program that is overwhelmingly for the elderly and heavily

funded, it's also funded out of general tax revenues. I have the good fortune to pay a substantial amount of money every year for Medicare, but I think it's in Medicare's interest to get these beneficiaries in. But I feel I have been influenced by reading these comments, and particularly like the University of Michigan and some of the other places, that this is well intentioned, but I'm concerned that it might be counter-productive, that it will discourage the enrollment of elderly patients and create a barrier because if I can't get enough in, then maybe I'll just leave them out, and that would be worse.

Like I said, what bothers me the most as somebody who works in this field and spends a lot of time trying to interpret it, are these studies that just arbitrarily exclude people. And I think we need to -- I agree completely with what the intent here is, I agree completely with what Nancy said about trying to facilitate and incentivize the enrollment of patients, but I don't think we want to set up barriers to their enrollment.

DR. GARBER: Barbara.

DR. ALVING: I think CMS is really making a very clear direct statement and it's about the money. And it says if you go back to CMS to put out millions of dollars because a great new device has been found to be efficacious in Phase Three trials or whatever, you've got to really have that evidence before they're going to again commit public money to funding that in the Medicare beneficiaries. To me that makes just total sense. And I think we who don't live at CMS don't even begin to understand the tremendous political pressures that I would imagine might be on that Agency to pay for this device out of somebody's congressional district, or that device, or this new drug.

This is a very straightforward statement saying if you want us to pay for something, show us the evidence. And that's why NIH is working with them to make sure that if we're doing clinical trials, we agree up front that yes, this might involve a coverage decision, this is what our trial is going to look like, these are the questions we need to answer to help them make a coverage decision, and we look at the population enrolled. Now if you don't want to use

your trial for coverage decisions, you still need to, you know, have the appropriate population, but that's a different thing.
DR. GARBER: Okay. Deborah, and then we're going to vote, and when we vote this time, I think you should explain your answers, because there are a lot of nos, I sense, but nos that mean very different things. Deborah.
DR. ZARIN: So, I think what we're hearing is two different philosophies. One is that Medicare wants to pay for studies that will do a good job of informing Medicare coverage decisions, and that's on one end. And the other end is, Medicare wants to remove the barriers for Medicare beneficiaries to participate in clinical trials, whether or not those trials might help Medicare make decisions, because as we've heard, there might just be one Medicare beneficiary in a thousand-person trial.
Is there a way to sort of incentivize the system, as was mentioned earlier, whereas the coverage of the trial would go on as long as it met these other requirements for whatever Medicare beneficiaries happened to be in the trial, but if it had a high enough proportion of Medicare

beneficiaries that it was going to do a good job of informing coverage, that more things could be paid, or somehow there would be -- I mean, that sounds quite naive, but the question is, is there any way to give an incentive to have the kind of trial where, say, half or more of the participants are Medicare beneficiaries, but without penalizing those trials that only happen to enroll three such people?

DR. GARBER: Well, I think you're hearing here two different views of how the incentives embedded in this type of requirement would work. One view is that if you only cover the routine costs, if there's a plan to make sure this trial will shed light directly on whether it works in the Medicare population, that's going to promote more enrollment of Medicare beneficiaries in such trials.

The other view which we've heard expressed is that adding a requirement of this kind will deter entry of such people, and this is very common with nonlinear penalties and rewards. If you don't get over the hump, it's a big disincentive; if you're near the hump, it can be a huge positive incentive.

So it boils down to different views about what the state of the world is likely to be, and presumably that will differ for different trials, different interventions, different diseases, so on and so forth. But I think everybody who has spoken agrees there should be incentives to get more people in the trials. There is just not agreement about how this particular incentive would play out.

In any case, it is time to vote. And as I said, this time I'll ask people to explain how they voted very quickly. We are still not through Question 2, let me remind you. Alex.

DR. KRIST: Well, I'm not sure whether I'm voting yes or no based on what I'm going to say. I think it's a yes, that I support this, but I support the concept that the protocol needs a discussion of the enrollment process of Medicare beneficiaries, and not necessarily that there has to be an adequate number of Medicare beneficiaries to make generalizable statements, but there has to be a discussion of the enrollment process of Medicare beneficiaries.

MS. DAVENPORT-ENNIS: Well, and perhaps this can be a yes, but it would be very

conditional, Alan, with this comment. Medicare will develop an incentive process available to investigators of clinical trials to enroll seniors in trials, allow the guidance to allow reporting out on the number of seniors voluntarily enrolled to determine the Medicare population's benefit from the intervention. I indeed do understand the goal, but regretfully simply cannot support the language as written.

DR. AUBRY: I would vote no as currently written, but I think it needs to be in here revised. And to summarize what I said earlier, I think it should be revised to encourage or state that enrollment of Medicare-aged subjects is an explicit goal of the study, or give a rationale that the results will be generalizable to the Medicare population.

And I just as a point of information would like to mention that the original executive memorandum signed by President Clinton did include a statement that a clinical trials policy should ensure that the information gained from important clinical trials is used to inform Medicare coverage decisions. So I think it should be in but it should be revised.

DR. BERGER: I vote no. First of all, again, I don't think it adds anything at this point in time and I think that less is more with discussion.

Number two, in terms of whether this is going to encourage or act as a barrier, it has a much greater potential to act as a barrier to enrollment than it's going to serve as an encouragement. And since really what we're talking about here is whether CMS is going to cover routine expenses when patients are enrolled in clinical trials, by definition, you know, it's a circular discussion. To the extent that they enroll any elderly, they're going to be gaining some information. And if the study is well designed as described in Question 1, then you should understand the strength of that evidence in terms of its generalizability to the Medicare population.

DR. GRANT: I would also vote no in its current wording, although I believe that the intent of the statement is well taken. And although I couldn't write anything out, I think the intent being that one could draw appropriate interpretations to the Medicare population and the

study be designed in that fashion, but as written, I have to say no.

DR. HLATKY: I would vote no for this, mainly because of my concern that we want to ensure access to trials by patients of Medicare age. That being said, I think that when the sponsors come back to us for a coverage decision and there was no generalizable knowledge towards this population, we can ask the hard question as to whether we ought to approve such a thing, but I think that should be separate from covering the expenses of those few people who are enrolled in the study.

DR. JANJAN: I vote yes with the intention of the prior statement. I think the issue of barriers to care are addressed in number three, because all subpopulations are included, so the few patients that are enrolled are protected in statement three. But I agree that if Medicare is going to use public money to fund these studies, that it is an important thing for them to use this data subsequently for coverage decisions.

DR. LO: I would vote yes, but only if there is substantial revision. I guess the point I would like to see is that there be some

discussion in the protocol about how the expected or projected findings will be interpreted to have any bearing on the question of what works and doesn't work for Medicare patients.
DR. SCHWARTZ: I vote no for the reason that the three Marks gave. And I'm glad we have them all clustered together so I don't have to distinguish the names.
DR. SUGARMAN: I vote no for the same reasons, and I think the implications are unclear.
DR. BERGTHOLD: I vote yes with the modifications of language that both Alex and Wade suggested and what I put forward, and that is that we clarify the language so that it's really clear about, that we're not, it's not a quota, but that it is required that there will be a discussion of how Medicare beneficiaries were either included or excluded, and why those results can therefore be generalized.
And part of that comes from having sat on several of these panels where people did come forward with proposals for coverage with no beneficiaries, nobody over 65 in their studies. And we were then as a panel stuck with trying to figure out whether this should be covered for the

Medicare population. So I think this is tremendously important and I think it should remain in.

DR. RYAN: I vote no. I think it's scientifically inappropriate for Medicare to put together a policy that requires studies to ensure sufficient Medicare populations in order to statistically determine the Medicare population's benefit from the intervention. It will require the study to be powered differently and increase the costs with Medicare.

DR. ALVING: I vote yes.

DR. GOODMAN: I vote no, because the incentive to include Medicare patients is already embodied in the basis for the Medicare coverage decisions later, not for the expenditure of costs in a clinical trial. If people come forward later with evidence that includes no Medicare beneficiaries, that's their problem, and in fact Medicare has put no money into that by definition, because there were no participants in the clinical trials.

So I don't understand how this incentive works. This incentive has nothing to do with the incentive imposed by the evidentiary

standard later for the coverage decision, so I don't think it has any role here, even though I absolutely think that there should be no restriction on, and encouragement for more Medicare-eligible beneficiaries to be in trials.

DR. GROSS: I also vote no. I'll go with Sandy and the three Marks for the same reasons.

DR. WARTMAN: I also voted no. I agree with Steve's comments and I also agree with the points made about this being a potential disincentive for enrolling.

DR. ZARIN: I reluctantly vote no, because I don't think this will work. But I sympathize with Steve's sense that it's also very hard for the MedCACsMCAC to say no at the time of coverage decisions when you get the argument back that the absence of evidence doesn't mean the same thing as the evidence of no effect, et cetera. So I don't know where to put the incentive in, but I don't think it would work here.

DR. GARBER: Okay. Number five, there is an informational question. Do we want further discussion or are people ready to vote on that? That is, any standard required through a national

coverage determination using coverage with evidence development. Okay, vote. We can just do hands, okay. All who agree --
DR. ALVING: It needs a verb.
DR. GARBER: It does have a verb, it just doesn't have enough, and too much verbiage. Okay, so -- yes, Sandy.
DR. SCHWARTZ: We finally got something we can all agree on without discussion, and now we're criticizing the writing.
DR. GARBER: Okay. Verb of your choice, something like include, all in favor, raise your hands for yes.
(Show of hands.)
DR. GARBER: And then nos.
(Show of hands.)
DR. GARBER: One no. Wow. Question 3. We're getting into deemed now.
DR. SCHWARTZ: And I suggest you do what you did before, and see if there's any discussion for each one.
DR. GARBER: Yeah. Anybody want to discuss point one, which is reviewed, approved and funded by a federal agency? Jeremy wants to discuss that one. The second one is, the study is

supported by centers or cooperative groups that are funded by a federal agency that has reviewed and approved the study. Okay, we've got some discussion for that. The study is conducted under an IND application reviewed by the FDA, et cetera. Discussion of that?
(No response.)
Okay. Question four, the study has been required and reviewed by the FDA as a post-approval study. So we've got discussion of everything except number three. Let's open the discussion of the first one, the study is reviewed, approved and funded by a federal agency. Jeremy.
DR. SUGARMAN: While number one has intuitive appeal, there are lots of things that are funded by federal agencies and they have different review mechanisms. For instance, you could have a K award or an investigator development award for a brand new investigator being approved to do some kind of research that would be just sketchily described by, say the RFA or the program announcement, not have a thorough review, not assured that it meets good clinical practices, not have requisite experienced

personnel involved with knowing that the trial would be done in a sound way, and study sections may differ in their expertise.

