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

May 16, 2012

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

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Panelists
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Vice-Chair
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James Min, MD
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Art Sedrakyan, MD, PhD
CMS Liaison
Tamara Syrek Jensen, JD
Industry Representative
Peter Juhn, MD, MPH
Guest Panel Members
Steven Goodman, MD, MHS, PhD
Jack W. Lasersohn
Peter J. Neumann, ScD

16 Invited Guest Speakers
Allan Korn, MD, FACP
17 Rick Kuntz, MD
Mark McClellan, MD
18 Lewis G. Sandy, MD, FACP
Sean Tunis, MD
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Executive Secretary
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1 PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, May 16, 2012.)

MS. ELLIS: Good morning and welcome, committee chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MEDCAC. The committee is here today to discuss desirable characteristics of evidence appropriate for coverage with evidence development.

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 employer's financial interests.

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 disclose if you or any member of your immediate family owns stock or has another

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form of financial interest in any company, Internet or e-commerce organizations that develops, manufactures, distributes and/or markets consulting, evidence reviews or analyses, or other services related to coverage with evidence development. This includes direct financial investment, 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.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the microphone and state your name.

For the record, the voting members

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present for today's meeting are Dr. Steve Phurrough, Rene' Cabral-Daniels, Dr. Mark Grant, Dr. Robert McDonough, Dr. James Min,

Dr. Sharon-Lise Normand, Dr. Jeffrey Rich, Dr. Ryan Saadi, Dr. J. Sanford Schwartz, and Dr. Art Sedrakyan. A quorum is present and no one has been recused because of conflicts of interest.

The entire panel, including nonvoting members, will participate in the voting. The voting results will be available on our website following the meeting. I ask that all panel members please speak directly into the mics, and you may have to move the mics since we may have to share.

This meeting is being web cast via CMS in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeness and voice during the meeting. You are also giving consent to the use and distribution of any personal identifiable information that you or others may disclose about yourself during today's meeting. Please do not disclose personal health information.

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If you require a taxicab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of the room.

And lastly, all CMS guests attending today's MEDCAC meeting are only permitted in the following areas of CMS single site, the main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

Now I would like to turn the meeting over to Tamara Syrek Jensen.

MS. SYREK JENSEN: Thank you, Maria. I just want to thank the panel for spending some time today with us. This is an unusual meeting and the agenda is a little bit different than past MEDCACs. This is a very important topic for the Coverage Group and the Agency, coverage with evidence development. I think this is the first step in how we're going to approach coverage with evidence development in the future, and so we are looking forward to

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the discussion today. Thank you.

DR. C. GOODMAN: Thank you, Ms. Syrek Jensen, Cliff Goodman here. We have just today for a full agenda on a topic with considerable potential impact on the conduct of Medicare

coverage decision-making and ultimately access to care for many Medicare beneficiaries, so we expect that all of our guest speakers, those providing scheduled public comments, and any who provide open public comments as well as my fellow MEDCAC members will be on point and concise today.

When it's your turn to speak, please do speak into the microphone. This does matter for the record, because if you don't do that, we won't hear you and our trusty court reporter won't hear you either, which means that the important things you have to say won't get into the record, so please do heed that.

We have today a time for scheduled public comments in addition to other expert input, and I understand that there will be nine such presentations today, each of which has been allocated a maximum of five minutes by CMS, those are the scheduled public comments.

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Given our tight agenda we need to adhere to those five-minute limits. Later on we will hear from our open public commenters, there are a few thus far, I understand, each of whom will be allocated one minute.

We suggest that all speakers and commenters think now about focusing your presentation on information that pertains directly to today's voting questions. There's a lot we could talk about in, around and about CED, but we need to get to these questions in particular today. So if you plan to present material that you find might be repetitive of previous speakers or that is simply background information about your organization you may represent, you might consider dispensing with that material and focusing instead on what you want this committee to know today about the questions before us. In any case, please do heed the traffic light system to which Ms. Ellis referred, and do know that we will need to proceed to the next speaker once you've used your allotted minutes. Any speaker who has not signed a disclosure form will need to do so.

And I hear on my cue to remind you to

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please silence your cell phones and other communications technology. Thank you for the well timed cue for that.

We will move to disclosures now, and I apologize, mine is a little longer than most.

Cliff Goodman, I'm a senior vice president of the Lewin Group. Lewin Group is one of

multiple business units of OptumInsight, which is a healthcare information and analysis firm, which in turn is a business unit of the health services company Optum. Optum in turn is one of the multiple subsidiaries of United Health Group. I hope you followed all that. I have no interest to declare pertaining to today's topic. Dr. Steve Phurrough.

DR. PHURROUGH: I'm Steve Phurrough, I'm the chief scientific officer at the Center for Medical Technology Policy. I was here at CMS during some of the formation of CED, and currently my company is spending time addressing the policies and other patient issues around CED.

MS. CABRAL-DANIELS: My name is Rene' Cabral-Daniels. I'm with the National Patient Advocate Foundation, and I have no conflicts to disclose.

DR. GRANT: I'm Mark Grant, I'm the director of technology assessment, Blue Cross Blue Shield Association's Technology Evaluation Center, and we do considerable work in the area of evidence appraisal, assessment, policy, recommendations. Otherwise, I have no conflict of interests to declare.

DR. MCDONOUGH: I'm Bob McDonough, I'm head of clinical policy research and development for Aetna, where I develop clinical policies, I have no conflict of interest.

DR. MIN: I am James Min, I am a cardiologist at Cedars Sinai. I think my disclosures are that I serve on a medical advisory board for GE Health Care, for a small startup stem cell company called Capricorn, and for a small startup company making new developmental CT scanners called Arineta.

DR. NORMAND: Good morning. I'm Sharon-Lise Normand, I'm a professor of biostatistics and healthcare policy at Harvard Medical School and Harvard School of Public Health. I don't think I have anything to disclose. I will say that I am vice chair of the Patient-Centered Outcomes Research Institute's methodologies committee, and so I have an interest in developing sound statistical methodology for gathering evidence in order to make decisions.

DR. RICH: Jeff Rich, I'm a practicing cardiac surgeon in Northern Virginia at Sentara Health Care. I really don't have anything to disclose. I do wish to say that I am the

current seated president of the Society of Thoracic Surgery, who certainly has a lot of interest in CED, and I was former director here at the Center for Medicare Management, where we discussed CED and has a particular interest in that.

DR. SAADI: I'm Ryan Saadi, I'm a vice president of CORDIS Corporation, which is part of Johnson & Johnson. I don't have any conflicts of interest.

DR. SCHWARTZ: Sandy Schwartz, I'm professor of medicine and health management economics at the Medical School and Wharton School at the University of Pennsylvania. I currently have research grants from Pfizer and have served as an advisor consultant in the

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general area of comparative effectiveness in evaluating research for Bayer, Blue Cross Blue Shield, Mathematica and UBC, and I'm on a national advisory board for research fellowship from the Association of University Radiologists, but that program is funded by General Electric.

DR. SEDRAKYAN: Art Sedrakyan, from Weill Cornell Medical College. I'm associate professor in the medical college, and directing the patient-centered comparative effectiveness program focusing on device evaluation and also regulatory aspects of device evaluation. No conflicts of interest to disclose.

DR. JUHN: Peter Juhn, Express Scripts. I have no conflicts to declare, and I am today's industry representative.

DR. S. GOODMAN: I am Steve Goodman, a guest panelist for today. I am associate dean for clinical research at Stanford and professor of medicine and health research and policy. I serve as a scientific advisor to the technology assessment program that Mark runs at Blue Cross Blue Shield and I'm also a member of the PCORI Methodology Committee, but I don't think they

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are real conflicts.

MR. LASERSOHN: I'm Jack Lasersohn, I'm a general partner of the Vertical Group, a venture capital firm specializing in medical devices and biotechnology. I have many portfolio companies, am an investor in many portfolio companies. None of those portfolio companies are currently involved in a CED process, although I imagine in the future many of our portfolio companies will be involved in the CED process, so I have no direct conflicts.

DR. NEUMANN: Good morning. Peter Neumann, director of the research center at Tufts Medical Center in Boston. I'm also a professor at the School of Medicine there. My center receives funding from multiple sources, including government, foundation and private industry, including the pharmaceutical industry, and we perform research on Medicare coverage among many other topics. I have no other conflicts to disclose.

DR. C. GOODMAN: Good, thank you all. Panelists, if during the course of the day it occurs to you that you might have forgotten to mention a potential conflict and you want to

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raise it, you can raise it during the course of the day and if need be, amend your conflict of interest form accordingly. Thank you.

Before we move to Dr. Jacques, I want to provide a few contextual touch points for the rest of today. Just leading off with the term, the term coverage with evidence development or CED is one of a broader and evolving set, or even taxonomy of coverage or reimbursement arrangements that call for something other than a thumbs up or a thumbs down coverage decision. All of these terms recognize that payers as well as clinicians, patients and other decision makers don't necessarily know everything that they need to know about many technologies at the time that they are approved or cleared for market entry, or when they're initially up for coverage.

This general type of arrangement is not at all unique to our federal government, or even to the United States for that matter. In fact there have been many similar arrangements know as conditional coverage, qualified coverage, performance-based reimbursement and managed entry, access with evidence development

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and others that have been used by government and private sector payers in the U.S. and other wealthy nations.

This concept has been an explicit matter of healthcare policy discussion at least as far back as the early 1990s, marked subsequently, for example, in 1998 with initial patient enrollment in the National Emphysema Treatment Trial or the NETT, N-E-T-T, that evaluated lung volume reduction surgery. As you're going to hear today, CED as such was initiated by CMS circa 2004.

In April 2005 CMS developed a draft

guidance for CED. Then drawing in great measure on a large number of public comments to the draft guidance, CMS published a revised guidance in July 2006 that was labeled National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development. So you see a progression there, okay, through the 2000s. CMS intends that CED provide market access to promising interventions that did not at least yet meet the statutory standard of reasonable and necessary. I recall that

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included among the eight principles in the guidance from 2006 governing the application of CED were the following. I won't read them all but I'll read three of them to you. One was that CED will not be used when other forms of coverage are justified by the available evidence; another stated that CED will in general expand access to technologies for Medicare beneficiaries; and another is that CMS expects to use CED infrequently, and I refer you to the 2006 guidance for other information. So those are some touch points and some background leading up to where we are now. And speaking of where we are now, it is time for Dr. Louis Jacques to provide a presentation from CMS and the voting questions. Dr. Jacques, I would say welcome, but I think you know the place.

DR. JACQUES: Yes, I am familiar, and I have no conflicts of interest, I'm not allowed to have any. Welcome to this meeting of the Medicare Evidence Development and Coverage Committee, or MEDCAC. We've convened this meeting to hear testimony and receive

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recommendations from the panel on the desirable characteristics of evidence used within the context of coverage with evidence development. On November 7, 2011 CMS posted an announcement on our coverage website soliciting public comment on CED for two months. Due to public interest in this topic we actually extended the comment period by an additional two weeks. I will not summarize all those comments today, they are still available on the CMS website, and I understand that various parties have published their own summaries of those particular comments. That said, the consistency among the comments may be described as follows: If CMS

is going to embark on a more robust CED initiative, we would like CMS to develop and promulgate evidentiary criteria to enhance the predictability of CED. That is why we are here today. I certainly understand that other public comments commented on other aspects of the CED initiative, but we are here today within the context of the MEDCAC specifically to talk about evidence.