With respect to clinical research, some federal agencies may not have particular clinical trials expertise in the review of protocols, and so I don't know that it necessarily supports the notion that just because something's been approved, that it's going to qualify as a good clinical study.

DR. GARBER: Steve Wartman.

DR. WARTMAN: Yeah. I would ask another question similar to the one you asked. For example, is the Department of Defense considered a federal agency? They fund studies, often through earmarks. Is that the kind of thing we're talking about here?

DR. PHURROUGH: DOD is currently covered under the clinical trials policy. CDC, NIH, AHRQ, VA and DOD are currently listed as deeming federal agencies. We are proposing to expand that to other federal agencies.

DR. GARBER: Deborah.

DR. ZARIN: I think the implicit question was by adding words reviewed, approved

and funded by a federal agency. Are we making a distinction between things like we just heard where they're funded by a federal agency but say through a congressional earmark or funded through a K award, versus an RO-1, where the specific study is scientifically reviewed? Is the intent to make that distinction?

DR. PHURROUGH: Yes.

DR. ZARIN: Then I guess what we're hearing is concern about those things. Would you say that a study being done through a K award at NIH as part of a career development grant but the particulars of the study were never reviewed by NIH, would you say that shouldn't be deemed or should be? I mean, is it your intention through this language to have that be deemed or not? Because if we understand the intention, I guess we could vote on it.

DR. PHURROUGH: The intention was that any -- deeming occurs through funding if that funding is based upon a scientific review of the protocol.

DR. ZARIN: So, I think we should say that, meaning funded by federal agency in the context of review of the specific study protocol,

something with those words in it.
DR. PHURROUGH: So, study reviewed and approved doesn't meet that?
DR. ZARIN: No, because what we're hearing about is more broad research plans, say, and within that broad plan someone does a specific study where the details of that study were never reviewed by the funding agency. Or Congress says to DOD, fund a study of breast cancer in Maryland, or something.
SPEAKER: How often do you think that's going to be a problem? I mean, we're going to be arguing in a few minutes that, you know, we can't anticipate everything that a doctor does in practice and things like this. And I think that, you know, for CMS or Medicare to work, there has to be some level, you know, some threshold level. I feel pretty comfortable with approval and funding by a federal agency. Is it perfect? No. The NIH isn't perfect either, but I don't think -- we're going to have a lot of problems here. I don't think this is where the issues are.
DR. ZARIN: Well, then, I would just say funded, I mean, that's even less -- if that's your intent, I would just use the word funded.

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DR. GARBER: Yeah. Mark.
DR. HLATKY: I think the original language explicitly named the federal agencies, and I wasn't really sure as to why you wanted to change it, not that I totally object. But I mean, if the Weather Bureau wanted to do a study or something, I didn't understand why we needed to change the original language.
DR. PHURROUGH: Because there are other federal agencies that fund health care studies that we may want to support.
DR. HLATKY: Couldn't we do that on a case-by-case basis to, you know, say we also added this --
DR. GARBER: That defeats the purpose of deeming.
DR. PHURROUGH: We could only do that through a national coverage determination. We'd have to reopen this decision, this panel would meet again, go through this process again to add another federal agency.
DR. SCHWARTZ: I'm not so concerned about the NIH or the VA, or the other ones that were previously on the list. I'm just not quite sure what the additional ones were.

DR. GARBER: But there are funding mechanisms where you never get a review of the kind of study that we are talking about. One that hasn't been mentioned is a NES-DIR, which could be used for very early developmental types of projects, which most people would say means it never underwent a thorough review, and you're relying primarily on the IRB review then, to be the main judge of the scientific quality. And that just has to do with the funding mechanism. This does not get into funding mechanisms, and even the existing policy only names the agencies, not the funding mechanisms.

As I understand deeming, though, Steve, the purpose is so that you don't have to assume there's another layer of review by CMS, so it means it obliges CMS to pay no matter what the quality of the study is, whether it meets Medicare's need or not; is that correct?

DR. PHURROUGH: That's correct.

DR. GARBER: Okay. Do people feel comfortable just voting with their hands, or do you want to explain your reasons? Okay. We'll vote with our hands. So yes means you agree with studies reviewed, approved and funded by a federal

agency, unspecified is sufficient.
(Show of hands.)
DR. GARBER: The nos.
(Show of hands.)
DR. GARBER: Okay. Next, the study is supported by centers or cooperative groups that are funded by a federal agency that has reviewed and approved this study.
DR. PHURROUGH: Can I just clarify the wording here? I think we -- we did not intend to, at least I don't think we intended to say that the supporting agency had to review all the studies. The supported center or group had to do the scientific review of the study. So if that clarifies what many were going to say, it ought to read, the study has been reviewed and approved by centers or cooperative groups that are funded by a federal agency, or something like that.
DR. GARBER: Yes, Cary.
DR. GROSS: I think this is a good time to bring up the idea of the IND-exempt studies. And I know we're trying to keep things global, but it would be helpful to think through the idea of cancer centers, NCI-designated comprehensive or clinical cancer centers. And some of the speakers

earlier raised the question of what about IND-exempt studies at these sites. So I'm wondering if we could modify the language here so that an IND-exempt study would otherwise be able to be approved, because this modification that's lower down in the list where IND-exempt studies seem to be being deleted is very concerning.

DR. GARBER: Deborah, and then Steve Goodman, and then Bernie.

DR. ZARIN: I guess it doesn't seem relevant to me. What this would say is that any study being done within a federal, I assume this really means research center, would be considered deemed, whether it happens to be IND-exempt or whether it's a surgical study, so the FDA doesn't come into play at all. I would just not confuse it by even naming IND-exempt.

DR. GROSS: Oh, no, but I'm saying if we want that specific type of non-IND study to be deemed, this language would need to be changed. So it doesn't say supported by centers, it would be conducted at centers. I'm just trying to view this through the prism of the interest of that type of study being able to continue. I'm not saying it's the same thing.

DR. PHURROUGH: Well, if you want to continue the IND-exempt, you'll just vote no on Question 4.

DR. ZARIN: I don't think IND-exempt status has to do with who is funding the study either. I mean, it could be funded by industry or an individual investigator, or by a cancer center or wherever.

DR. KRIST: Doesn't number 4 say that for IND-exempt studies, you would follow the other processes in place, so if you said yes to 3.1 and 3.2, then that would mean the IND-exempt studies would follow the yes, they would be deemed because they're deemed, so 4 just means that the IND-exempt studies would have to follow the same rules as every other study.

DR. GROSS: That's what I'm saying, that if you look now at 3.2, many IND-exempt studies that are conducted in cancer centers, if they're not sponsored by the center -- that's how I read it -- they're not sponsored by the center or cooperative group, or by the federal agency, it looks like they would not be deemed, so what if it's something that is funded out of institutional funds or even a nonfunded study?

DR. GARBER: Bernie.
DR. LO: It strikes me that the point of deeming is that CMS just says someone else has reviewed this so we don't have to do it. So it strikes me that the operative issue here should be, has the center or cooperative group actually reviewed that study individually. The federal agency just supported the entire center or group, but we're assuming, I think, aren't we, that the center or group has reviewed that protocol. And that makes it different than Question 4, where my understanding is in an IND exemption, the investigator just says I'm exempt because I meet all the criteria and no one need review it.
DR. GARBER: Except the IRB.
DR. PHURROUGH: And perhaps I need to clarify too, from Cary's comment, that this 3.2 doesn't require the study to be funded by the cooperative center. It defines the cooperative center as one who is funded or supported by another federal agency, and that cooperative center has reviewed and approved a trial. So the trial itself does not have to, the money does not have to flow from the federal agency into the cooperative center into the trial.

DR. GROSS: So the word supported by does not mean funded by. The study is conducted and approved by the center.

DR. PHURROUGH: The wording ought to be similar to the first one, the study is reviewed and approved by a center or cooperative group that is funded by a federal agency.

DR. GARBER: Steve Goodman, did you have your hand up?

DR. GOODMAN: Yeah, just a question, but I think it's obvious from looking at the other questions. This is simply, trials that are not judged deemed by this process, subsequent questions deal with, could they be deemed by other processes as well. So this is not an exclusive list. They get in, but we will discuss other safety nets for the others, right?

DR. GARBER: Wade?

DR. AUBRY: It's been said.

DR. GARBER: Okay. Can we vote on this? Raise your hands for yes, as revised.

(Show of hands.)

DR. GARBER: Any nos?

(Negative response.)

DR. GARBER: The third one we can just

vote on without discussion; has anybody changed their minds about that? Okay.

DR. ZARIN: Wait.

DR. GARBER: Okay, Deborah?

DR. ZARIN: My understanding is, again, most IND studies are not reviewed by the FDA, or not necessarily before they're conducted.

DR. GARBER: Yes, so this only applies to those that are reviewed by the FDA.

DR. ZARIN: Well, you have no way of knowing, so I would just say a study conducted under an IND and you just have to go with it, I think. In other words, the FDA has the right to say within a certain time frame that you can't do it, but they could decide not to review it and you could proceed, but the public, you're not going to know whether they happened to review it and decided you can proceed or they just didn't think it was worthy of review at this time.

DR. PHURROUGH: We recognize that as an issue with IND trials, that the level of review varies among INDs, it's a policy that has been in place now since the beginning of clinical trial policy. We are not uncomfortable with it as it is.

DR. ZARIN: I was just suggesting taking the phrase out, reviewed by the FDA; I think it's redundant.

DR. BERGER: I think the presumption is from a responsibility perspective, if the FDA doesn't make any comment, it's presumed that they are giving you a tacit endorsement that there's no deficiencies.

DR. ZARIN: Right.

DR. GARBER: So that means leave it in, right?

DR. BERGER: Yeah.

DR. ALVING: We could make that whole phrase much simpler. Couldn't we just say the study is conducted under an investigational new drug application IND, period? I mean, that assumes that's the FDA, and it's redundant to say if no deficiencies are identified by the FDA, because otherwise they wouldn't get the IND.

DR. WARTMAN: That's true, but I'm told by people who work at the FDA that it's not the same as an NIH scientific review process.

DR. ALVING: Well, I know, but generally the IND goes on top of the other reviews, so that is one more layer.

DR. GARBER: Can we vote with just hands? Okay. All in favor of yes on number three.

(Show of hands.)

DR. GARBER: Okay. Any nos?

(No response.)