To fully appreciate CED, I think

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requires some sensitivity to the circumstances surrounding its birth. As CMS reasonably embraced an evidence-based medicine paradigm over ten years ago, we were challenged to develop coverage policies for certain items and services where we believed that the enthusiasm was disproportionate to the persuasiveness of the then current evidence base.

This is particularly of concern when we've had reasonable grounds to believe that the reported health outcomes are not readily applied to our beneficiary population, specifically the elderly, the chronically disabled, and those patients with ESRD who are treated with dialysis. Commonly there are reasonable grounds to believe that the course of the disease itself or the response to medical management are meaningfully impacted by, for example, advanced age.

While some would include the 1996 National Emphysema Treatment Trial or NETT in a list of CED-based policies, I think it's fair to begin the modern era of CED essentially in the early to mid 2000s, and on this particular list I started with the 2004 decision on

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positron emission tomography, PET, for the diagnosis of dementia. As you can see, some CEDs appear to have been more impactful than others. I'm sure there are lessons to be learned here as we tackle CED in the future.

For example, there are a number of CEDs, great impact despite our willingness to pay for the item or service in the context of a CED study, no protocols have actually been developed. In other contexts in fact CED has worked I think quite well, and we have in fact revised policies based on evidence developed within CED.

Approximately three weeks ago the White House released the national bioeconomy blueprint, and I would refer you to page 31 of that for a paragraph on CED, which I will read

simply so that it will be in the record. Expanding the coverage with evidence development program to drive innovation. Reimbursement for medical treatments is a powerful driver of industry investment. Under coverage with evidence development, CED, programs, Medicare reimburses for promising new technologies that do not currently meet the

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standards for full coverage. The CED program requires more evidence to be collected to determine the full potential benefit of new technologies. The CED authority has existed for more than a decade but has been applied sparingly. The Centers for Medicare and Medicare Services, CMS, is poised to implement the next phase of CED by better defining the parameters and guidance for CED so it can be used more widely and effectively as a driver for innovation. CMS believes that the lessons learned during the initial implementation of CED can inform its more frequent use and create predictable incentives for innovation while providing greater assurance that new technologies in fact fulfill their initial claims of benefit. And the URL is there at the bottom, in case anyone wants to consult that. And so we will now move to questions for the panel. First, two definitions, binary coverage paradigm, a yes or no final coverage decision without planned reconsideration or prespecified clinical outcomes. Non-binary

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coverage paradigm, qualified coverage decisions that may evolve as evidence base changes over time, with planned reconsideration based on the achievement of prespecified clinical outcomes. CED is an example of a non-binary coverage paradigm. Question 1: Are there significant practical differences between binary and non-binary coverage paradigms? If the answer favors yes, please discuss the advantages and disadvantages of non-binary paradigms. Question 2: Can an evidentiary threshold be defined to invoke CED? If the answer favors yes, please discuss how this threshold should be identified. If the answer favors no, please discuss the impediments and recommend strategies to overcome them. Question 3: How would an evidentiary threshold to invoke CED be influenced by the

following: A, whether the item or service is a diagnostic versus a therapeutic technology; B, the severity of the disease; C, the safety profile of the technology; D, the availability of acceptable alternatives for the same disease/condition; E, other factors; F, a

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combination or tradeoff involving two or more of the above.

Question 4: How would an evidentiary threshold to invoke CED be influenced if the outstanding questions focus only on the generalizability of a strong but narrow evidence base to: One, additional settings; two, additional practitioners; three, broader clinical indications for related or unrelated disease. An example of a related condition might include a different stage of the same cancer. An example of an unrelated condition might include the use of a cancer drug for a rheumatologic disease.

Question 5: Can an evidentiary threshold be defined to trigger an evidentiary review to determine if CED should cease, continue or be modified? If the answer favors yes, please discuss how this threshold should be identified. If the answer favors no, please discuss the impediments and recommend strategies to overcome them. Please discuss whether the factors discussed in questions three and four are relevant to question five.

Realizing that some people prefer sort

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of a visual aid as opposed to words, with assistance from the chair and vice chair we have developed a visual aid for these particular questions, and I think it may be helpful for some people in terms of framing the considerations for today. In this particular graphic the vertical Y axis indicates the direction of health outcomes that accrue with the use of particular item or service. Up is better and down is worse. The horizontal X axis intersects the Y axis at zero, where there is no overall improvement or worsening of health outcomes that can be attributed to the item or service. Though the X axis is not marked to indicate any specific time period, the accumulation of evidence whether positive or negative increases over time as we move to the right.

For items and services that are subject to regulatory approval prior to marketing, consider the Y axis also identified

the commencement of commercial availability to Medicare. You will notice two more horizontal lines, one green and one red. The green line serves graphically to identify the transition

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threshold between non-coverage and CED. The red line graphically identifies the transition threshold between CED and broader coverage. I separated the three lines so you can more readily appreciate them as distinct lines. The relative position of these lines may depend on the factors we will discuss today, and the black double arrows are meant to illustrate this flexibility.

Slide 14 adds a simple evidence line. The black line identifies the mean estimate of the impact of an item or service on health outcomes. In this case the mean is consistently more positive as evidence is generated over time. There are for this illustration confidence intervals around the estimate over time. Here the confidence interval narrows somewhat as time progresses. At any point in time we can see the mean estimate is accompanied by an optimistic and a pessimistic confidence interval. Experience has shown us that in real life stakeholders may hold correspondingly optimistic or negative or pessimistic opinions about the sufficiency of evidence to support

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coverage, CED, or non-coverage. Thus we thought of a way to represent this for the questions, and we used the green and red arrows to acknowledge their potential effect on coverage policy.

There is of course no guarantee that every item or service would follow a linear or consistently upward trajectory. We have seen unfortunate examples where initially promising technologies have over time been found to be useless or harmful.

That's the end of my questions and I will turn things over to Cliff.

DR. C. GOODMAN: Thank you very much, Dr. Jacques, thank you for the narrative explanation and the great pictures, both are complementary insofar as clarifying where we stand at this point.

We will now move to the scheduled public comments, of which there will be nine, and as noted earlier we are allocating five minutes to each of those and we will need to keep those times.

Our first scheduled public commenter is Dr. Michael Mack, who is the STS past

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president, representing the Society of Thoracic Surgeons. Welcome, Dr. Mack. We're glad you're here today.

DR. MACK: Thank you very much, and thank you for the opportunity of making this presentation. As well as being the immediate past president of the Society of Thoracic Surgeons, I am also chair of the steering committee of the transcatheter valve therapy registry, which is a newly formed vehicle for CED. I have no conflicts to report.

So STS, the Society of Thoracic Surgeons, and ACC, American College of Cardiology TVT registry emanated from an idea in February of 2011. It was embodied in the STS-ACC request for transcatheter aortic valve replacement that was filed with Medicare, with CMS on September 22nd.

On November 2nd the Food and Drug Administration approved the Edwards Lifesciences SAPIEN transcatheter valve device, and in that approval ordered Edwards to continue to evaluate the outcomes with the SAPIEN THV valve through a national transcatheter valve registry. And on

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December 1st, nine months from the idea to form this, the STS and ACC launched the national TVT registry by working in close collaboration with both CMS and the FDA, and it does serve as we view it, an ideal vehicle for CED. We were the bottom registry mentioned on Dr. Jacques' slides.

So there are key characteristics for the successful CED policy, and the first is coordination among all relevant stakeholders, early discussions among stakeholders, and flexibility of the CED data collection mechanism. Indeed, there were seven stakeholders that were involved from the beginning with the construction of the TVT registry and that includes the American College of Cardiology, the Society of Thoracic Surgeons, the Duke Clinical Research Institute, the FDA, CMS, and NHLBI. In addition, Edwards Lifesciences, the sponsor of the first group device, has worked closely with us. And this started 15 months ago, and nine months from idea to execution.

We feel that CED should permit collaboration and generate buy-in from relevant

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stakeholders, including the professional societies, government agencies, industry and other payers. Currently many manufacturers of similar products in the same class often design their studies differently or with different or disparate evidence. This TVT registry is agnostic to device.
Further, different government agencies also have dissimilar evidentiary needs, and we've gone to great lengths to incorporate the needs of FDA and CMS in constructing this database. The vision here is to have a common platform from the pre-IED process through postmarket surveillance, and expand to global harmonization of international databases, so that out of U.S. data can be used. We have coordinated with the Valve Academic Research Consortium and have common definitions that will be used throughout the process.
So, the TVT registry is a new database, there's web-based entry, it's harmonized with the STS clinical database of surgical outcomes, it's linked with CMS data, and uses VARC definitions, and it's an example of bringing these resources to bear to
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facilitate coverage.
Given the limited statutory time frames of issuing an NCD, it was important to start it early and get it going, and as I mentioned, we were able to accomplish this in a nine-month period of time. An individual CED must be adaptable and able to evolve in order to respond to the changing evidentiary and technology landscape which may introduce new or different indications.
Data collection should be usable to identify anomalies, tag the causes of adverse events, and identify the reason for changes in outcomes, and I think we have been able to do this. Data collection through the TVT registry allows for the necessary flexibility and can evolve alongside the changing environment. The TVT registry was able to target specific areas for clinical practice improvements, reflect actual practice patterns, assess national and regional averages, and support quality improvement. We would be able to monitor off indication and off label usage, real world usage, indication creep, and real world outcomes by an annual report.
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DR. C. GOODMAN: Less than a minute

left, Dr. Mack.
DR. MACK: In summary, the TVT registry and STS support a non-binary coverage paradigm. Evidentiary thresholds can be defined to invoke CED. Early coordination among the stakeholders is important. It needs to be flexible. The TVT registry embodies all of these. Some examples of CED that come to mind immediately are monitoring outcomes in low versus high volume programs, off indications including bicuspid aortic valves, end-stage renal disease, and alternative approaches to the transcatheter approach. Thank you.
DR. C. GOODMAN: Thank you very much, Dr. Mack, and we appreciate especially your points regarding coordination of stakeholders, early discussion and flexibility of data collection, your points are well taken, sir, thank you.
Next is Dr. Ralph Brindis, past president of the American College of Cardiology, representing the American College of Cardiology. Welcome, Dr. Brindis.
DR. BRINDIS: Thank you. Again, my

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name is Ralph Brindis, I'm the senior advisor for cardiovascular disease at Northern California Kaiser, clinical professor at UCSF, and I'm representing the ACC as past president and previous chair of the management board of the national cardiovascular data registry.
The ACC believes that coverage with evidence development is an extremely powerful mechanism that offers tremendous values to payers, clinicians, but most importantly, our patients. We believe that CED has been demonstrated to be an ingenious technique allowing the diffusion of diverse innovative cardiovascular technologies and services into the marketplace, while simultaneously promoting timely clinical safety and effectiveness evaluations. The ACC supports the use of CED to provide CMS beneficiaries with prompt access to new technologies and services when the early evidence suggests but does not convincingly demonstrate enough benefit for the beneficiaries.
Now registries have an important role, as mentioned by Dr. Mack, in CED. In partnership with randomized clinical trials,

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registries such as the NCDR provide a valuable cost effective mechanism to help meet the needs of CED evaluation and fostering improvements in

quality of care. The concept of CED-mandated registry participation when appropriate promotes a powerful national research and data collection infrastructure to assess treatments in relatively moderate patient subgroups not well suited for randomized clinical trials such as referred by Dr. Louis Jacques, renal failure in the markedly elderly.