DR. SCHWARTZ: And Bernie votes yes. He told me to vote yes on the next two.

DR. GARBER: Okay. Number four, three was some discussion. The study has been required and reviewed by the FDA as a post-approval study. Wade.

DR. AUBRY: My question maybe is just one of clarification. Does this mean that it's a study that has a protocol and that it's been required, reviewed and approved? Number four is the only one of these four points that didn't use the word approved. And I'm aware that for some FDA-approved products, that there will be a post-marketing study required but that the study is never done, and sometimes the labeling is changed on the basis of that. So are we talking about one that actually has a protocol that has actually been approved?

DR. PHURROUGH: Yes.

DR. AUBRY: Then I think that should be explicit.
DR. GARBER: Nancy.
MS. DAVENPORT-ENNIS: And I had a question. As I'm reading this and I see post-approval study, and my question is, are we referring to an IND-exempt trial here? And if so, it's my understanding that they may or may not have been reviewed by the FDA but they would have been reviewed by the IRB board in the institution where the trial is being convened, so is post-approval there referring to IND-exempt?
DR. PHURROUGH: This is a specific terminology that does not mean any trial is covered that's created after approval, it's a specific study required by FDA as a condition of approval.
DR. GARBER: Okay. All those in favor of number four, raise your hands.
(Show of hands.)
DR. GARBER: Nos, any nos?
(No response.)
DR. GARBER: Now we're on to Question 4, on the top of page five. Since the self-certification did not occur and CMS does not

intend to include this in the revised policy, CMS is proposing to require IND-exempt studies to follow the other processes allowed under the revised policy. Does the panel agree? Yes, Steve, go ahead.
DR. PHURROUGH: Unfortunately we left out a vote. We have misnumbered these. This is the IND deletion.
(Dr. Phurrough and Dr. Garber conferred off the record.)
DR. GARBER: So this is going to be slightly confusing. What's listed as Question 4 is actually Question 5. Question 4 is this item in quotes right under the bold-faced question directly under Question 3 which states, the drug under study is exempt from having an IND under 21 CFR 312.2(b)91), and the question is, do you agree. This is page four, look under Question 3. It says in bold face, Question 4, the current policy listed a fourth temporary option, et cetera, et cetera, so should it be deemed to meet the current standards if the drug under study is exempt from having an IND under 21 CFR, et cetera, et cetera? So this should be like number five under Question 3 basically? This is

above the text that occurs in Question 4. This is the one that was distributed today, I'm sorry, not the one that was in your --
DR. PHURROUGH: You will have to go away from your ballot sheet, it's not on your ballot sheet. Pull out from your handout the list of all questions we started with, go to page four of that, and I apologize, we just left that off the ballot sheet completely.
DR. ZARIN: Alan, I don't see a question in this.
DR. GARBER: The question is should this qualify as deemed, just as in the others in Question 3. The drug under study is exempt from having an IND, it's the IND-exempt question, okay? So you might think of it as like the fifth subquestion under Question 3. Deborah, did you want to make a comment?
DR. ZARIN: It seems to me that that's the same as what you're now calling Question 5, but I would -- either way, I would say that, again, the initial panel deemed it in the interim while it was in theory creating a self-certification process.
DR. GARBER: Yeah, you're right. So

why don't we discuss it now, since we're there? Question 5.

DR. ZARIN: I would argue that IND-exempt implies nothing about scientific review. It might have been, you know, it might be NIH-funded and get a lot of scientific review; it might be someone doing it in their garage who made the study up and is just doing it for the fun of doing it; it might be occurring within a drug company after their review. So I would say it's not an appropriate basis for deeming, because we know no more about the scientific quality of that study than we would know about the scientific quality of any study that had no reviews, say a study of two different surgical procedures or something like that.

DR. GARBER: Other discussion? Yes, Cary?

DR. GROSS: So that being said, if we changed, or Medicare changes, CMS changes to remove the deemed status from the IND-exempt studies, this is why in my mind this and the previous questions are very, very closely linked. The only way an IND-exempt study would then be funded is it meets one of these criteria in

Question 3. So I'm just asking the panel to think through before voting yes or no on this, to think what is in the Question 3. How many studies are we going to say are now non-deemed or will not be paid for as a result of this decision? I'm concerned it might be a ton. I just don't know the answer.

DR. WARTMAN: I would like to pick up on that point because I think that's where we need clarification, because if we're going to put these type of studies under those same hoops as the others, since the majority of them as I understand them are investigator-initiated, funding is very scarce and it would have I think a very chilling effect on these, we'd have to worry about their continued life.

And you know, I would also raise the issue, we know that IRB approval is out there for these, which I think is important. Granted, some IRBs can be different in terms of how they review scientific merit and things of this sort, but I think if we put these kind of studies which are largely investigator-initiated through those hoops, we're going to have a very chilling effect on this kind of study.

DR. KRIST: One of the ways I was reading this, though, is Question 4 is just if you're IND-exempt, does that mean you're a deemed status. And then we're going to get to Question 6, which is okay, for nondeemed studies, should there be another process for determining whether they're covered or not. And we might say IRB approval is justification, I'm not arguing for that, but so whatever, if we said yes to 4, that it would have to go through the normal process that would apply to step three, deemed or not deemed, and then Question 6, whatever we decide with that as well.

DR. WARTMAN: Well, I think your point is interesting. You know, you've just taken us out of the linear thinking that we've had as a group, so it's going to take a minute or two to digest that.

DR. GARBER: Deborah.

DR. ZARIN: I would say that if you want to deem IND-exempt studies, then we should scrap pretty much everything we talked about and say that Medicare will pay for any study that has IRB approval and perhaps that occurs at an institution that comes under the common rule, so

it either occurs at an institution that receives federal funding or occurs under the FDA version of the common rule. In other words, there's no point in specifying all those things before that has to do with proxies for scientific merit, and then suddenly saying this whole category where we know nothing about the scientific merit, we're going to deem those also just because they might be good.
DR. GARBER: Okay, thank you. Mike, did you have your hand up?
DR. RYAN: Yeah. I think we're drawing a conclusion here that all IND-exempt studies are of low scientific merit and they're done in garages, and that's just not the case. I mean, the clinical study that is exempt from the requirements of an IND is not exempt from regulatory oversight, and the FDA has clear criteria about IND exemption. You still have to go through IRB review in most institutions, informed consent, post-marketing safety, peer review, and so we certainly have that level of it. It's important to recognize that there's a large number or large body here; the estimates are that it could be upwards of almost half of some of the studies and some oncology studies are IND-exempt.

If you walk away from that, that's a huge body of research, and you have to understand what impact that would have on research in the United States.
DR. GARBER: Steve.
DR. PHURROUGH: But let me reinforce what Deb said. The difficulty is, why should we as an agency attach special status to IND-exempts, why shouldn't it be any diagnostic that's approved by an IRB, or any device or any whatever? What is different about IND-exempt trials over any other trial that doesn't get approved by a federal agency? Why in fact should we give them special status? Now we've heard this thing about these cancer patients, and we as cancer researchers always make sure the trial is good. Well, every researcher would tell you that. So why should we attach special dispensation to IND-exempt trials versus any other kind of trial that isn't deemed under 3?
DR. GARBER: Jeremy, then Bernie.
DR. SUGARMAN: I just think we have to be very careful to recognize the limitations of the IRB system in reviewing scientific merit. This has been referred to several times. IRB review and oversight is going to be necessary but

certainly not sufficient to look at questions of scientific merit beyond data and safety monitoring. Under federal regulations, they're not constituted to having the necessary expertise to review all of the clinical trial methodology, in addition to the burden question which was raised.

DR. GARBER: Bernie.

DR. LO: I went back and looked at the text of 21 CFR 312, and my understanding from reading it is that you can only get an IND exemption if you're studying a drug product that's already lawfully marketed in the U.S. So the thing you're administering has already passed FDA approval. Then it has to be conducted in compliance with IRB and informed consent but also, it cannot involve a change in route of administration or dosage, or in a patient population that significantly increases risk. Now that last criterion, my understanding is that it is a self-check by the investigator. If the investigator says yes, I'm using an FDA-approved drug, yes, I've got IRB approval, and no, I don't think I'm administering this drug in a way that's going to increase risk,

and no one else needs to oversee that judgment other than the IRB.

But these are -- these aren't things that people are doing in their garages. My sense is they're drugs that are being used anyway. So I think that's the layer, if you're going to argue for a layer of safety for deeming this group, it's got to be with the fact that these are FDA-approved drugs.

DR. GARBER: Nancy.

MS. DAVENPORT-ENNIS: And I think to my colleague's point, I have to agree with that. And while I know that I have not talked about patients today nor cited any specific patient cases, IND-exempt studies are often indeed those studies that may even have more stringent IRB oversight as they're being implemented within the scientific community, and they are often offered in research hospitals across a broad spectrum of diseases. So from a scientific and medical perspective, indeed, I do think they need to be deemed. I do think that they are certainly having a level of scientific oversight.

And I certainly concur that based on personal experience with an IND-exempt trial that

indeed was the only option in the United States for my family member, that indeed, it was very well managed in a research institution and it was held to a very high standard, and the results indeed are reported out and they are published. And I think the committee just needs to be mindful that IND trials cut across many diseases, not just cancer.

DR. GARBER: So, Mark?

DR. GRANT: Just a question of clarification here. Really, we're not talking about whether to deem IND status according to this question, or to deem IND trials.

DR. GARBER: Yeah. Actually, if you go back to question, what's really Question 4 printed on your list -- we've gone back and forth on this here, but you're right, Mark. The voting question is not about deeming. The original voting question is what you see here as Question 4, not that CFR line above. And if you think it should be deemed, then you should say no to this Question 4. And what this question is asking, should it be required to follow the other processes allowed under the revised policy which we have discussed up until now? If the answer to

that is yes, then you vote yes. And if you think it should automatically be deemed because IND-exempt does not need to meet any of these other standards, then you should vote no. So this is the actual printed voting question that you have in your sheet with the number 4. Barbara?

DR. ALVING: One last question. What precedent, in other words, what has been going on during these past five years of clinical trials policy? What has CMS been doing, do we know, what has been the general practice?

DR. GARBER: Well, Steve is not here at the moment.

DR. ALVING: I know, but there are some other people in the room from CMS. I wondered if they would know in general what's been going on.

DR. GARBER: Wade, did you want to address that?