The national cardiovascular data registry now has seven registries, mostly episodic and hospital-based, but also an ambulatory care registry, and we're proud to be associated with the STS with our valve registry in addition. The NCDR represents now over 15 million patient records and is in 2,200 of our nation's hospitals. The NCDR infrastructure supports research related to effectiveness, diffusion of new technologies, is utilized now aggressively for postmarket surveillance, working with the FDA in particular in this area, looking at device performance trends, off label use and so forth. And importantly

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for our patients and our hospitals and clinicians, quality improvement and translational research opportunities.

Very important now, the registry in a very cost effective manner can be putting CED to work to generate high fidelity clinical and economic outcome studies by merging our episodic, the hospital-based records with our ambulatory care registry and through a novel paradigm of probabilistic matching, taking rich clinical data from registries and merging it with medical claims data to get a true picture of longitudinal disease processes.

Examples through the leadership of Mark McClellan, Sean Tunis, Steve Phurrough has been our ICD registry which is now answering questions related to subgroups for potential extension of coverage. And again, through Dr. Mack's work with our TVT registry, we will maybe be able to answer questions related to potential off label use in terms of coverage with evidence development in that registry.

The registries can identify and close gaps, reduce waits through inefficient care variations, and implement effective continuous

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quality improvement processes.

We would encourage CMS to make sure when using CED to look at well-defined clinical questions in their formulation, using clinical experts and professional societies most likely

to provide the services in question. We would encourage that a regional time frame for evaluation of data be collected as part of CED. We would encourage that data analysis be planned to be transparent in how CMS will use the data collected through CED. We would encourage that there be inherent mechanisms for modifying data captured elements as knowledge evolves through ongoing analysis during this CED period.

We would also encourage that there be transparent evaluation period that describes how CMS will determine whether evidence collected through the CED mechanism is sufficient to justify national coverage. We also would encourage that there be flexibility to reflect the changing clinical science with periodic evaluation and updating as needed of the coverage of evidence development itself.

DR. C. GOODMAN: You want to close

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very soon, Doctor.

DR. BRINDIS: Okay. A non-binary paradigm, chronic therapy for evolving disease in patients may not fit into a binary paradigm and these thresholds need to be flexible. Thank you very much.

DR. C. GOODMAN: Thank you very much, Dr. Brindis. Note is particularly taken of your use of registries as a data source for looking across the life cycle of disease, your mention of comparable effectiveness, practical time frame transparency and then adaptive valued approach, points well made. Thank you, sir.

Next is Dr. Mark Perman, who is the president of the Registry for Prostate Cancer Radiosurgery. Welcome, Dr. Perman.

DR. PERMAN: Good morning. I am a radiation oncologist in Stuart, Florida. I have nothing to disclose. I will do something difficult for me today, I'm going to try to talk in CMS speak instead of medicine, so please bear with me if I don't use the terms absolutely correctly.

I am pleased to speak to you about our

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experience with CED in Florida. We have found that non-binary coverage does differ from binary coverage in that it allows access to care when otherwise it would be denied to patients. That was particularly the case in 2010 when a MEDCAC was held about radiation therapy in prostate cancer, and it showed that

there were gaps in the evidence and since there was no national coverage determination, the local contractors were permitted to make coverage determinations. As a result, several contractors are now using a non-binary approach to cover stereotactic body radiosurgery for prostate cancer, covering patients that are enrolled in a registry.

We created the RPCR to fill in the gaps in the evidentiary trial. We had presented our plans to CMS to define the data elements of the registry and as you can see here, it's just some of the demographics that, what we have been collecting, and some of the things are objective like the survival and PSA, but also toxicity and other things that are important to monitor.

Right now we have 22 centers and we're

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soon to have about 40. We've grown beyond Florida, we are now national, and this is to prove that we do exist, we now have over 900 men that we've accrued. We have done this in about a year and a half.

And finally, we think that collaboration among stakeholders to define what needs to be collected, and I think the biggest point is that once the agreed upon criteria are met, the local contractor would remove the registry requirement and would move to unrestricted coverage, and that's it.

DR. C. GOODMAN: Thank you very much, Dr. Perman. Again, your points are well taken regarding the non-binary approach, your role of registries to fill evidence gaps, the collaborative approach, and pointedly at the end, when to stop CED. So thank you, your points are very well taken.

Next is Dr. Norman Foster, professor in the department of neurology and director for the Center for Alzheimer's Care, Imaging and Research, at the Brain Institute, University of Utah. Dr. Foster, welcome, sir.

DR. FOSTER: Thank you for this

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opportunity to comment on coverage with evidence development trials. I'm representing only myself, I paid my own travel and lodging expenses, I've not received any payments or honoraria for attending or for this testimony.

I have submitted a written statement that extends my comments today and lists my disclosures. Most importantly, I'm involved in a CED study and also, I receive payments from

Medicare for direct patient care.
DR. C. GOODMAN: Doctor, I apologize, sir. Dr. Foster is not presenting Power Point slides so you may want to take down what's on the screen now. He will be speaking from prepared remarks. Please proceed.
DR. FOSTER: Thank you. As mentioned, I direct the Center for Alzheimer Care, Imaging and Research at the University of Utah, and I maintain an active clinical practice, primarily evaluating patients with cognitive disorders, and I have been involved in clinical research for the past 30 years focusing on clinical trials, brain imaging and improving health services. I'm also principal site investigator at the University of Utah for a CED study, the

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first one that was listed on the Power Point earlier called Metabolic Cerebral Imaging and Incipient Dementia, Early and Long-Term Value of Imaging Brain Metabolism. Daniel Silverman at UCLA is the study principal investigator.
This study is the result of a national coverage decision for FDG-PET in dementing diseases, which indicated that CMS would reimburse FDG-PET scans in patients without dementia in a selected clinical trial. My colleagues and I contributed to the literature suggesting that FDG-PET could inform diagnosis and treatment in the otherwise indeterminate condition often called mild cognitive impairment that often leads to Alzheimer's disease.
Consequently, proving the value of FDG-PET in clinical practice is a goal that's very close to my heart. My commitment to this study has been critical because we have encountered many significant barriers and unexpected challenges in participating in this study. I hope our practical experience with this study will be helpful in your deliberations today.

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My comments as a user of CED studies is that they should be designed to address some of the problems that we faced. A general guidance for CED studies should be formulated and published, because I found that institutions are not prepared to handle the billing and regulatory issues for these hybrids of clinical care and clinical research.
Studies designed for NIH review are often ill suited to CED studies and may have different outcomes in mind. One of the problems is that

there is no way to review CED studies when they are undertaken by CMS. Barriers to patient participation should be minimized. It's important that studies truly reflect clinical populations. Studies should not be onerous to participating sites, adequate reimbursement is needed for the effort involved. There should be a single contact at CMS who can resolve carrier issues. Protocol should be simple and focus on process and patient outcomes identified during routine care. Longitudinal outcomes are important, and often could be obtained just as well through telephone contact if reimbursement were

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available. Fifth, successful studies are likely to be formulated by a committed collaborative group of experts established in response to a specific RFA. I strongly support the concept of coverage with evidence development, it's an important avenue to new clinical discovery. In fact, in our experience already in this study we've obtained valuable novel information that's making a difference in how we evaluate and how we manage patients. It's changed my clinical practice, for example. We hope to participate in future CED programs, but improvements are necessary. We have incurred considerable unreimbursed expenses that are difficult to justify to our department and our institution. Nevertheless, getting CED studies right will have important benefits for patients and will transform how we practice medicine. Thank you.

DR. C. GOODMAN: Thank you very much, Dr. Foster, and thank you very much for calling attention to the practical experience of designing and implementing CED, and I think that the points that you made are very useful

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guideposts for any agency or organization that wants to go about doing CED, and these points are much appreciated. Next is Dr. Bruce Quinn, representing, from Foley Hoag here in the Washington area. Welcome, Dr. Quinn.

DR. QUINN: Good morning. I am an employee, these comments are my own. I have been a university pathologist and a Medicare administrator, but much of my career has actually been in strategy consulting. We get to this MEDCAC when the coverage group faces a policy problem which has

its roots in missing data. You have to stop until we define exactly what that missing data is. If and when you define it, you might invest in claims analysis, modeling, registries or RCTs. Which ones can or can't fill that defined missing data you don't know until you define exactly what the missing data is for that problem.

When you design the trial, how would you fund it, consider industry or NIH or PCORI or the payer. When would you use the payer? Perhaps if no one else will fund it, the payer

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is the funder of exclusion. Or when the payer, what the payer wants isn't a good match to other funders so it has to fund it itself. Or the payer could actually save money and get an ROI by doing the trial. Or the payer buys a seat at the table where it would not otherwise have a voice. Or the payer solves some other kind of problem by doing the CED, so you can't look at the CED and figure out why it's there. Or finally, the payer may do CED although it doesn't make much sense, which is what we would want to avoid. If you are the payer, what will you fund? CED is a funding mechanism, not a research mechanism, and it turns out a lot of factors tend to push you toward the registries. As Dr. Foster just described, if the CED is only ten percent of the cost, you get hung up. So, Medicare has this world of Medicare services. If you can use binary or non-binary coverage, there's this black box in between and that's this MEDCAC. We know that diagnostics have a lot of missing data, so I'll focus on that. In fact people have been complaining about diagnostics and being overused and missing data for a century, going

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back to 1912.

There are all kinds of problems with evidence for diagnostic tests so I'm not going to belabor this, plus I don't have RCTs to show causality and so on, but instead of giving examples of the problem, my approach is to talk about causes of these problems. So for example, in the BRCA gene and breast cancer, evidence is rated as only a fair association between the BRCA gene and breast cancer, but it causes breast cancer. The cystic fibrosis gene causes cystic fibrosis. The evidence is rated fair because there are no RCTs, there's only expert opinion that observational data is correct.

Evidence is often downgraded if you don't have a double blinded trial to get the highest level. You generally can't do double blinded trials with diagnostics. If you had a cancer test double blinded you'd give half the doctors fake data whether the patient's test was cancer or not, which makes no sense. RCTs help establish causality, a pivotal factor. The diagnostic test may work by correlation, not causality. Troponin is

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well correlated with MI but Troponin does not cause an MI, if you give Troponin it doesn't cause an MI.

Q. Another RCT problem with complex tests like PET scans, if you just shove a hundred women with cervical cancer into a PET scan whether they need it or not, it probably won't be very helpful. So we order that imaging when there's a specific situation, a specific previous test, a specific patient symptom that leads to the need for the test. It is not really a standard RCT anymore.

The next test can have weak data, but in genomics you can have retrospective data that's very strong, though not a high level of evidence, and it creates equipoise problems that are absolutely real in terms of the moment.

Finally, I would say diagnostic tests are like Herceptin. Imagine 200 women with breast cancer. 100 go into a Herceptin arm, only 30 can possibly respond, let's say 15 do, and those 15 responders are washed out in the whole population. So we enrich for the Herceptin test, we enrich for the subsequent

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test, positivity; now half the patients respond and we can pick them up, so it's a scientific victory.

With the PET scan it actually does 100 patients with the test, only 30 percent have a changed diagnosis and management, half of those live longer, and you're down to the same 15 out of a hundred that's going to get washed out.

Finally, industry economics, let's say three companies make PET scanners, one of them invests $50 million in a breast cancer accuracy trial, but everyone knows that it applies to all three brands of scanners, so they're inhibited from investing.

DR. C. GOODMAN: Less than a minute, Dr. Quinn.

DR. QUINN: Sure. Finally, the FDA

blocks clinical use in patients until you've fully vetted the test and approved it, so you tend to get FDA approval before it's medically safe. So I would be looking not so much at just this decision, but rather CMS paying for local coverage or non-coverage, or fixed coverage, or the non-binary coverage with evidence, and it's the choice between those and

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their pros and cons that actually drive the CMS decision. If you have defined the data carefully you can say what is missing, is it a safety issue, a usage issue, the decision impact, do you need to know more about the accuracy, and that class of problems of missing data will help tell you whether the CED is going to solve it or not.

So in summary, I would say there are four levels, a policy problem, missing data, the type of trial design, and a funding mechanism. And if you define each four of those, you can walk people through the stakeholder agreement that you need to have a rational choice. Thank you.

DR. C. GOODMAN: Thank you very much, Dr. Quinn, and we appreciate especially your discussion of the four levels of consideration, and notably the relationship between the quality of evidence and the circumstances for initiating CED, including for diagnostic tests. We very much appreciate your comments. Thank you.

Next is Elizabeth Halpern, who is counsel with Hogan Lovells, representing the

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Medical Device Manufacturers Association, known as MDMA. She will present from text only, no Power Point. Welcome, Ms, Halpern.

MS. HALPERN: Thank you. As I was introduced, my name is Beth Halpern, I am counsel with Hogan & Lovells. We represent MDMA and several other clients on Medicare coverage in general, and CED specifically. I am pleased to be able to speak today on behalf of MDMA. MDMA represents hundreds of medical device companies and our mission is to ensure that patients have access to the latest advancements in medical technologies, most of which are developed by small research-driven medical device companies.

MDMA's members also devote considerable resources and effort to improving and extending the clinical evidence to help Medicare beneficiaries, other patients and

providers make the most appropriate diagnostic and therapeutic decisions. MDMA, therefore, supports the Center for Medicare and Medicaid Services efforts to improve the CED process, to reduce barriers to innovation, and improve health outcomes for Medicare beneficiaries.

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Our primary concern is that such efforts do not inadvertently limit patient access to advanced medical technologies.

With this concern in mind, I would like to briefly summarize our answers to the questions to the panel, and our written statement provides more detailed responses to those questions.

So first, MDMA believes that there are significant practical differences between binary and non-binary coverage paradigms. Non-binary coverage paradigms can be rewarding for all parties involved, reducing barriers to innovative care and improving the evidence base for treatment and diagnostic decisions. However, they are more difficult for CMS, providers and other stakeholders to implement. They require careful analysis by CMS in conjunction with excessive discussions with stakeholders to evaluate the evidence available prior to the decision, identify the clinical outcomes to be measured under a CED approach, establish an appropriate method of collecting data, collect and analyze that information, and then determine if the outcomes have actually

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been achieved. Because non-binary coverage paradigms apply only until the planned reconsideration occurs, they also expose technologies to greater uncertainty about future coverage decisions than binary coverage paradigms do. If the non-binary approach is not implemented appropriately, transparently and predictably, it can result in limited access to treat options and can discourage future innovation.

So second, we'll try to address questions two through five all together. We do believe that an evidentiary threshold can be identified and should be identified to invoke CED and to determine when to trigger the end of application of CED for a particular item or service. These thresholds, however, likely will vary by item or service due to the factors identified in questions three and four, as well as the opportunities to develop evidence with and without CED.

Factors such as whether the technology is diagnostic or therapeutic, the severity of disease at issue, availability of acceptable treatment alternatives or diagnostic

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alternatives, and the safety profile of the technology alone and in combination can have a significant effect on the type and amount of evidence available and opportunities to conduct further research. Just as patients and physicians must weigh these factors to decide on the best course of action for a patient, CMS also should account for all of these factors and the interactions among them when establishing evidentiary thresholds for invoking or ending CED.

Ultimately, the appropriate evidentiary threshold for each application of CED can only be identified through extensive input from knowledgeable stakeholders such as physicians, researchers and the manufacturing community. The manufacturers' input into a particular area can be essential to CMS's ability to understand the evidence supporting a technology, any gaps in that evidence, and any additional research efforts underway or planned to address those gaps. It also is critical to define a meaningful endpoint for any studies conducted under CED, and identifying appropriate research methods that would impose

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minimal burdens on all stakeholders.

All these factors together are essential to establishing clear predictable coverage policies that support access to appropriate care, and encourage innovation.

And finally, in addition to defining a threshold for each specific application of CED, we encourage CMS to continue to work on revising its guidance document that will define thresholds in general terms and help improve the predictability and transparency of CMS's coverage decisions. Consistent with the CMS 2006 guidance document on CED, we would recommend that the revised guidance ensure that CED continues to be used infrequently and not when other forms of coverage are justified by available evidence.

MDMA is confident that appropriate use of CED can help improve health outcomes for Medicare beneficiaries, but we also recognize that CED involves considerable investment of time and resources by CMS and stakeholders, and therefore it should be applied only when

necessary. CMS should seek revised stakeholder input on a revised draft of this guidance, and

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should seek comments on any changes to the thresholds defined in the guidance as it gains more experience with CED.

DR. C. GOODMAN: You will want to wrap up soon.

MS. HALPERN: Okay. MDMA appreciates this opportunity to present our views to the MEDCAC on CED. We support CMS's efforts to revise the CED guidance to reduce barriers to innovation and improve health outcomes for Medicare beneficiaries, and we're looking forward to working with CMS on this issue in the future.

DR. C. GOODMAN: Great, excellent. Thank you, Ms. Halpern, and thank you in particular for your specific answers to the five questions and your emphasis on the need for continued work on revising the guidance document on an ongoing basis. Thank you, Ms. Halpern.

Next is Ann-Marie Lynch, who is the executive vice president for payment and health care delivery policy at the Advanced Medical Technology Association, otherwise known as AdvaMed. She's not presenting Power Point.

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Welcome, Ms. Lynch.

MS. LYNCH: Thank you very much, good morning. My name is Ann-Marie Lynch, executive vice president for payment and health care delivery policy at AdvaMed, a national trade association representing manufacturers of medical devices and diagnostic products. Our member companies produce life-saving and life-enhancing medical devices and diagnostic products and health information systems that are really transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. Our members range from the largest to the smallest medical technology innovators and manufacturers. I have no conflicts to report. We appreciate the opportunity to comment here today in this public forum, and we look forward to ongoing discussions with CMS on issues related to coverage with evidence development and evidence generation. The medical device industry has long supported the use of sound evidence to inform medical practice. However, we become concerned when a CMS decision that requires CED in order to

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allow certain Medicare beneficiaries access to medical technology adds a significant requirement to manufacturers and providers and delays access for other Medicare beneficiaries. It appears that CMS is seeking through this MEDCAC meeting to identify criteria for determining when the available evidence for a product is sufficient and when it suggests that coverage conditioned upon additional evidence development is warranted. The question being addressed at the MEDCAC refers to an evidentiary threshold for CED, and we're concerned that it's not feasible to define with any precision such an evidentiary threshold for medical procedures or services because it would vary widely depending on the item or the service being evaluated and the clinical needs of the individual patients. In our written comments we raised the following key concerns: First, rather than attempt to define an evidentiary threshold for CED, CMS should engage in a meaningful dialogue with developers and manufacturers prior to the initiation of a national coverage decision or a decision regarding CED in order to determine
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whether and if additional data collection is needed. If CED is needed, CMS and the manufacturer should collaborate to determine the type of evidence and the method of data collection that would be necessary to reach a coverage determination about a new or innovative treatment. CMS would benefit from drawing on the expertise and experience of the clinicians, scientists, engineers, and other experts working with or employed by the medical device companies regarding evidence generation. This manufacturer's input is valuable, particularly given that our clinical and scientific experts often have unique knowledge regarding existing data and ongoing studies. This exchange would allow both CMS and the manufacturers to determine the best pathway to timely coverage for Medicare beneficiaries. Second, CMS should use CED infrequently and only when the Agency is expanding coverage for new or innovative technologies. The CMS guidance on CED issued in 2006 included eight principles to govern the use of CED, or coverage with evidence
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development. AdvaMed continues to agree with

those principles.
Third, recent national coverage activity suggests that the Agency is increasingly employing coverage with evidence development. Although CMS has not defined what is or is not reasonable and necessary for coverage purposes, it appears that CMS is raising the evidence bar compared to previous national coverage determinations, leading to more national coverage determinations calling for CED in more circumstances.
Fourth, in recent national coverage decision proposals, CMS has mandated the type and design of clinical studies that it will accept under CED. We believe that CED should be the exception, not the norm in national coverage decision-making. In cases where CMS and stakeholders agree that CED is the best option for coverage, CMS should seriously consider study design proposals by stakeholders and shouldn't arbitrarily rule out particular study methods that could generate sufficient evidence to address specific clinical questions about an item or service being evaluated.

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Fifth, we don't believe it's feasible to identify or define a specific evidentiary threshold for invoking CED or for the CED study itself. Every medical intervention will have different factors that must be considered with respect to evidence, and we don't believe it's possible to determine a one size fits all evidentiary threshold.
Sixth, finally, what CMS has initiated, we continue to have concerns regarding data collection requirements and the way the CED study is carried out. When Medicare coverage is contingent upon the collection of additional clinical or scientific data that is beyond FDA's determination of safety and efficacy, CMS should first collaborate with stakeholders to clearly identify the research questions that data collection efforts should address. They should also be sensitive to the cost and challenges associated with data collection, and refrain from requiring more than the data that is necessary to answer those clinical questions that are posed. Third, they should work very closely with stakeholders to clearly identify

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scientifically supported study endpoints and the duration of data collection in advance.
AdvaMed's more detailed comments were

submitted for the record. In summary, we believe that CMS's decisions about coverage criteria and the CED process should be clear and should not result in delayed access to promising technologies for beneficiaries or the physicians who treat them. We appreciate the opportunity to share our views on this important issue and will be pleased to answer any questions regarding these comments.

DR. C. GOODMAN: Excellent, thank you, Ms. Lynch. We appreciate AdvaMed's very close attention to this issue, as it has over the years. Your points are well taken regarding the criteria for evidentiary thresholds that may be difficult to define based on differences in items and services, and we appreciate your point on engaging in dialogue with technology sponsors and other experts in collaborating on evidence needed and study design. Thank you very much, your points are well taken.

Next is Alyson Pusey, who is the director of reimbursement and health policy at

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the Biotechnology Industry Organization, that's BIO. Welcome, Ms. Pusey.

MS. PUSEY: Thank you. As introduced, my name is Alyson Pusey, I am the director of policy and reimbursement with BIO. BIO members are involved in the research and development of novel interventions to prevent, treat and cure diseases with the most advanced science. My comments today focus on some of the themes raised in the voting questions, and I ask the committee to refer to our written comments which provide detailed responses to each question.