DR. AUBRY: Let me sort of add to that question. I would suspect that being a former Medicare Part B medical director that a number of these IND-exempt trials are covered under usual care just because they're FDA-approved drugs, and you know, it may not always be clear to the carrier that it's part of a clinical trial, unless

the provider explicitly looks for that.
DR. GARBER: And they have no incentive to do that.
DR. AUBRY: Yeah. So a lot of this would be, you know, like in cancer chemotherapy, like testing a different combination of regimen or something, that might just be viewed as, you know, just regular reasonable and necessary services of using FDA drugs. So that's a question I would have for Steve when he comes back.
One last point. In order to determine what the impact is, you would have to take that into consideration in terms of what, you know, what's being provided under the current clinical trials policy in order to really understand what's going on.
DR. GOODMAN: I'll hold my question until Steve can answer the last question, so you might want to repeat it.
DR. PHURROUGH: So what am I answering?
DR. GARBER: What you're being asked about is what is the current Medicare or CMS practice with regard to the IND-exempt studies? Do these get reimbursed typically?
DR. PHURROUGH: Yes.

DR. AUBRY: Under the policy or under usual care?
DR. PHURROUGH: Well, they get reimbursed based upon the code that's submitted on the claim. If you submit the claim with the appropriate modifier that says they're in a clinical trial, they will get reimbursed under the clinical trial policy. If -- it comes out of the same fund, but we only know that it's in a trial if the appropriate modifier is added.
DR. ALVING: Are you satisfied with what has been happening now?
DR. PHURROUGH: No. There are some trials with some drugs, particularly outside the cancer world, that we think are inappropriate, that we have funded, and we don't have much ability to not fund them since we say we'll pay for them.
DR. RYAN: Are there defined criteria that you can look at in those studies so that we don't throw the baby out with the bath water here?
DR. GARBER: Well, this refers to the criteria we've just spent the rest of this meeting discussing. If you think that those are appropriate criteria, then you would say yes for

this, unless you think there's something different about the IND-exempt trials. Steve, are you ready to ask your question?

DR. GOODMAN: Yeah. I guess this all just comes down to what's the minimum acceptable level of scientific review, right? Because the prior criteria guaranteed some level of additional scrutiny in addition to an IRB, right? So all this is saying is that if for some reason, which is a lot of trials, no other eyes have been laid on it except for the IRB's, would you fund the expenses? Is that really what this is all about?

DR. BERGER: Yes, for drugs that are already approved at the same dosage and in populations where you're not going to put patients at extra risk.

(Inaudible colloquy between panelists.)

DR. GOODMAN: So we don't know. In theory, nobody is at profoundly excess risk, but in theory the study might not have a tremendous amount of scientific value. So if you set the bar relatively low, which is what you're doing when you say IRB approval, because they don't reliably look at the science, then you're going to encounter some of the problems you have now.

You're going to fund a number of studies, or maybe it's a lot, I don't know, that may not have a tremendous amount of scientific value even though they don't put patients at tremendous risk. If you apply a much, much higher standard, which is to extend them through these other routes, which I actually don't even know how you would do that, I mean, if it's IND-exempt, you know, exactly how would you submit it to these other routes? You can't get federal funding, you wouldn't submit it to the FDA, that might not be appropriate. So wouldn't that, you know, what's the balance here in terms of funding suboptimal studies versus defunding a huge number of valuable studies, in some ways the life blood of many institutions and certainly younger investigators, if they can't depend on this funding source. Although to the extent they could get it funded under usual care, maybe it's not as bad as I think.

So I guess Question 6 is, as Alex says, is can we construct any other filter for these studies? So if neither of those two options are acceptable, leaving it to the IRB or forcing it through this probably inappropriate filter, is

there any other way we can construct a system?
DR. BERGER: I have a suggestion. What I would suggest, and I don't know if this works for everybody, but the question is, you're not going to get a perfect policy here. Either you're going to underfund studies that you think may be of value, or you may fund some studies you don't think are of value. And so what I would suggest is a modification of the second bullet to say that the study is an IND-exempt study and it has been reviewed and approved by centers or cooperative groups that currently receive funding by a federal agency.
DR. ALVING: But that's already covered.
DR. GARBER: Yeah, we already voted on that, and the majority voted yes. Bernie's had his hand up for a long time.
DR. LO: Could I ask a clarification from Steve? You said under current CMS policy, there have been some problems with studies with IND-exempt agents. Can you say a little bit of what the problems were, was it excess risk or was it sort of lack of scientific merit to the studies?

DR. PHURROUGH: Lack of scientific merit of the studies.
DR. LO: But no concerns about risk to the participants?
DR. PHURROUGH: One of the studies was with a drug that had significant side effects.
DR. GARBER: Nora.
DR. JANJAN: As a radiation oncologist, I can tell you that a lot of what we do is not funded, is IND-exempt. Because what happens is the drug gets out and then we combine it with radiation therapy. And oftentimes it's very difficult to get pharmaceutical support for those trials. And we just, without an IND-exempt status, could not do chemoradiation trials. And a new device comes out, same kind of issue. The bottom line is, in various specialties this would make a huge impact on outcomes. There are TOG mechanisms, other mechanisms, but they can only do so many radiation trials. So it becomes very difficult for us in my specialty to make advancements without the IND exemption available.
DR. GARBER: Nora, are your studies ever reviewed by a federally funded cancer center or are they done without that kind of review?

DR. JANJAN: Well, they're done at federally, across the country most of them are done at major cancer centers because that's where the radiation therapy occurs.

DR. GARBER: So if you were to say yes on this, this would not preclude conducting those studies with Medicare funding, because the majority of people said that in the answer to the previous Question 3, that that would get them in.

DR. JANJAN: I guess I'm okay. Well, the seven factors, then, are the ones that we're talking about under processes and the revised policy then; is that correct?

DR. GARBER: Well, under the big Question 3, we just discussed about whether studies should continue to be deemed, so your studies would still be deemed if they're conducted under the auspices of a cancer center.

DR. JANJAN: Yes.

DR. GARBER: So if you were to say yes to this, that IND-exempt studies have to follow the other processes under the revised policy, your studies would still be able to be conducted.

DR. JANJAN: Okay. Well, then, that's fine. Thank you.

DR. BERGER: By calling this out separately, that still applies. (Speaking off microphone.)
DR. GARBER: Deborah actually stated exactly what this means, I think, at the outset. And that is that if you were to vote no for this, it would say that you could ignore all the criteria we've been discussing all day if it was an IND-exempt study. If you vote yes, it means that you need to meet the criteria, including the deeming criteria, in order to be qualified for funding -- for reimbursement rather. Mike?
DR. RYAN: Yeah. There's been a lot of discussion about NCCN and cancer centers. It's important to recognize that while those centers are incredibly important, the vast majority of cancer care in the United States is really provided in a physician office setting. And I can tell you as a sponsor of a large number of these types of trials, it is difficult to find enough sites to conduct these trials in the United States. We're starting to do more of these off site because we simply can't find enough patient capacity to run the kind of trials that you need to run. And if you limit this just to NCCN cancer

centers, that's going to be problematic.
DR. GARBER: Are we ready to vote? So now, let me just clarify. We're actually going to vote on the Question 4 that's in your written ballots, we're not going to cross off the stuff that's in the text, okay? Question 4 is, since the self-certification did not occur and CMS does not intend to include this in their revised policy, CMS is proposing to require IND-exempt studies to follow the other processes allowed under the revised policy. Does the panel agree? All the yeses, raise your hands.
(Show of hands.)
DR. RYAN: So if you say yes, you're saying that IND exemption by itself is no longer a criteria for deemed appropriate, right?
DR. GARBER: You have to meet the other criteria, yeah. It is saying that being IND-exempt is not enough to be deemed. Get your hands up high if you're voting yes, please.
(Show of hands.)
DR. GARBER: Okay. The nos?
(Show of hands.)
DR. ALVING: How about not voting? It needs to be fleshed out, discussed, and developed

more with more background.
DR. GARBER: Okay. Abstentions.
(Show of hands.)
DR. ALVING: Well, I think it's a very important decision and that's why it's hard to, there has to be more of a middle ground, maybe a chance for appeal if you go with the yes, which sounds very good, but yet some opportunity for appeal for some study that doesn't meet those criteria, or something.
DR. GARBER: Well, we are going to be -- Question 6 is going to be getting at some of these questions in a more general context than IND-exempt studies.
Question 5. Should CMS consider studies that have been approved by but not funded by a federal agency as deemed? And by this, I think the text made clear before that it's something that got approved by the NIH, for example, but did not reach the fundable level, and similarly for other federal agencies. Bernie?
DR. LO: Yeah, could you say it a little more, what do you mean by approved? Because some stuff is approvable, but you know, it has a very, very high priority score, like 200.

DR. GARBER: That's still approved.
DR. LO: Right, but that usually means it's not very good.
DR. GARBER: Right.
DR. LO: And you could have 126 and just miss by a point.
DR. GARBER: Yeah. It could be a 245.
DR. ALVING: That needs a definition as well. Approved needs a definition.
DR. GARBER: Yeah, that's correct. It includes some stuff that just barely misses and some stuff that wasn't close.
DR. WARTMAN: Yeah, I think that Bernie's point is exceedingly well taken, and if we indeed decide to vote favorably on this, we have to have a quartile or percentile or something like that included that is some type of margin of safety. Because truly, there are studies that are approved but whose ratings are just abysmal, and I think that would be a great concern.
DR. GARBER: Yeah. Deborah.
DR. ZARIN: There's also oversight requirements that come with federal funding, but I wouldn't think would carry with federal nonfunding. So for example, if NIH funds a study,

you have reporting requirements, GSND requirements, presumably you don't change the protocol dramatically from what was funded, whereas just having a history of having had a protocol approved, it seems like it leaves a lot of leeway between that and what actually occurs.
DR. GARBER: Nancy.
MS. DAVENPORT-ENNIS: Yes. The comment that I'd like to make about this question is that maybe we also need to further define a time period for this approval, because my concern is that we could have a study that has been approved, it's not funded, it becomes deemed. Three years later it's still not funded and the focus of the area of study could have changed, there could have been significant changes around the subject.
DR. GARBER: Yeah. I think most people who have been in an NIH study section know that approved doesn't mean a great deal. Okay. So, are we ready to vote on this? Yes means that if it's been approved but not funded, that it should be considered deemed. All the yeses, raise your hands.
(Show of hands.)
DR. GARBER: Okay. No?