CMS is interested in whether an evidentiary standard can be defined to invoke CED. BIO believes that there is already a well established evidentiary threshold applied to coverage of most drugs and biologics. Drugs and biologics are subject to a rigorous evidence-based review by the FDA and in some cases a post-approval marketing study. In addition, Medicare and its contractors currently use an evidence-based system to determine coverage for off label uses of drugs and biologics. By using this authoritative

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compendium of medical literature to define medically accepted indications, the statute in Medicare's citing protect beneficiaries' timely access to drugs and biologics, while also ensuring that Medicare's coverage policies are

truly evidence-based. CED is best used to expand patients' access to therapies that would not otherwise be available. It is therefore not necessary or appropriate for FDA-approved products and medically accepted uses of drugs and biologics. CMS is also interested in understanding the advantages and disadvantages of non-binary coverage paradigms. Non-binary coverage paradigms have a few disadvantages, one being that it creates a substantially less predictable coverage and reimbursement environment. BIO continues to stress, as we have in previous comments, the importance of a predictable and transparent and clearly defined CED policy. CMS recognized the need to provide for a predictable coverage and reimbursement environment when it first developed the principles for applying CED and this need is still relevant today, and should therefore be

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reflected in new guidelines. Clarity and predictability are particularly critical for many of BIO's emerging company members who depend on private equity investment to fund their development. If under a newly designed CED policy manufacturers are unclear about the rationale for CMS's application of CED, the investment in new medical technologies will be severely interrupted, and patient access to improved drugs and biologics may be delayed. Therefore, CMS must communicate why CED for a given technology is considered necessary, and identify a priori the outstanding evidentiary questions that must be resolved. The process for collecting evidence must be understandable and each data collection activity must have a well defined endpoint. I also urge strongly that CED should not be an open and undefined data gathering exercise. CED decisions should have clearly defined time frames that dictate when sufficient evidence has been collected to support review for full coverage. We acknowledge that while this

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timeline may be different for various products and services, it should be part of an ongoing dialogue between CMS, the interested stakeholders, and appropriate expert advisors such as clinical epidemiologists and Scientologists -- scientists, not Scientologists.

(Laughter.)
In addition, CMS needs to carefully weigh the additional costs and burden imposed on stakeholders for the types of studies it considers sufficient for CED purposes. Finally, any application of CED must be developed in a transparent and predictable manner with the opportunity for stakeholder comment to ensure that CMS reaches an appropriate decision for patients. To achieve this goal, CED should occur only within the auspices of the NCD process, and should have predictable procedures and timelines to establish a valid coverage determination. BIO, again, appreciates the opportunity to comment on evidentiary characteristics of CED, and we encourage the Agency and the MEDCAC to continue to solicit input from stakeholders in order to

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develop a CED policy that is transparent and predictable. Thank you.
DR. C. GOODMAN: Thank you very much, Ms. Pusey. We understand that BIO contends that CED should be a way to expand access. I think we heard you say that BIO contends that CED is not appropriate for FDA-approved products. Your point is well taken regarding that CED from your standpoint might result in a less predictable environment and that you look for predictable timelines and other factors that might make that environment more predictable. We thank you for your points.
Next up is Dr. Richard Frank, and he's the vice president for global clinical strategy and policy for healthcare systems for GE Healthcare. Welcome, Dr. Frank.
DR. FRANK: Thank you, and good morning. My affiliation is correct as Dr. Goodman has stated now, not as was listed on the CMS website. And furthermore, I'm vice chair of the PET group for the Medical Imaging & Technology Alliance, on whose behalf I will be verbalizing some of the key points from the letter we submitted to the docket on

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April 16th. The Medical Imaging & Technology Alliance appreciates this opportunity to provide input.
In response to question one, yes, there are significant practical differences between binary and non-binary coverage paradigms. Non-binary coverage paradigms involve greater uncertainty not only about the ultimate coverage decisions but also about the

types of studies that will be used to collect data, the endpoints that will need to be achieved, and the time frames for completing data collection and then reconsidering the coverage decision. To minimize the burdens associated with non-binary paradigms, CMS should ensure that studies conducted under these paradigms employ well-defined relevant and pragmatic endpoints. These studies should be limited to what is necessary and sufficient to inform a decision for coverage. The data collection must be achievable within a reasonable predefined time frame. Stakeholders from academia, professional societies and industry should be included in an efficient process of evaluating the evidence available

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prior to initiating any additional data collection exercise.

Consistent with CMS 2006 guidance on CED, non-binary coverage paradigms should be used rarely and not when other forms of coverage, for example binary coverage paradigms, are justified by the available evidence. In particular, MITA believes that the labeled indications from FDA-approved technologies should be covered under binary coverage determinations.

With regard to question two, MITA believes that an evidentiary threshold can and should be defined prior to invoking CED, but we believe that the threshold may differ depending on the type of technology and the indications or applications under review. CMS should work with stakeholders to develop clear guidance that will explain the general criteria for determining whether there is enough evidence for CED but not enough for a binary coverage determination.

In the past discussions of CED have used terms such as suggestive to describe the clinical evidence that could support use of CED

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but otherwise would be insufficient for a positive coverage determination. This would represent, I believe, the area on Dr. Jacques' graph between the green and the red lines. The lack of a clear definition of this term or of that space on Dr. Jacques' graph has hindered stakeholders' ability to understand when an item or service might be a candidate for CED rather than non-coverage or coverage without evidence development. Thus, CMS guidance should explain the applicable terms to improve

the predictability and transparency of future coverage determinations, and to continue innovation.

With respect to question three, diagnostics are different. Diagnostic technology is subject to different regulatory standards for approval than are therapeutic technologies, and so also should be subjected to different evidentiary thresholds for coverage. As in the PET CED, CMS should measure diagnostics against their intended use, such as to achieve diagnostic outcomes such as diagnosing a condition, management of disease progression, or helping to determine a

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treatment plan, as opposed to or in contradistinction to classical therapeutic outcomes.

CMS should be sensitive to the fact that the acceptable alternatives may be different for each patient as judged by the patient and his or her physician. CMS should support beneficiaries' access to appropriate diagnostic and treatment options by providing coverage for a range of technologies and allowing physicians and patients to select the best option for each patient.

With regard to question four, MITA believes that the labeled indications of FDA-approved technologies should not be subject to CED. At times CED might be appropriate for additional considerations after considering the factors identified in the previous question.

With regard to question five, MITA believes that an evidentiary threshold that triggers review to determine whether CED should cease should be defined at the time the CED decision is announced.

In conclusion, MITA appreciates this opportunity to present our views on CED to the

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MEDCAC. We are hopeful that we can continue to work with CMS to ensure that the Agency has access to the clinical evidence necessary to make informed decisions to enable access to new products and services with reasonable boundaries, and to encourage innovation in imaging technologies. Indeed, MITA has convened already one workshop on this topic and is currently organizing another on the specific subject of endpoints for coverage decisions with regard to diagnostics. Thank you.

DR. C. GOODMAN: Thank you very much, Dr. Frank, and we appreciate your attention

specifically to the five questions at hand. We understand your position on the circumstances of using thresholds, that they should differ for different applications, appreciate it, and clarifying the circumstances for initiating CED. We heard you say that diagnostics are different, and we heard you say that from your standpoint, the labeled FDA indications would not be subject to CED. Thank you, sir, very much.

And I want to thank all of our nine presenters for their concise and to the point

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remarks and for staying within time, much appreciated, and we took very careful note of the points that you made, and they were made well.

We are now going to move to addressing our five questions, and as Dr. Jacques mentioned earlier today, our format for today's MEDCAC meeting is different from others. We're going to have expert speakers address the respective five questions and what we're going to do is actually for each question as we go, we're going to have a discussion for each and we will actually, where noted and necessary, where there's an up or down yes or no vote for Ms. Ellis's purposes, we'll take those votes. As I think you're going to see, the yeses and nos are probably a little less important than the meat of the discussion that we're going to have.

In each case we're going to have, as I said, an expert speaker initiate the discussion or presentation of the points to be made for each question. When that speaker is done and he, in this case they are all hes, they will each have 12 to 15 minutes maximum to address

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the respective questions. When each person has addressed that question, we will have a panel discussion as well as comments as appropriate from our other expert presenters. So while each expert presenter has been designated at least one question, they have also been asked to think ahead of time about comments that they might make with regard to the other questions on the table. This way we get as much as we can from our expert speakers.

I will note for our panel that we will be able to inquire of the expert speakers, including the main presenter and the others, and if you so wish, if you have a particular question to address that's on point for a given

question to one of our earlier presenters, that's okay too. As we move from one question to another, our vice chair, Dr. Steve Phurrough, is going to provide some wrap-up summary comments just to make sure that we capture the essence if not the full consensus of the discussion. Dr. Phurrough, am I missing anything else?

MS. SYREK JENSEN: Open speakers.

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DR. C. GOODMAN: Ah, yes. I'm supposed to note that although next on our agenda, or soon on our agenda would be presenters from public commenters signing up for the day, thus far we have none today, so we don't need to address that point. Thank you, Ms. Syrek Jensen. Dr. Phurrough, did we miss anything else? Okay.

So, our first person to address a question is Dr. Allan Korn, from the Blue Cross Blue Shield Association. Dr. Korn will not have Power Point slides, he's going to speak from the podium. I should add, Dr. Korn is senior vice president for clinical affairs and the chief medical officer at the Blue Cross Blue Shield Association. Welcome, Dr. Korn.

DR. KORN: Well, it's a pleasure to be here. I will disclose that as part of my responsibilities, I do oversee the Technology Evaluation Center and I have no other conflicts, because, like Dr. Jacques, I'm not allowed to.

First I want to address some of the challenges faced by the private sector in dealing with coverage with evidence development

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and then leave you with three solid criteria that I think should be included in any studies, so let's just jump right in.

Services provided to help plan members generally fall into one of three categories. The first obviously is covered, meaning that items or services fall under the scope of what is commonly defined as medically necessary. The second obviously are items deemed not medically necessary, and thus are not covered. That's sort of the two, the standard way of approaching a claim. Now investigational services or services for which there is not sufficient evidence to provide routine benefits to patients, investigational services may include devices that have received regulatory approval for at least one indication but not

necessarily for the indication at issue, to which we refer now, as you know, as off label use, and that could be for a drug or a device. Now I want you to know that Blue Cross Blue Shield has sought an alternative to binary coverage for more than 20 years. Initially we called it a third path, now it's called coverage with evidence development. The very

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nature of insurance and its oversight by state insurance commissions has brought great stability to the insurance market, but by so doing has made it very difficult to achieve alternative payment methodologies. A legal analysis by a prominent law firm of six states looking at both law and regulation revealed the following: One, yes, care could be provided in the context of a clinical trial, meaning that a service or item otherwise deemed as investigational would be afforded coverage under the terms of an insurance contract. It would, however, be the principal investigator who would need to determine member eligibility for enrollment. Two, only state-licensed entities may offer insurance coverage, and that would be subject to state law and regulation. So far, so good. Three, any benefit payable must be contained within the, quote, four corners of the policy, end quote. Still okay. Number four, in many states, such a benefit extension as coverage with evidence development would be considered must be filed

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for and approved by the insurance commissioner of that state. Five, should a plan decide to discontinue coverage with evidence development, further approval would be required even if such non-coverage was requested by its customers. Regulators, however, might be resistant to the perception of, quote, lowering benefits, end quote. And most importantly, number six, states generally absolutely prohibit discrimination between individuals in the same class in any manner whatsoever. If the number of members, for example, wishing to participate in a trial exceeded the number of open spaces, subsequent members would be excluded from the trial even though they have the same condition as the enrolled member, likewise for those diagnosed after the trial closes or who live in

inaccessible geographical locales. Such events would violate antidiscrimination provisions of state insurance approval. There could be, therefore, the expectation or even the requirement that such members would be allowed to enroll in clinical trials of their choice,

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even if unrelated to the questions and/or issues originally studied.