(Show of hands.)
DR. GARBER: Okay. Now we go to Question 6. Now you do have cards, we don't have to use them unless you really want to, you're going to write down your numbers, but people in the audience might be interested. So anyway, let's have a discussion of these, all four together, and then the least desirable is one, most desirable is five, and these are additional methods to approve studies for Medicare coverage.
DR. PHURROUGH: These are not necessarily ones that we are recommending. We have had a fair amount of public comment around this particular policy, so these are various options that have been discussed and suggested, as was the last question. And so what we're interested in is, one, is it a good idea, and two, is it doable? And since most of you have fit into one or all of these categories, you can help us determine whether it's doable or not. The first one obviously doesn't fit into that category. The first one, the CED one is just to say, again, it's just to codify that if we require a trial through a national coverage determination, then that trial is approved and doesn't need any other approval

authority other than our NCD.
DR. GARBER: Yeah, Mark?
DR. GRANT: Just actually a question about number one, then. For trial or research required through CED, then, this doesn't say anything about a protocol being approved to do a trial, CED, I mean --
DR. GARBER: Well, CMS is involved in approving those studies.
DR. GRANT: But is that protocol approved by CMS?
DR. PHURROUGH: Yes. For CED projects we specify specific trials. On occasion we will specify a specific NIH trial, for instance, or in some cases we will go outside federal agencies and review the protocols ourselves and approve them.
DR. GARBER: Steve Goodman.
DR. GOODMAN: This is to some extent going back to the previous question, but most surgical trials wouldn't fall into any of the categories that we talked about in terms of approvability. They wouldn't go through the FDA, it wouldn't be funded necessarily through the NIH -- well, some could be, but many, many that I've done within institutions would not be funded

through the NIH, they were self-funded or they were funded in other ways. Does this mean, and I'm just picking this particular class, which is a very, very large class, actually it should be a lot larger than it is, and that maybe is one of the problems. Does that mean that all surgical research that's not funded by the NIH which doesn't go through any other filters would go through this in the United States?

DR. PHURROUGH: Go through?

DR. GOODMAN: Go through one of these other approval processes in order to be deemed if we don't --

DR. PHURROUGH: Right now there is not other process, so you have to -- we have to develop it, you need to --

DR. GOODMAN: So if we don't accept IRB approval, then -- if that's going to be accepted, then all of that research in addition to everything else would have to flow through one of these in order to be deemed, right?

DR. PHURROUGH: Yes.

DR. GARBER: Is there any discussion of the first one, coverage with evidence development?

That seems pretty straightforward. I don't think you need to flash your numbers. Why don't we just go on to number two. Okay, flash your numbers, and this is number one that we're rating right now.

(Panelists displayed numeric ratings.)

MR. GARBER: We're not tallying these now, because you also will put them in the written ballots.

Okay. The second one, establish a federal inter-agency panel to review study protocols. I think we might have a little discussion, although I guess the vote is the discussion in some cases. Steve, let me just ask a question for clarification here. This could be for any number of purposes. For example, having a panel for just tough cases that sort of slip through the cracks where you thought there was a lot of merit, potential merit to a study but it didn't meet any of the other criteria, or is it something to be used routinely?

DR. PHURROUGH: It would be difficult for us to say we have a review process for trials that don't meet the current policy and then pick and choose those trials that we review. It would

have to be fairly broad, if you have a trial that doesn't meet the policy and you want us to review it, then send it up. The difficulty, first of all, is someone has to fund the federal agency, and then someone has to fund the work group within CMS that would receive, collate, prepare, everything that happens at NIH to get their approval process done.

DR. GARBER: Wade, then Steve Wartman, then Alex and Steve Goodman, and then Sandy.

DR. AUBRY: I have a question. Isn't there a precedent for this in lung volume reduction surgery? And also, I wondered how this is different than Number 4. Number 4, I think, my understanding is there was some meetings between CMS and FDA to look at those kinds of issues, so it's already ongoing.

DR. PHURROUGH: Well, LVRS was an early CED, it was not a federal panel kind of issue. We really have not, there was a discussion from the beginning of the clinical trial policy in 2000 as to whether this ought to be an option, never implemented because of the resource-sensitive issues. This could be considered a federal panel, an advisory panel, we could convene the MedCAC on a

monthly basis to review protocols.
(Laughter.)
DR. GARBER: Yeah, we just don't get to Baltimore enough. Steve?
DR. WARTMAN: I think before we make light of this particular recommendation, I want to speak in favor of it. I think, and I alluded to this earlier and I think some of us have also thought about this, which is the need for some type of communication amongst federal agencies which notoriously have poor communication. You know, regulations and definitions and all kinds of things tend to differ, and it's necessary to some extent for the programmatic elements to communicate with the funding elements in these sorts of things.
I think we have a dysfunctional, some dysfunctionality in that realm when you look at the broad array of federal agencies and what they cannot do together. Yet they all impact on each other, and on patients ultimately in various ways. So there has to be some type of rationalization of this. Now this may not be the right vehicle to do it, it may be too costly, it may be expensive, it may be logistically tough, but I just want to make

the case that some sort of rationalization or harmonization among these agencies, particularly between the program side and the funding side, I think is a good idea.

DR. GARBER: Alex.

DR. KRIST: I had more of a clarification for this question, because there's two ways to look at each of these. One would be in the ideal world what would we do, and then the other one is it feasible and can we do it. As we're voting on this, what do you want us to be thinking about?

DR. PHURROUGH: Well, I think you need to recommend both to us. First of all, is it a good idea, would it work. If resources were not an issue, would this be a good way to manage the process? And then, assuming that resources are an issue, is it actually doable? You may decide you can't determine whether it's doable or not, because you don't understand the resource stream, but we would like the recommendation to have some grounding in whether the resources are available to do it or not.

DR. GARBER: Steve Goodman.

DR. GOODMAN: I still confess to being

very confused. The problem seems to be here a concern about funding too many or some number of trials that are of minimal scientific value, so it's mainly, it's a resource question. Theoretically the patients are not being put at excess, you know, tremendous risk, although any risk for no scientific value is concerning. And here we're talking about an enormous investment of resources, resources that we're trying to avoid being spent to solve that problem of expending too much resources in that domain, at the risk of putting a chill on a huge chunk of medical research.

I don't understand. I mean, this could be 10,000 trials. I mean, what's the product that we're talking about to save the money on some subset, I don't want to say it's negligible, but you are paying a sense of premium for not having that extra layer of scientific review by funding some number of trials that don't provide that much scientific value. But how much are we willing to spend? Is the amount we're going to spend on these fixes, you know, astronomically more both in terms of resources and in terms of the consequences for the medical research community?

Is that commensurate with the problem that we're trying to solve?

DR. PHURROUGH: Well, currently these trials are not funded. We're talking about something over and above what's currently funded. There is no mechanism to fund these trials that you're talking about, surgical trials and so forth, currently.

DR. GOODMAN: I misunderstood what you said before. You said that IND-exempt trials --

DR. PHURROUGH: Well, IND-exempt is a separate issue. I was thinking you were talking about the vast number of surgical trials. IND is one issue, versus everything else outside of IND.

DR. GOODMAN: Okay.

DR. GARBER: Next, Sandy.

DR. SCHWARTZ: I don't know what the right answer is, but we have a big problem here if we don't do something. For example, one, I would go back and change my vote on IND-exempt. But two is, we still have a lot of trials out there. What we're doing is we discriminate on the trials based on their funding source instead of on the merit of the design. So if I get funding from the federal government, then I can take advantage of having

the routine patient care costs covered by Medicare. But if my funding comes through the Robert Wood Johnson foundation, there is no mechanism for me to get that reviewed because it's not funded by a federal agency. If I'm doing something that's related to -- so anything that is not federally funded is automatically excluded if we don't do something here.

So I think the question comes down to what Steve's asking, and I think that's untenable and unacceptable. Science isn't defined by who's funding it, and I think we're either providing support for Medicare patients to be enrolled in good studies or not, and then the question comes up, what's the most expeditious way to do it. But I don't think, in my mind I don't think there's a choice of leaving it just as far as we've gone so far.

DR. GARBER: Cary.

DR. GROSS: If the current game plan is to basically not fund surgical trials, and again, the challenges we have, could this Question 6.2, establishing a federal inter-agency panel, be modified so that that panel would only review certain types of studies?

DR. GARBER: That's not stated here, and you can have all kinds of different views. But the point to make, as Sandy said, is this will only apply if you didn't make it through the other hoops. So it's not for review of studies that would otherwise be approved, it's ones that would otherwise not be approved. Barbara, then Bernie, then Deborah.

DR. ALVING: Well, it would seem that trials that aren't, that don't have other funding sources really can't rely on CMS alone, I would imagine, that they really need a combination of CMS funding and other funding. So I think if CMS is going to look at these trials, they have to say is it really economically feasible to do the trials.

The other thing is, couldn't CMS as needed convene an ad hoc panel for particular situations, protocols that could come from both government and nongovernment consultants, who would be, let's say a large pool, just to be available to be called on as ad hoc reviewers for specific situations?

DR. GARBER: So, can I just ask, Steve, can suggestions like that be written on the

ballots?
DR. PHURROUGH: Sure.
DR. GARBER: So Barbara, for your suggestion and for anyone else who has suggestions of that kind, just write on the ballot underneath this, alternative suggestion, and we'll assume if you write it down, you find that highly desirable. Deborah, you had your hand up?
DR. ZARIN: I was just going to try to guesstimate some volume here. In ClinicalTrials.gov right now we get about 250 new trials registering per week. About half of those are U.S. studies and probably about half of those receive federal funding. So you're talking, just from what we're currently getting, 60 or so a week, and I'm sure we're not getting all the studies out there. Just so when people think about having a panel, get ready to roll your sleeves up.
DR. SCHWARTZ: What's the alternative then? Is the alternative just to exclude them just because we don't have a mechanism to deal with them?
DR. GARBER: Okay. Wade and then Bernie.

DR. AUBRY: I just wanted to -- doesn't this mean that this would set up a new process, but absent a new process like this, it would be up to CMS internally to make some determination, or perhaps the contractor medical director? That's a question for Steve.

DR. PHURROUGH: Well, unless we change the policy, we don't have to do anything, because currently the policy says if you're not federally funded, you don't get paid. So we would have to change the policy, and if we changed the policy to allow payment for non-federally-funded trials or anything else that was not deemed, we would have to, in changing that policy, define what the new process would be.

DR. AUBRY: I understand.

DR. GARBER: Bernie.

DR. LO: I would suggest we try to think of other ways to get scientific review of protocols and then deem those processes. Some examples we might want to think about are private foundations like Robert Wood Johnson or Doris Duke, professional societies. If the Society of Cardiac Surgeons or General Surgeons puts together a review panel and submits their review process to

CMS, CMS could say we like the process and we will defer to it to review a specific protocol. That, if you could trust the process, would be a lot simpler than having CMS review every single protocol.