Now other somewhat more technical but nonetheless significant issues are raised, such as it is possible or even probable that a principal investigator might not be a contracted network provider. So unless a plan has funded an entire trial for the exclusive benefit of its members only, which is both unlikely and unrealistic, because trials will have been established and partially funded by others through grants, academic institutions or industry, we would have no control. In such circumstances where members generally pay entire co-pays for going out of network, we would have virtually no reasonable options for handling the claim, the administration of such occurrences would be difficult if not impossible.

Then by merely declining coverage with evidence development as medically necessary, well, that would serve to amplify the antidiscrimination concerns noted above, and then would further subject any denials to external review, and the insensitivity of

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external review to state law and the PI and other concerns of trials create extraordinary difficulties.

Now other issues are raised, and these have to do with such things as adverse selection or use of insurance funds to cover indirect costs of those who are uninsured or insured by others are secondarily, but nonetheless they exist. And finally, you need to know that self-insured customers using us as administrators need to be subject to, or are obligated to offer such coverage to their employees.

So it may be, so far at least, that evidence generation and a private health insurance model are incompatible. This is a subject of ongoing thought, consideration and legal analysis state by state.

Now let's assume for a moment that we overcome some of these issues. Let's assume that we actually get to the point where we

begin participating in such trials. Let's get to some criteria that we might consider. Another domain of this coverage with evidence construct is now worthy of our

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consideration, and that is financial risk versus reward. Now the motivation for such trials are complex. Knowledge about clinical value is foremost, but reimbursement for innovators, as we have heard this morning, is not far behind. Once the item or service is priced, the revenue of the innovator is secured and the liability of the purchaser is thus set, or so it might seem.

Sadly, this is not the case. Coverage with evidence development trials, after all, only have utility by definition when the balance of benefits and harms is not known. When the harms occur the liability accrues only to the purchaser. It would seem that in exchange for early reimbursement prior to such time that the medical necessity of an item or service is established, innovators should share in the financial liability associated with such untoward results.

Given the financial pressures on those who finance delivery of healthcare items and services, and that would be taxpayers, employers and families, such shared accountability would create substantial

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discipline within innovator communities to choose their requests wisely. Aligning incentives is an enduring goal of CMS, CMMI and among those involved in helping to restructure our dysfunctional delivery and financing systems. Coverage with evidence development should be no exception. Here's a suggestion for our criteria.

Moreover, we recognize there are social consequences with a fee for service payment system that rewards utilization rather than outcomes. We believe that coverage with evidence development should be forward looking, focusing on the best strategies to manage patients with chronic, complex and/or multiple conditions, rather than perpetuating a technology-by-technology, gizmo-by-gizmo or service-by-service approach. Including such complex patients should be a focus of CED. Hence, my second suggestion for a criteria.

And one last comment, a comment about harms. They are historically unreported due to such unfortunate but well documented

occurrences as publication bias, conflicts of interest, ghostwriting, et cetera. We chase
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benefit exhaustively but as Naomi Allison, who runs the Technology Evaluation Center, is famously quoted as saying, quote, we do very little marathon training for finding the harms, end quote. If coverage with evidence development trials are not explicitly designed to find them, we will have had provided a grave disservice to those who have placed their trust in us, the beneficiaries of Medicare, Medicaid and the private insurance markets. We must include a rigorous pursuit of harms as a criteria for any CED trials.

So now that binary decision-making is no longer the exclusive domain of payers and purchasers make all the above possible, and we should consider and include them in our trial designs, and I thank you.

DR. C. GOODMAN: Thank you very much, Dr. Korn. Dr. Korn, I wonder if you would come back down to the floor so that you can sit with our other experts at this point. We're going to ask our other experts in a moment for comments on Dr. Korn's initial remarks. At this point, panel, especially with regard to question one, do you have any comments you
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would like to address to Dr. Korn directly, and then we'll get further comments from some of our other experts as well.

And I will remind you that question one on the table is, are there significant practical differences between binary and non-binary coverage paradigms? If the answer is yes or favors yes, please discuss the advantages or disadvantages of non-binary paradigms. Any questions at this point? Yes, Dr. Normand.

DR. NORMAND: I just wanted clarification from Dr. Korn regarding his last comment about harms, and that trials should definitely look or seek for harms as a measure in those. I just wanted to get clarification. When you state that, are you asking about anything beyond which, for example, an FDA trial would seek for a new device or a new drug?

DR. KORN: Yes, it is. I think one of the important things that we need to consider is the tail, and so using a private insurer or perhaps CMS as an extension of a trial to look at the longer-term implications of what happens

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to people, I think is important. And I think we need to make certain as we formulate the questions that we don't formulate the questions so narrowly that we either overlook those patients who might be subject to that, it's just something that we need to think about very very carefully.
DR. NORMAND: So the answer is yes, that you do think that for CED, you would want more than what's required in FDA to initially approve something?
DR. KORN: On the drug or device side? Certainly on the device side, and I think on the drug side, we would be very very concerned about any off label use of a new product that isn't subjected to a very rigorous process.
DR. NORMAND: Thank you.
DR. C. GOODMAN: Thank you. Dr. Steve Goodman is next.
DR. S. GOODMAN: Hi, Allan. I liked your comment at the end about focus on the whole care process for complex patients, but the decisions that often CMS faces typically are in fact technology by technology, device by device. So could you just clarify what the
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implications of that particular position about a more holistic view, care of complex patients, with the fact that CMS is in fact making these decisions on a, you know, technology-specific basis?
DR. KORN: Steve, there's no easy answer. We have sort of fallen into a pattern and we do exactly what you state. And so if a genetic test turns into something, the assumption is you'd better do the test before you do it, whether or not there's any treatment or action that could be taken. I think we need to sort of take a step back and rethink this in a more holistic way, so that at the end of the day we're paying for the treatment of a patient, rather than a series of tests which in retrospect we add up and say oh, this is what we paid for, this is how we treated the patient, without really understanding whether it was the optimal sequence of events or combination of events to get to the outcomes we want. So it's a hard question, I don't have an easy answer, but I'm here to plead, we need a rethink here in terms of how we define patient centeredness in this context, and I think it's
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an important point, and I really hope we do

take a step back and think that through very carefully as this CED process matures.
DR. C. GOODMAN: Thank you. Dr. McDonough is next. Dr. Korn, you just may want to stay up there, unless you want the exercise of standing and sitting. Dr. McDonough.
DR. MCDONOUGH: I had one thing that you said I didn't quite understand, innovators should share in the cost of the untoward results. I'm just wondering what you meant by that and how coverage with evidence development would affect that.
DR. KORN: As I think I mentioned, obviously access to technology is the goal for all of us. So is early reimbursement by the innovator, and once the price is set, one would assume that our costs are fixed, but they're not. When bad things happen then all of the consequences of that fall to the payer, purchaser, taxpayer, family, business, whatever. And I do believe that in the construct of these trials, when such adverse events occur, the cost of those harms be shared, not just by the insurers and

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government, but by those who innovate. They incur, I believe, some responsibility for sharing downstream harms as well as enjoying the benefits of earlier reimbursement. And I think that would create an extraordinary discipline and an alignment of incentives for all of us to look at those most promising technologies and get them out there as quickly as possible. And where further bench or trial research is necessary, that that be done before we submit the broad population to it. Yes, early adoption of technology produces good, but you know, our experience tells us it also leads to harm and occasional death, and so I think it's something we have to approach with considerable caution, and I'm suggesting that we align incentives a little more closely.
DR. C. GOODMAN: Thank you. Mr. Lasersohn is next.
MR. LASERSOHN: Thank you. Actually I want to follow up on this specific question as well on liability. So in the context we're talking about, this would be a CED trial of some kind that would normally require some form

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of informed consent from a patient, which really should deal with the liability issue. Are you suggesting there is some intrinsic

problem with informed consent in this circumstance?
DR. KORN: No, I'm not. I think the common rule, and Mark has said, I think, make certain that patients are fully cognizant of what is occurring. In the context of what we're doing now, we're not calling it a clinical trial either, we're calling it coverage with evidence development, meaning I'll tell you what I'm doing if you pay me. Well, that's all right, but implicit in the need to do CED is the fact that the benefits and harms are pertinent, and if the probability of harms turns out to be quite high, there is a huge liability for those of us who agreed to early reimbursement, and really no responsibility for those who got it out early. So I would say this is a form of trial, but it's not a clinical trial, we have to give it a new name. And what you're asking for is coverage, clinical trials center around coverage, and so I think it's an important

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concept at least to think through, I know it's challenging, but I think intellectually it makes sense, that we all have similar motivations to get to the safest and most promising innovations as quickly as possible.
DR. C. GOODMAN: Thank you. I just want to remind our panelists, we do want to focus as much as possible on this question one at this point with regard to the distinctions between binary and non-binary coverage paradigms. We'll go next to Dr. Juhn and then Dr. Sedrakyan.
DR. JUHN: I wanted to pick up on something that you mentioned about this third wave that the Blue Cross Blue Shield Association has been looking for, another alternative to either coverage or non-coverage. Can you give us any examples of where you actually have gone down that third wave or that third path, and if so, how that could bear on this question of the different paradigms?
DR. KORN: We have been unsuccessful because of the reasons noted in being able to implement it, because of the regulatory environment within which we work. Now it may

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be that an individual plan in an individual state with an individual local innovator has done something, I would not have knowledge of that, but from the national perspective the answer is we couldn't do it.

DR. JUHN: One follow-up to that. So have you looked at specific technologies and gone down the path and then realized it was a barrier to proceeding further, or have you not even considered using it?
DR. KORN: If I could take off my shirt you would see scars on my back that are railroad tracks. We have tried many times and it's a source of real frustration for us all.
DR. C. GOODMAN: Thank you.
Dr. Sedrakyan.
DR. SEDRAKYAN: Dr. Korn, I want to go back to the harms question. Obviously it implies that CED can help us identify these harms and that no binary decision that will be made will help us to understand these harms over a period of time. Now some of the harms will take a very long time to develop, so it has an implication on how long the CED should last when they're testing for effectiveness and

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safety. Can you elaborate?
DR. KORN: Sure. What I would imply here, and again, we should probably pick this through together. A CED has a beginning and an end, that's what I'm talking about. Now I think as an innovator you would want to know downstream if there are additional things that might be important, it would be good to know, but I think that liability would end with the end of the CED period, that's what insurance is actually for. Once they agree it's covered, it's going to be covered. So it would be self-limited liability to, I guess limit it to the time of the CED study.
DR. C. GOODMAN: Thank you. I know we have a few more comments from the panelists, but before we do that, I want to make sure that our other expert speakers have an opportunity to address this question number one. Do any of you at this point have any comments to fill in on question one, the binary versus non-binary approach, and we'll start with Dr. Sean Tunis. Dr. Tunis is the founder and director of the Center for Medical Technology Policy, and Dr. Tunis, you're up first.

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DR. TUNIS: Thanks. I have a couple reactions to Dr. Korn's comments, which I think relate mostly to question one. One is, I do want to give Blue Cross Blue Shield Association full credit for one of the very early, you know, successes of the CED model, which was the coverage of the autologous bone marrow

transplant in breast cancer which is, you know, I think a great success, although obviously it's underscored lots of difficulties, but it's certainly path breaking, so it's at least encouraging in that respect.