DR. SCHWARTZ: Well, hopefully it's less paperwork, but for instance, heart and lung associations give out awards on their own, they have scientific reviews. There are a lot of other people who have incentives and the skill to do this kind of scientific review, and if we could deem some of those, then CMS wouldn't be in the business of reviewing protocols and we wouldn't have to come to Washington or Baltimore every week.

DR. GARBER: I don't know how different that is from number three here.

DR. LO: It's not federal, Alan, it's private.

DR. GARBER: This doesn't specify in number three. Steve.

DR. GOODMAN: I have another proposal along those lines. I think this is very much like IRB review. There's no way we're going to set up a national IRB to look at all studies. I think

that where we ultimately want to go, and maybe I'm wrong, this is a big question, is a system where we have more like the cancer center reviews, distributed around the country in all major medical centers. And this is, they're starting to move to this at Hopkins, and I'm sure it exists to some extent in other centers as well, where in the department of internal medicine there's a scientific review committee, in the department of pediatrics there's a scientific review committee. And you can say, if CMS could actually -- well, pediatrics wouldn't be a concern for CMS, but if CMS could play a big role in incentivizing medical centers to set up these panels, they could say, you know, for the next five years, we'll -- in the next five years if you want to have continued payment of costs for Medicare-eligible patients, we want to see your center develop its internal review policy. And, you know, there will be a honeymoon period for a certain amount of time. And every major medical center that wants to do this has to invest in doing that, because they get something big back for it.

I think, ultimately, that's the only thing that's going to work. I don't think that

any centralized panel is going to even begin to handle the volume that is going to be generated by this. And there is a lot to gain from the medical centers themselves for setting these up. I mean, I think a lot of them are concerned about the same things you are, for different reasons, and they would appreciate -- well, I don't know about appreciate, but they would understand that it's in everybody's interest to have this level of review. It does add to the overall review burden in the institution, but many institutions are recognizing that this is necessary.

So we might want to think of that sort of model or something along those lines as well, perhaps together with Bernie's model, which could augment that system as well.

DR. GARBER: Okay. Do you want to flash your cards now? This is for number two, establish federal inter-agency.

DR. JANJAN: But is it for the ideal or the feasible?

DR. PHURROUGH: Feasible.

DR. SUGARMAN: If I don't particularly like two and three, but those are the only options I have, I'd like to have an option like what

Bernie had on there.
DR. GARBER: You should write it down on your ballot sheet.
DR. SUGARMAN: But I mean something that I think that the group could vote on so it's not just one person.
DR. GARBER: I think that would be good if the group could come to a vote about a specific proposal. Let's go through these and if somebody has something that suggests that people can call us on, great.
(Panelists displayed numeric ratings.)
DR. GARBER: The third is establish multi-stakeholder panel to review study protocols, discuss funding issue, which I assume means funding of the panel.
DR. KRIST: Would we want to lump three in with the other proposals we've heard, so if we like these other things, then we should vote well on three.
DR. GARBER: Does anybody want further discussion before you flash your cards? Nancy.
MS. DAVENPORT-ENNIS: I'll make it quick. The only thing I'd like to say about the multi-stakeholder is it would include patient

representatives, representatives from the federal agencies, providers as well as national organizations such as those earlier cited.

DR. GARBER: Okay, thanks. So, you want to flash your cards?

(Panelists displayed numeric ratings.)

SPEAKER: This is one panel for the country?

DR. GARBER: It could be multiple, don't get hung up on those.

DR. SCHWARTZ: Alan, so are we, when we're voting, are we voting that we will suggest that this would encompass something along the lines of what Bernie was saying too, or is that separate?

DR. GARBER: Well, what Bernie was saying before, I thought would involve actually writing down in some detail. I mean, I agree it's very similar to what Bernie was talking about, but Bernie's technically was not a multi-stakeholder panel, it was a different organization. Steve?

DR. PHURROUGH: Just so we're all clear on what we think we're voting on, number three is different only from number two in the composition of the panel. It will -- this does not include

developing standards for other entities or deeming other entities to approve protocols. This is a panel, whether it's one or six, that will have protocols flow into them and they review them and tell us yes, they're good or not.

DR. GARBER: The fourth one is basically CMS piggybacking, as I understand it, on other federal agencies' work, work with other federal agencies to incorporate into their current study panel scoring process an item that asks, does this study meet the requirements of the Medicare clinical trial policy? Barbara, do you have anything to say about that?

DR. ALVING: I think I would have to think about it. One of them would be then, so what? I mean, what would that mean, that they say yes, it does, or no, it doesn't, and then what are the next steps? Does that give the investigator then the right to go to CMS and say look, I have my certificate? You know, what would that mean?

DR. PHURROUGH: That sort of is the concept, that if NIH said this does meet the CMS clinical research policy standards, then it would be deemed, just like if they funded.

DR. ALVING: I think overall, it's a

very good idea and should be fleshed out. But I think it does, then, make everybody aware of who pays for this and what do you hope to get out of it. It puts the Medicare population front and center, so I think it's a good idea, and could be fleshed out a little bit more.

DR. PHURROUGH: One thing you may not have thought about that I'll bring up is if this becomes the IND-exempt outlet, or the outlet for all surgical trials, you may get from NIH hundreds of thousands of requests for funding recognizing they're not going to get funded, but they're going to get the Medicare approval stamp.

DR. ALVING: Oh, so they just want the good stamp of approval then?

DR. PHURROUGH: Yes.

DR. ALVING: Well, then, we could also say do we want to accept these trials for review, which already goes on in some institutes. So there are ways to -- so this should be fleshed out between NIH and CMS.

DR. GARBER: Deborah, and then Steve Wartman.

DR. ZARIN: I was just going to clarify. I thought this was circular, because I

thought we already said that you met CMS clinical trials policy if you were approved and funded by other federal agencies.

DR. PHURROUGH: This is not funded.

DR. ZARIN: So you mean for things that weren't funded by other agencies. That just seems overly burdensome to those other agencies, to me.

DR. WARTMAN: I had a similar comment. Also, am I right in what you just said, that this would be incorporated in the judgment of the request for funding, it would become a judgmental issue in terms of where the proposal is rated in terms of points or whatever?

DR. PHURROUGH: No. As Barbara said, there's lots of discussion that would have to take place, but it would be sort of a yes or no on the reviewer's checklist that had nothing to do with the NIH funding process, just an additional workload for the reviewing person.

DR. GARBER: Yeah, I would assume this would be a separate rating system, so that's what could be done.

DR. AUBRY: I would like to say that I agree with Barbara on this and I, that there is, I think this is actually an idea that would be

helpful both to the, you know, the proposer of the study and to CMS, and I think one of the goals is to develop better evidence for Medicare coverage decisions, so I would agree that it needs to be fleshed out, that there are some complexities and issues with this in terms of burden, but I think it's, the question really goes to add a scoring system, it doesn't guarantee anything as I read it.

DR. GARBER: So, are people ready to flash there cards?

(Panelists displayed numeric ratings.)

DR. GARBER: Now, we are at a decision point. Would the committee like to break, or continue going through? Okay. I'm going to turn it over to Alex since I have to leave, along with a few other people. Thank you for a great job.

DR. KRIST: Okay. Well, do we want to entertain any of the other things that were proposed from Bernie and others, and specifically vote on either of those topics before we go on to Question 7.

DR. GROSS: I would like to vote on a mechanism to establish a deeming process for professional societies and private foundations.

DR. GOODMAN: Yeah, except the institutions are the medical centers themselves, so why not, if we're going to do that, we absolutely have to include them.

DR. SUGARMAN: I just think you should just have an equivalent mechanisms clause, and an equivalent mechanism review that included the scientific merit of the study and not specify whether it's an institution or a foundation as an embodiment. It leaves it open, it lets, you know, a thousand lights shine, and then use an assurance mechanism perhaps similar to what OHRP does for a federal-wide assurance, so you would have some kind of an assurance mechanism that is an equivalent level of review.

DR. KRIST: Since it hasn't been flushed out, why don't we keep it broad, and we'll vote here just to give you some advice on whether a process to deem institutions as viable to these studies is appropriate.

DR. PHURROUGH: Let me ask for some clarification too for those who are proposing this. Would you assume that it would be CMS who approves their deeming status as being competent to doing this? Okay.

DR. ALVING: They're also going to want funding, the administrative gut check.
DR. PHURROUGH: Okay, March 1st.
DR. GOODMAN: I just want to say, the kind of thing we're talking about here is very big, and deserves in many ways, you know, this could be a whole day discussion right here, so we should not be too -- we should be pretty humble about, you know, the nature of this mandate because we haven't discussed it. This could well be the subject for many panels in the future and a whole panel on to ensure is scientific value of all research done in the United States. So let's, you know, not push too hard, but raise the issue and make some preliminary discussions about maybe where we can move.
DR. KRIST: The alternative is, I think all the comments have supported, this message is what you have sent and these ideas have started to be laid on the table and maybe a vote necessarily, I don't think helps from that standpoint, but it can be grounds for further discussion.
So why don't we move on to Question Number 7 with that context.
So for Question 7, it's defining what

routine clinical services are, and A through E are listed here under the voting question, and then what they're asking us to vote on is, do we believe that these changes clarify the definition or routine clinical services, yes or no, and what changes would we suggest. I'm going to assume that the group wants to talk about this before we vote on it. Does anyone want to talk about this?

DR. ALVING: I think I would like to just have a definition of item. Does that include drugs? If someone is getting a statin and it's covered by Medicare outside of trial and now you want to compare statin to some other agent in the trial, is that still included and is it still covered, even though it's now in an investigational study?

DR. PHURROUGH: Anything that Medicare pays for is either an item or a service.

DR. ALVING: Okay. So item equals drug, device?

DR. PHURROUGH: Anything that Medicare pays for is either an item or a service.

DR. ALVING: I've got five more years.

(Laughter.)

DR. PHURROUGH: It is not more defined

than that. You could try and categorize drugs and procedures and devices and box it into one or the other. It's somewhat irrelevant. If we pay for it, it's an item or service. So before part D, outpatient services were neither -- I mean outpatient drugs were neither an item or service, now they are an item or a service. That's as good as I can get you.

DR. KRIST: Linda.

DR. BERGTHOLD: I was just going to ask, we're really only being asked to comment on changing the term routine costs to routine clinical services, everything else is the same, right?

DR. PHURROUGH: Yes, that is one question we're asking. We are also asking you to tell us, is A through E under the new definition more clear than the previous one.

DR. BERGTHOLD: Well, I thought A through E was the same as the previous.

DR. PHURROUGH: No. It's no change in what's covered, it's just reformulating the wording to some extent.

DR. KRIST: So the idea being, we've heard there is some confusion about what are

covered items and services and what ones aren't, and does this clarify that.

DR. JANJAN: I have a question with regard to E. If something is done, say the investigational agent causes a cardiac complication and an EKG is required to evaluate that. Is that part of an investigational cost or is that routine clinical because you have a Medicare patient who is of a certain age? I mean, is this going to better define what's investigational?

DR. PHURROUGH: Remember, Medicare defines, as we have in the next two questions down, investigational just means the item or service that's being studied. Everything else is a routine cost. Even though you may call it investigational, it is not investigational, it is a routine cost. So your EKG for someone who had a heart attack because you gave them too much of whatever in your trial, or had an adverse reaction or whatever, is a routine cost and it's covered based upon this particular vote.

DR. AUBRY: That would fall under E, right?

DR. PHURROUGH: Right, E.

DR. KRIST: Other questions or comments on Question 7 before we vote? Okay. Can I see a show of hands for everyone who says yes for Question 7?
(Show of hands.)
DR. KRIST: And a show of hands for everyone who says no on Question 7?
(Show of hands.)
DR. SCHWARTZ: And Bernie voted yes.
DR. KRIST: We'll move on to Question 8.A first. So, CMS is proposing an additional category of administrative services and investigational clinical services be added, and should CMS adopt the following definition, and the definition is written below for administrative services? Once again, any questions or comments for clarification on Question 8.A? If there are no comments or questions, then we'll just move to voting on Question 8.A, so could I see a show of hands for everyone who says yes for Question 8.A?
(Show of hands.)
DR. KRIST: And a show of hands for everyone who says no for Question 8.A?
(Show of hands.)
DR. WARTMAN: I just have a comment.

DR. KRIST: Okay, Steve.
DR. WARTMAN: What about changing -- is the term investigator, is the term investigator salaries technically correct, or should it be investigator time and effort, just a semantic question?
DR. KRIST: I'm assuming in this context it's the salaries related to the clinical trial, that's all you would be considering, but --
DR. WARTMAN: I mean, I guess salary is not an administrative service, it's time and effort. It's a minor point.
DR. PHURROUGH: You can certainly offer some suggestions, write in some suggestions if you'd like.
MS. DAVENPORT-ENNIS: And that was going to be my comment. Certainly this could be a yes vote from our perspective if we can make some recommendations around amendments, because indeed, administrative services do accrue in order to be able to complete a trial.
DR. KRIST: Okay. Now we're on Question 8.B. I guess all we had to do was have Alan leave and we'd just start moving right along.
DR. BERGER: The vice chairman is doing

an infinitely superior job.
(Laughter.)
DR. KRIST: For 8.B, we're looking at adopting the definition for investigational and clinical services, definitions written below, and I guess there are three parts to this. Part one, the item or service is currently -- actually, I guess those are parts of the definition, and we're being asked to accept this definition or not, yes or no overall. So there's a text for the definition and then the three components, and we'll look at each of these components individually, I think is the way it's set up. So item number one is the item or service is currently available to the Medicare beneficiary outside the study -- I'm sorry, I'm misreading this. So we'll look at the definition first, which is just the paragraph there about investigational clinical services. Any questions or clarification on that? Okay. I'll look for another show of hands from everyone who says yes for the definition.
(Show of hands.)
DR. KRIST: And a show of hands for everyone who says no for the definition of

investigational clinical services.
(No response.)
DR. KRIST: Then we'll look at number one, which is, the item or service is currently available to the Medicare beneficiary outside the study.
DR. BERGTHOLD: I think available is a little bit unclear. Do you mean reimbursable? I mean, I can think of plenty of services that are available.
DR. PHURROUGH: Yes.
DR. KRIST: Yes, reimbursable.
DR. PHURROUGH: Covered.
DR. KRIST: Barbara.
DR. ALVING: If you're going to use this, let's say item, let's say maybe a drug, in half dose or a dose that is investigational, or you're going to use it in a new population, is it covered then, is it still considered, you know, does it still meet the coverage.
DR. PHURROUGH: Yes. This definition is if we were to pay for it outside the clinical trial, we'll now pay for it inside the clinical trial. So if the dosage changed, if it would have been paid for outside the trial, then we'll pay

for it inside the trial. And we pay for most off-label indications, so if you're talking about off-label stuff, unless we expressly noncover something off-label, it's unusual that we don't. There are some exceptions to that on a local basis, but that's unusual.

DR. KRIST: So I guess what we're voting on with the one, two and three is, if we say yes, we're saying that the item or service, if it's currently covered for Medicare beneficiaries, then we're saying it should be covered in the context of the trial as well, right?

DR. PHURROUGH: Even if it's investigational.

DR. KRIST: Even if it's investigational. And then we'll do the same for two and same for three.

DR. RYAN: I guess we go back to the device industry and her comments earlier, especially on item one. You know, I think what we're trying to advocate here is that it's important to cover the cost of services and items that are used in clinical trials. So what was proposed under item one here was to change it to read the item or service is currently available to

Medicare beneficiaries outside of the study, included but not limited to items that have been designated by the FDA as having received HDE status and has the item or service in a study that meets the requirement of the policy.

DR. KRIST: By available, this is meaning, again, it's already a covered benefit, so that wouldn't necessarily apply to what you're describing. But once again, you probably need to replace the word available in the sentence to cover, so if the item or service is currently covered to the Medicare beneficiary outside the study, and that would be irrespective of what the item or service was.

DR. RYAN: So you're saying that the HDE services would be covered if they were deemed a clinical trial?

DR. KRIST: Well, we're going to look at HDE specifically with number three, right? So that will be with number three. With number one we're just talking, if the item or service is already covered, and it's the item under investigation, would it be covered in the clinical trial.

DR. PHURROUGH: Until you get to number

three and talk about HDEs, this definition would include an HDE that was covered outside the trial. Some rarely are, there are only a few that cover Medicare beneficiaries in general, two of the major ones are noncovered, so that doesn't fit this definition, which is why we are addressing these separately. Item number one does not include something that we have noncovered under an NCD, but if we would pay for it outside the trial, we would pay for it inside the trial.

DR. KRIST: Ready to vote? Okay. Let's see a show of hands for everyone who would say yes for number one.

(Show of hands.)

DR. KRIST: And a show of hands for everyone who would say no for number one.

(No response.)

DR. AUBRY: That's as revised?

DR. KRIST: Yes. Now question number two, the item or service is required through the NCD process for CED and is being evaluated for its effect on health outcomes. Ready to vote? Everyone who would say yes for this?

(Show of hands.)

DR. KRIST: And everyone who would say

no.
(No response.)
DR. KRIST: Number three, are folks ready to vote on number three?
DR. AUBRY: No.
DR. KRIST: Wade?
DR. AUBRY: I would like to have some clarification about national noncoverage and HDE exemption that was brought up in the testimony. And I would like to know whether if we say yes on this, does that mean that we will have in some cases a policy where you will have a national noncoverage decision coexisting with an HDE exemption, or would an HDE exemption then preempt the national noncoverage, which would be unusual, I think, but would it all be rolled into one policy with this exception?
DR. PHURROUGH: Well, we are asking you, and I realize the question doesn't clarify that, we are asking you to recommend for both categories. If the HUD is noncovered nationally, should we cover it in the clinical trial policy if it's the item under investigation in a trial. And two, if it's not noncovered nationally, should we cover it in the clinical trial policy. So, an HDE

either has a national noncoverage or it has no national coverage. We do not have any national positive coverages for HDEs.

DR. AUBRY: It's unsettled, so that means carrier discretion?

DR. PHURROUGH: Carrier discretion, yeah. So in general, if we don't specifically, if we don't in this policy specifically say that an HDE is covered under the clinical trial policy, even if noncovered nationally, it would not be covered for those two particular issues that we heard about today, intracranial stent and artificial heart, which are two where we have national noncoverages.

DR. AUBRY: Well, my reaction to that is that they are somewhat inconsistent with each other, and that there should be one policy either to provide coverage under clinical research or clinical trials policy and then if that is done, if it's a qualifying clinical trial, then at the same time the national noncoverage should be reevaluated. So it seems to me that there should be one national policy rather than two national policies.

DR. KRIST: Deb?

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DR. ZARIN: I guess I'm still having trouble with this. I can imagine two different scenarios, one where an HDE is noncovered actually, and someone has designed a clinical trial that would in fact, if it worked out, would gather the kind of information that could presumably lead to it being covered, because it's going to answer a question that wasn't answered originally which led to the noncoverage, and I would think Medicare would want to encourage such studies and it would make sense.

I could also imagine a situation, for example, where two HDEs that are noncovered, I'm making this up, and they're both noncovered and someone devises a study comparing A to B, with questions that would in no way be relevant to a change in the coverage decision but sort of as a way to get coverage for these things that Medicare has already decided it wouldn't want to cover. And I don't see how, in the kind of scientific review we've come up with, you could distinguish between those two kinds of scenarios.

So I'm kind of stuck about whether overall this would be a good thing for Medicare beneficiaries or a bad thing.

DR. WARTMAN: I have a point of clarification as well. Are these considered investigational items under FDA regulations?
DR. PHURROUGH: No.
DR. WARTMAN: Thank you.
DR. KRIST: Barbara.
DR. ALVING: I feel like I'm sitting on the tip of an iceberg, and you've got all of this knowledge and experience, it's like being on an FDA panel. You know what they're thinking, I mean, you know they're thinking something, but you just don't know what, and I think I might be in the same situation here. So, I don't know if you could give us any more background about making this, since this is a really stark question.
DR. PHURROUGH: There really isn't. Congress told FDA to come up with this categorization of HUDs for small populations, sort of the orphan device policy similar to orphan drugs, and said that if it meets certain standards, then you'll give it a humanitarian device exemption, which confuses people because when they see HDE, they think IDE. This is in no way related to IDE. This is just like a PMA or a 510(K), they have been approved to market this, it

can be sold, it just has to meet certain standards.

For us, though, it just doesn't meet evidentiary standards for our coverage, it rarely will meet that level of evidentiary standards for the typical device that we look at. So we have, we can either do as we do now, allow contractors to make decisions in most cases around HDEs, or in some cases we've made national decisions that predated the HDE.

So both of these two that we've talked about and heard about today, the artificial heart and intracranial stent, we already had national noncoverage on. So FDA comes along and says we're going to give it an HDE. So what should our policy be nationally? Should we establish a policy completely separate from this that says if you're an HDE, you're covered, period, so we don't worry about it. It's an orphan device, sort of like an orphan drug, you don't need to be involved as the MCAC. We don't want it in the clinical trial policy. We're just going to write a rule that says they're paid for.