I also wanted to endorse this notion, you know, that if we were to go down a path of the non-binary approach, Dr. Korn's point about needing to have aligned incentives between the payers and the patients on the sort of, you know, both the innovation side, but also, you know, sharing the risks going forward, and something on the innovator side in terms of early access, but I think that aligning these kind of incentives is critically important.

There is, you know, I think a key point which relates to this harms question. I think that part of the motivation for CED is

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that there is potential for some sort of undiscovered harms associated with delayed access to promising important technologies, and I think that has to be kind of underscored. That by having an excessively high threshold, let's call it for the sake of argument, for a technology that might ultimately prove to be both quality improving and perhaps cost reducing, there is the harm of delayed access that has to be factored in and considered as we're, you know, formulating the paradigm.

And the last point I just want to make, and I'll say this because Allan is a friend even though I'm poking at him a little bit, I think with respect to the antidiscrimination and the regulatory barriers, I think the insurance industry generally is extremely talented at changing regulatory policy when there is a business imperative to do that. And to the extent that CED becomes an approach that's acceptable and fortified, you know, with the insurance industry, I think those regulatory issues could be successfully addressed. And hopefully we're still friends after today.

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DR. C. GOODMAN: After what he has been through, you're still one of his best friends, I can assure you. Thank you, Dr. Tunis.

Dr. Rick Kuntz is next. Dr. Kuntz, by the way, is senior vice president and chief scientific, clinical and regulatory officer for Medtronic. Thank you, Dr. Kuntz.

DR. KUNTZ: Part of my disclosure is

that I also am a member of the board of governors for --

DR. C. GOODMAN: Dr. Kuntz, before you go on, can everyone hear Dr. Kuntz at this point? I think we need a little help with the mic, so let's do two things. Let's up the amps on the mic, and Dr. Kuntz, you nearly need to swallow that microphone.

DR. KUNTZ: Thanks. My viewpoint, this question about binary versus non-binary may be a little too simplistic. There are a lot of options available to CMS about making decisions even after a national coverage decision has been made.

What I would like to do is emphasize the fact that are there a lot of portfolio

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research tools, and many of my comments today are based on where does CED as it's defined and with the history of CED so far fit into this portfolio of tools to do research. Many of the comments that have been made so far today really do support the fact that we need more data, we need more surveillance data, there's no question about it. We need to understand how to apply our therapies more specifically to patient subsets to go forward.

The question is, as Dr. Korn pointed out, is this model of a study under coverage with evidence development a model to address most of the questions that are being asked today, and that's what people have to focus in on.

So, we at our company will spend $400 million this year alone in trying to address a lot of issues that are applied to both premarket and postmarket. So, I think what we would like to do is focus in on not so much whether it's actually binary or non-binary, but what is the role of this tool, is it restricted to registry format only because they have certain restrictions themselves, and how can we

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better, have more of a stakeholder share of the meetings, both at CMS and other research entities, to understand how we can put these devices and drugs into perspective to better serve the public.

DR. C. GOODMAN: Excellent, thank you very much, Dr. Kuntz. Other comments, Dr. Sandy? This is Dr. Lewis Sandy, senior vice president for clinical advancement for United Health Group. Welcome.

DR. SANDY: Thank you, and just in

terms of disclosure, I do work for United Health Group, Optum is part of that health group, the Lewin Group is part of Optum, and I have the same disclosures as Dr. Goodman. Two comments.

I think Dr. Korn really outlined the challenges in the private sector in a nutshell. I think the issues are, you know, private insurers have two kinds of coverage, the fully insured and the self-funded, both of which have significant barriers. So one of the things I think in terms of developing new CED paradigms, think about paradigms that can be a systemic paradigm that both the public and the private

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sector can use.

The second piece is on the binary coverage paradigm versus non-binary, and this brings me to think about the idea of a learning health system that the IOM has espoused, and I guess when I think about what we do at United Health Group and United Health Care in particular, I'll speak to this later, we never use a binary coverage paradigm because we are always continually reevaluating our coverage in the face of new evidence.

DR. C. GOODMAN: Point well made, thank you, Dr. Sandy. I believe Dr. Neumann was next, and then Dr. Goodman. Dr. Neumann, and these questions can be to Dr. Korn or the other speakers as well.

DR. NEUMANN: This is for Dr. Korn. I was struck in your remarks on legal regulatory issues, Allan, and of course some of the other technical challenges are important as well, but I guess my question is, is it your opinion that if we were, or if you were to successfully address some of these legal regulatory issues, that the other technical issues, data issues, the surveillance safety issues are sort of

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workable and addressable?

DR. KORN: Yes, and those issues are state by state, there is no one face, but we do know how to deal with the other aspects of clinical care, it's just a real challenge for us. The one success we had was with autologous bone marrow transplantation was the result of, if you will, that the association held among plans, which then gave an unrestricted grant to NIH and that's where that came from. So it wouldn't work -- I mean, it worked there, but as I mentioned, envisioning a trial only of Blue Cross members, it wouldn't fit this

paradigm.
DR. C. GOODMAN: Thank you.
Dr. Goodman.
DR. S. GOODMAN: A quick question.
How often do you know that coverage, initial coverage decisions by the plans are formally reversed? Because that's another alternative to the third way.
DR. KORN: I don't have those data, Steve, and that's a tough way to go as you know, once expectations are set. It's been done, but it's painful.

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DR. C. GOODMAN: Dr. Goodman, share with us your purpose for asking that question, and what you thought of the utility of the answer.
DR. S. GOODMAN: Well, obviously the alternative to a non-binary decision is that you have some mechanism, is that you make a binary mechanism, but you have an alternative further down the road to reverse it, without explicit directions for how research should proceed. And in fact the FDA has done that, it's tough for them too, they take drugs off the market, it's a very arduous process, arguably it doesn't happen often enough, and sometimes the initial decision in retrospect was wrong. So it is a capture mechanism for errors, for frank errors and, you know, depending on how robust that process is, that takes the pressure off the initial decision in the same way that a CED, a non-binary decision would. So I was just wondering what experience that Blue Cross Blue Shield had had with that.
DR. C. GOODMAN: Good, thanks for making that point. Dr. Schwartz.
DR. SCHWARTZ: Thank you. My question

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relates a little bit to what Steve just said, and Al's response, in terms of we recognize that in an ideal word, everything's fluid and as more information becomes available decisions are changed, and in clinical practice that's what happens, but on a regulatory basis that doesn't happen, and so there is this energy of reactivation that you have to overcome before you induct it at your level.
And so I wanted to ask anybody, but I was thinking about something Rick said about, I was thinking as other people were talking, that the reason you go into coverage with evidence development, as Rick said, you have this portfolio and he raised the question of what is

the best tool for answering these types of questions, then it seems to me inherent -- well, answer that question first, and then I'll do a quick follow-up question for Sean.
DR. C. GOODMAN: Dr. Kuntz.
DR. KUNTZ: Yes, thanks, Sandy. You will hear a little bit more about this, but I think what we would recommend is to have more of a stakeholder meeting up front with CMS to go over those tools and to make them conditions

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of coverage that might not utilize the kind of, so far as we've seen, the classic CED registry. Some of the decisions about coverage are the same thresholds for all of the decisions we make about recommending therapies for patients. So it's a, the blanket position about coverage does address most issues that carriers want to know about, whether it's more beneficial, so it's a broad range of questions that can be answered and asked, and so far we see that the tool CED has not been framed as a scientific question, they're generally null hypotheses, there's no expectation of when the CED will sunset after reaching a certain decision, nor what the path will be if a certain amount of data is obtained, which are fundamental in other clinical research vehicles such as randomized controlled clinical trials or even research tools that are done under an observational framework. Usually there are closed questions so we understand what's happening.
So there might be a combination of either increasing the rigor of CED as it is today to address those issues, or to bring in

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the stakeholders and look at the other tools to address the issues that are burdening CMS about coverage that could be answered with other vehicles. We have a lot of money to spend on clinical research that we would be more than happy to address and utilize if we can know what the questions are for coverage more specifically, and we might be able to use more customized and specific tools to get the questions answered.
DR. SCHWARTZ: It seems to me as I understand it, and maybe Louis could clarify if I'm wrong, the reason we go into coverage with evidence development is because there is, that there are interventions for which there is apparent but not sufficiently definitive evidence of, or evidence of benefit but it's

not sufficiently definitive to be sure, and a coverage decision has to be made. But what struck me in sort of the discussion that's gone on so far is that, so that the goal should be to get the information you otherwise would have had before, but once you go into coverage with evidence development you're going to collect different types of information, you get into

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the harms issue, you know, that longitudinal analysis allows you to look at.

And so you really are, you know, getting to the question here, in some sense changing the information on the basis of which you made a decision. So it's not an exact parallel, and I think that's inherent in the process and we just have to recognize it. I'm not being very articulate here, but I just wonder if that makes sense to the four of you.

DR. C. GOODMAN: Dr. Tunis, briefly on this point.

DR. TUNIS: I think more directly to clarify what I think Dr. Kuntz said in response to this, I think what I heard was if there could be a dialogue and clarity about what, for a specific technology in your portfolio, what the evidence expectations are for both coverage and post-coverage, that it's possible there could be agreement on how to meet those, how to satisfy those potentially without the function, the policy mechanism of CED as the vehicle to get there. In other words, you get the evidence that everybody wants both to obtain coverage and then following coverage, but you

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wouldn't use CED as the kind of forcing mechanism to achieve that. I just wanted to see if that's what your comment amounted to.

DR. C. GOODMAN: Did you want to add, Dr. Kuntz?

DR. KUNTZ: Yeah, thanks, since I opened up this can of worms, I guess. That's exactly what you had summarized, if we look at what specifically needs to be addressed to satisfy patients and their providers with evidence that they need to make good decisions, the process for CED which is an open registry is probably not the most efficient process as historically has been performed so far. And in other vehicles, there are a multitude of processes where one can understand exactly what the sample has required, what the tests would demonstrate, and then one could actually do a challenge of the value of the information by

proposing what would perfect data look like and what would satisfy those conditions. So I think that my response is either we raise the rigor of what CED has done to match these goals, or we consider using better early stage other vehicles to address those issues that are

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already in place and have much more track records of success.

DR. C. GOODMAN: Thank you. We do have some more panel questions but I'm reminded that because of the way question one is worded, it actually demands an answer of yes or no from our panelists. So, I think we probably have a pretty good idea of where you want to go on this yes or no question, and let's do that before we continue our discussion, I just want to make sure that we get this in.

All panelists will find, talking about clear instructions, you've got a little card, which is blue and yellow, and you've got a little no card, which is blue on white. And we do, for the record and because of the way this is being transmitted, need to actually go down the row on this. So I will pose the question and we'll start with Dr. Phurrough, who will need his cards back, I am sure.

So this is a yes or no. From your standpoint, then, as a panelist, are there significant practical differences between binary and non-binary coverage paradigms? That's a yes or no.

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(The panel voted and votes were recorded by staff.)

DR. C. GOODMAN: Dr. Phurrough.

DR. PHURROUGH: Steve Phurrough, yes.

MS. CABRAL-DANIELS: Rene' Cabral-Daniels, yes.

DR. GRANT: Mark Grant, yes.

DR. MCDONOUGH: Bob McDonough, yes.