DR. ALVING: But it's not fair to the patient. I mean, well, there's a huge disconnect.

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FDA says it's approved but then the federal government says but we aren't going to pay for it. So A, how do these patients ever get it? It sounds like it might be in a good category for covering with evidence development, or are you going to say it's such a small category that you're never going to get evidence?

DR. PHURROUGH: It doesn't necessarily meet our CED standards, either, the way our current CED standards are written.

DR. RYAN: How does it fail to meet those CED standards? I'm just curious.

DR. PHURROUGH: Pardon?

DR. RYAN: How does it fail to meet the CED standards as currently written?

DR. PHURROUGH: It varies by HDE, but in general the CED standard says there's a fairly significant amount of evidence, it's just not the same level which we --

DR. RYAN: But by definition these are orphan situations, right, so there's not going to be large amounts of it.

DR. PHURROUGH: Correct. And our current coverage policy doesn't have categorizations for orphan kinds of devices. So

this is just an option for us to get HDEs covered. We think it's a reasonable option that says it only has shown probable benefit, so let's, while we're paying for it, get more evidence. The real question is, should that include things that in the past we have had an NCD that said we don't see there's evidence to support it so we're noncovering it.

DR. ALVING: What if a patient -- I mean, if there are big, I mean, what's the pressure there? Are patients feeling that it would be valuable or are you seeing any hints, or is it more driven by the device industry that just wants coverage? And that's maybe where you need a panel to decide, of some sort depending on the device, that you still have a category where you could get coverage with evidence development, but you decide which of those should go into that category.

DR. KRIST: Nora, then Mark, then Sandy.

DR. JANJAN: I think we're making this way too difficult. If right now the decision is made based on the local regional group on whether something is covered from a political feasibility

point of review, it just makes no sense that somebody in Kansas might not get a stent and somebody in New Jersey does. That's not equitable. And if it's an FDA-approved agent, I think that you're going to need to have a national policy on these issues so that it's across the country, patients have the same access to care. I think that's the simple issue from what I see.

DR. PHURROUGH: That's what we're asking.

DR. JANJAN: So to me it's a nonissue. You need to do it for everybody.

DR. KRIST: Mark?

DR. GRANT: The first, just a quick comment about, the FDA approval on a device does not necessarily mean efficacy has been demonstrated.

I just have two sort of conflicting, or two concerns about this. On the one side, it's great to develop evidence and we want to develop evidence. On the other hand, the number of individuals among which these devices are going to be used will be, because they're humanitarian use devices, relatively small. I'm concerned about the quality of the evidence that's derived from

that and I have a hard time separating the potential difference between these two.

DR. KRIST: Sandy?

DR. SCHWARTZ: Well, I think that if this is approved, adopted, whatever, it's just going to be -- I mean, you just have to recognize that it's just going to be a back door way to get it covered. And so the question, I guess from Medicare's perspective is, you know, what's the best way to make this decision. So you say right now this is made primarily locally with the potential, not necessarily actual, but the potential for variation.

One alternative would be to modify the coverage of its development criteria so that this would fit into that. You know, for most things it would be substantial evidence, but for these HUD types of things or stuff, that would be another category that might be covered with that. My concern with this is that it will become a back door to be covered, everyone then will be, quote, in a study or something, in order to be investigational, but you may not get the useful data coming out, you know.

And I would just second what Mark said,

just because the FDA approves a device does not mean it's clinically useful or beneficial. It's just not everybody in the room knows that, a lot of people here do, but the FDA's job is different than the NIH's job, different than AHRQ's job, and different from CMS's job.

DR. KRIST: So, Marc, and then Nancy.

DR. BERGER: I'm just curious. I know you mentioned two cases where there are national noncoverage decisions where this is affected. How many other devices are there in this boat where they are in this kind of limbo of noncoverage and they have no way to get more information?

DR. PHURROUGH: I think there are 40, in the low 40s of HDEs that have been given by FDA over the last five years or so.

DR. RYAN: Can we ask the person who testified?

MS. HANDKE: I think, Dr. Phurrough, just to clarify, there have been about 40 HDEs approved by FDA over the past five years. The vast majority of them are for pediatric patients. To my understanding, there are only two devices that had an existing old noncoverage decision. That one dated back to 1986, that I referred to

earlier. And Scott with Boston Scientific is not here, but I believe that coverage decision was made in 1996, the same year the actual qualifications for FDA were put forth.
So these were the two devices that got caught with old national coverage decisions that were put into place prior to the HDE regulation coming forth. So we're a little bit in a box here, and I think it's important to realize that when you step back and think about it, we would not be seeking, a company that had so few devices under an HUD would not be seeking a national coverage decision, because we recognize the importance of maybe a local decision with this, we have a few number of patients.
As Dr. Phurrough had stated in his opening comments, it is almost nearly impossible to reach the evidentiary standard that is necessary for reasonable and necessary. We recognize that, but we also need a pathway, we need an open door for coverage to address a health care policy that was developed 20 years ago.
DR. RYAN: So you've got a device that the FDA has given an HDE to as having probable ability to improve patient care, and the issue is

that given the small number that's involved, you're never going to meet the standards of a national coverage decision, which is already in effect.

DR. BERGER: That's very helpful. So if I put aside the two cases which are in limbo, it seems to me the government shouldn't talk out of two sides of its mouth. A lot of us do that and it's not a good thing to do. So that if there has been no national coverage decision and the FDA gives an HUD exemption to a device, I think it makes sense that those devices should be covered under an appropriate clinical trial to gain additional information. That feels right to me and makes sense as the way the government should handle things.

I have no clue what you do with these two exceptions, and I don't know that I would feel comfortable voting on something around those two exceptions, since I know so little about those two devices that I feel unable to render a reasonable bit of advice on those two exceptions.

DR. PHURROUGH: Well, we are not specifically asking you to discuss specific devices, but --

DR. BERGER: I understand that, so if you divided the question into two potential halves, if there has been a national noncoverage decision, should it be covered in a clinical trial, to me that's an exception question and I don't want to talk about it, personally. I can't give you any advice on that.

On the second half of that question, if the HUD has had no national coverage decision made and it's up to the different local providers to make a decision, should it be covered with a clinical trial, I would say yes. That would be the way, I can parse that one, I can't parse the first one.

DR. SCHWARTZ: Well, the way I think I might handle the first one, Marc, is to base it on, the goal here is to try to facilitate and encourage the collection of data that could allow you or us to make better decisions as a society, or as a program. And so the way I would do it is to go and see, is the information that's being collected as a trial, is the study such that it's going to provide useful, or has a high probability of providing useful information or not. My concern with this is just that it not be a back

door way of avoiding things, and that any policy that's developed be used to encourage and facilitate the collection of data. I mean, you can't go wrong estimating my knowledge of the heart issue, but I do know that just about every piece of data that you can possibly collect on those patients is being collected, it is not a way to avoid getting the clinical information and ultimately doing that. But that's what I think the objective or the goal should be.

DR. KRIST: So Deborah, you had your hand up, and then Wade afterwards.

DR. ZARIN: Thanks. Is this, Steve, the way three is written, does it mean a study that meets the deeming requirements? I mean, is this a study that receives federal funding?

DR. PHURROUGH: Yes.

DR. ZARIN: So then I in a way take back my objections. So you're saying that some federal agency has decided to fund a study and the focus of the study is a device that there's an old CMS noncoverage decision on. I would think if we have taken that deeming to mean that it's a scientific review, it has a reasonable likelihood of producing useful information, I would say

that's reasonable. I was worried initially that it was going around the deeming process, but within the deeming process I feel totally comfortable covering this.

DR. KRIST: Wade.

DR. AUBRY: It seems to me that we should vote on one question rather than two questions, and if we decide that number three is reasonable for the reasons stated, it would seem to me that what CMS should do is revisit the national coverage decisions and decide whether they should be left to carrier discretion. I mean, there are three options when you revisit a national coverage decision: you can keep it the same, you can leave it carrier discretion, or you can reverse it. So it may be appropriate to, in those cases where there is a national noncoverage, it seems to me that's inconsistent with providing coverage through the clinical trial policy.

DR. PHURROUGH: We just finished doing that for the intracranial stent and we're in the position we're in now where we, for us through an NCD process to make this happen, will require us to change other policies, either our coverage policy, our coverage guidance document that says

here's our review, NCDs, or our CED policy that says here's how we review that. Either or both of those would have to be changed for HDEs to be covered, or for the noncoverage to be removed and left at contractor discretion, because of the standards we've applied. So yes, we can do that, this is just an option that we find to be simpler at the moment, and we think a good thing to require these devices to be collecting more evidence.

DR. RYAN: Is it possible to provide coverage for these products, in light of the noncoverage decision, until such time as the criteria for noncoverage decision can be revised to really handle issues of orphan drugs? Because you're never going to get that kind of data and volume to meet the criteria.

DR. PHURROUGH: No. We have to change our policy before we can provide exceptions to the policy.

DR. KRIST: So for number three, we're going to, just to be prepared, break it out into two votes. We're first going to vote if there is no national coverage decision, and then we're going to vote if there is a national noncoverage

decision, so there's going to be two votes. So put a line through that box for each of the votes in order to record this. Do folks have more statements or are we ready to vote?

DR. GOODMAN: Well, I think something else that maybe, this whatever we are now, the MedCAC, should recognize that the standards for making decisions about these types of drugs and devices in these situations may need to be different than what's reasonable for more common things, so that might be something else to think about going forward. Not every study needs to have p values of .05 with type two errors of .8 and all that. There are situations where you just have to make decisions with a greater degree of uncertainty and live with them, and maybe that's something else that needs to be thought about going forward.

DR. KRIST: Okay. We'll go ahead and vote for number three if there is no national coverage decision. Raise your hand if you would vote yes.

(Show of hands.)

DR. KRIST: And raise your hand if you would vote no.

(Show of hands.)
DR. KRIST: For the second part of number three, if there is a national noncoverage decision, raise your hand if you would vote yes.
(Show of hands.)
DR. KRIST: And raise your hand if you would vote no.
(Show of hands.)
DR. KRIST: Okay.
DR. PHURROUGH: Well, thank you very much. This has been a very fruitful day, a lot of fruitful discussion, it's somewhat different than most of our MCACs, and I think this has been very helpful. We will put out a transcript and some summary of this meeting in the next several weeks, and we'll put out a draft policy sometime after the first of the year for you to review. Thank you very much.
(Whereupon, the meeting concluded at 3:33 p.m.)