DR. MIN: James Min, yes.

MS. NORMAND: Sharon-Lise Normand, yes.

DR. RICH: Jeff Rich, yes.

DR. SAADI: Ryan Saadi, yes.

DR. SCHWARTZ: Sandy Schwartz, yes.

DR. SEDRAKYAN: Art Sedrakyan, yes.

DR. JUHN: Peter Juhn, yes.

DR. S. GOODMAN: Steve Goodman, yes.

MR. LASERSOHN: Jack Lasersohn, yes.

DR. NEUMANN: Peter Neumann, yes.

DR. C. GOODMAN: Thank you for that necessary step, we appreciate it, and we got it

on tape and on the audio and so forth, we needed all that. Thank you. Dr. Normand was next, followed by Dr. Phurrough.

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DR. NORMAND: Thank you. And I wanted to follow up with what Dr. Schwartz was asking. I don't want to put words in your mouth, Dr. Korn, but I think it's important to everybody just to understand the difference between the binary and non-binary, I heard you say that for devices you felt that the harms question, you need to look at data ongoing, you felt that there was a different issue when it came to devices rather than, let's say drugs, when I asked you about harms for the update process. I have now interpreted that to mean that a binary, you can't have a binary decision on devices just because you require more information on harms. Have I misinterpreted what you have said on that? And please help me think through that, because I have a follow-up on the harms question that you asked, or that you mentioned.

DR. KORN: When a drug makes it through the FDA process, we have reasonable information about safety as well as efficacy. Devices have a different pathway, and so I think there are far more significant safety issues to be addressed when we're talking about

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devices in the regulatory process through which they proceed to reach the market. I think that's a different pathway than we have for drugs and so we should be very thoughtful of that in the design of CED studies in devices.

DR. NORMAND: Just to be clear, I mean, you'll shut me down, I know you will. But in terms -- so the question seems to be with a device, I hear that and understand that, but does that therefore imply that there could never be a binary decision for a device, because their will always need to be CED with it because of the harms issue and because of the regulatory process? That's what I'm trying to ask.

DR. KORN: It's a very interesting question and I think we would have to define those devices that represent potential new safety issues. I mean, many of them, if you go from a digital to an analog dial, I don't think that's a big thing, but with the right criteria the answer is probably yes, much as we do for drugs.

DR. C. GOODMAN: Thank you. And Dr. Normand, I would just add that from the
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standpoint of the betterment of the Medicare beneficiary population and protection, we care about adverse events across not any particular class of technology, but across all sorts of interventions, drugs, bio, devices, medical-surgical procedures and so forth, so we care about adverse events for all of those.
DR. NORMAND: I understand.
DR. C. GOODMAN: Thank you.
Dr. Phurrough.
DR. PHURROUGH: My question is a general question for the group, or perhaps for the panelists. It involves somewhat Steve's questions and the question that was just asked for an observation that a non-binary decision may in fact fall outside what's typically defined now as the current coverage process. So you have an NCD now that follows some extended length of evidence development and then the Agency needs to decide, are we going to do a yes-no, are we going to do this non-binary that then requires some additional evidence, and I think I heard comment that you need to sort of expand that coverage process to earlier in the development so that we have
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better tools to use other than CED. Is that -- did I hear that correctly? Are we looking for some way to get the evidence development before we get to a point where we have to make some binary decision?
DR. C. GOODMAN: Dr. Kuntz.
DR. KUNTZ: Rick Kuntz. I think that's a good way to summarize it. I would just add that the CED as I currently understand it, and from the history, has been a general registry applied when there are open questions, and it hasn't been an efficient mechanism in many cases. So to thwart that eventuality, it would be good early on when it would be, consideration for an NCD would be made, that the stakeholders get around the table to understand exactly what are the concerns, so that a timely and early proper study to address those issues more effectively can be designed, and it might be a registry.
But if the decisions are made later, the practice having been established, and the retainers have been established, and then the registry is applied on top of that without a direct hypothesis, the likelihood of obtaining

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answers to potential specific questions that haven't been articulated is very very low. So it's just, again, an appeal to be more rigorous and early in the discussion.
DR. C. GOODMAN: Thank you.
Dr. Tunis, on this point?
DR. TUNIS: Yes. So to try and answer your question, I think there is an intense, you know, two different things going on here about how do we better generate the evidence needed to address the uncertainty to get to coverage? You know, one mechanism that doesn't involve CED and does stick with the binary approach is, you know, better guidance from Medicare, from the Blues, et cetera, about what the evidence expectations are for coverage, and I think Richard Frank said this and Rick Kuntz. So just clarifying what the evidentiary expectations are potentially could improve the efficiency of generating that knowledge. CED or a non-binary mechanism is actually trying to take on not just how do we get better evidence, but intentionally providing earlier access than would otherwise be the case when there is considerable
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uncertainty, because you want to have both early access to the technology and address the uncertainties.
So they're related but I think they're different, and that the non-binary really has an explicit, supporting innovation and early access for promising but unproven technologies, as opposed to the other approach which is being clearer about what the evidence expectations are up front.
DR. C. GOODMAN: Good, thank you for that point, Dr. Tunis. Ms. Cabral-Daniels.
MS. CABRAL-DANIELS: I would like to thank everybody for the wonderful information, I am certainly learning a lot and I thank you for that. I really appreciated the information with regard to, the non-binary coverage paradigm will probably involve a series of decisions, we're not going to have one as we do with binary. However -- and I really appreciated the information with regard to patient access and adverse events and the patient role, but I was a little bit underwhelmed by the information with regard to the role that
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patients can play in a proactive manner, not

simply as a member of a partnership with patient-provider, et cetera. And so I wonder if anyone can speak with regard to how the non-binary coverage paradigm itself might allow a patient to be involved in this process.

DR. C. GOODMAN: Thank you for that question. Do any of our expert speakers have a note on that? Dr. Korn and Dr. Kuntz, and let's keep this brief. We're going to bring this to a wrap pretty soon.

DR. KORN: It could be an extraordinarily helpful tool for a patient who today after seeing a news item, you know, NBC evening news, is out demanding the coverage, knowing that their own physician says we really don't know. And if you really want to try it, had to do it, we're going to enroll you in this particular observational process to find out if it really works. What a wonderful mechanism that would be, to be able to rely on everybody's expectations, and I think it would be wonderful.

DR. C. GOODMAN: Dr. Kuntz.

DR. KUNTZ: I just want to make a

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comment, and I want to thank you for making that comment because it is important to put that into the record, and also make an annulment of designing CED and whatever vehicles we have to basically understand the coverage part. And you know, myself and other members of the board here who have a relationship with PCORI and we obviously understand the crucial part of understanding patient value and preferences in research, and then understanding what that means with respect to interpreting the outcomes from these clinical studies.

DR. C. GOODMAN: Thank you. I'm conscious of the time, so, I do see some hands up, but I want to ask now from the panel, and it can be the folks who've raised their hands to start, but briefly, what's the kernel of the answer aside from the yes and no? We said yes, this is an important distinction. What's the kernel of the answer to the advantages and disadvantages of non-binary paradigms? I want to put a wrap on that and move on. Dr. Schwartz, briefly, the kernel of the answer.

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DR. SCHWARTZ: I think we need to recognize that this is going to differentially affect different types of innovations, it's

going to primarily affect innovation in devices and procedures and things like that, because the evidentiary base that is usually brought to Medicare is less established in standard ways than, say, with many drugs, so I think we have to recognize that.

And the advantage obviously is you have the potential to get innovations for which there is some evidence but not sufficient evidence yet, and I think earlier Allan emphasized the point that this is also a two-sided coin, and there are harms that haven't been adequately evaluated.

I would like to mention just one thing because I think it's really important. There were three speakers or four speakers on registries. We've learned a lot from registries, but registries, to put sort of an economist's hat on, becomes almost like a natural monopoly. If people are required or strongly encouraged, or professional societies control a registry, you know, those are the

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ways that you enter a registry, we have to make sure there is public access and transparency to those registries so that they can be broadly analyzed by a group of people.

The tendency in most registries today is by well meaning scientists who are working rigorously, but then it's like a lot of other things in academics, it becomes intellectual property. And so when we make regulatory decisions, and it's I think implicit to this aspect of CED, we have to make sure on the part of the people holding a registry, that there is normal access for people to analyze that registry.

DR. C. GOODMAN: Thank you, Dr. Schwartz. Back to the kernel of the answer will be McDonough and Grant. Dr. McDonough.

DR. MCDONOUGH: I think one of the biggest advantages to coverage with evidence development that we kind of haven't talked about --

DR. C. GOODMAN: Directly into the mic, please.

DR. MCDONOUGH: Sorry, I'm mumbling. Is that the, it can result in studies that

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would otherwise not be done because of certain barriers, so it provides a funding mechanism.

The disadvantages, I think, are the uncertainty that it can impose upon the coverage process and the difficulties in implementation.

DR. C. GOODMAN: Well stated, Dr. McDonough. Dr. Grant, on the answer.
DR. GRANT: A couple things. One is a potential advantage but it's also a disadvantage, and one thing that's I think been alluded to here is this notion of evidentiary requirements, but the potential advantage is the requirement to be more explicit, which really now is I think absent, about the model for the making of the decisions. And not just the decision model, everybody's got a model in their head about how we're effecting decisions, but that's also a potential disadvantage as well, because I don't think we've gotten there, but I think that's what these people have alluded to.
Another one is what Sean was describing as the opportunity clause, and being explicit about them, because there's just a huge crate of them, for patients, for the

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producers of the technologies, for everyone, and once you lay out the opportunity clause, you know, and have to figure that into the decision-making process, I think being explicit about that is a tremendous advantage to knowing who benefits and who's at risk, and I will leave it there.
DR. C. GOODMAN: Good, thanks, Dr. Grant. Dr. Saadi.
DR. SAADI: I think we actually got through a number of things here, so one thing I did not hear and I kept waiting to hear it, but it was the patient part of CED, is this going to be discussed when the outcomes are important, which comes down to the patient. I think we're not going to consider it in a binary decision or non-binary in that situation, so I think we have to have some discussion about whether the patient is willing to take risks when the information is not perfect; otherwise, we're not going to get there.
DR. C. GOODMAN: Good, thank you very much. I see a couple of hands up. In the interest of time, in a moment I'm going to ask

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Dr. Phurrough to provide some summary comments. If you still have something important to say on this question, I know a few of you do, we will have time later on in the day, not at the very least at the close of the day, but perhaps before then, to weigh in on this issue once again.

Dr. Phurrough, I know you're still writing quickly and I will speak a little slowly so you can finish that sentence, but Dr. Phurrough, if you can provide a couple of sort of summary bullet points on what you've heard, and then we'll move on.

DR. PHURROUGH: All right. In general the panel, or not in general, may I say the panel believes that there were significant distinctions between binary and non-binary, that there were advantages and disadvantages to both, that in fact a binary decision that included the option for reversing that decision at some time in the future in fact could be termed a non-binary decision in and of itself. There was a lot of discussion around the need to ensure that harms are significantly evaluated and that non-binary decisions may

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make that a bit more easy to do. There was discussion around how CED fits in the entire evidence development process that you can develop if you more clearly have processes in place to define what the evidence development needs to be prior to the coverage decision, then you're going to obviate the need for CED in many cases but there still will remain the need for CED in those circumstances where you're trying to take promising technologies and move them into practice earlier in the life cycle. And finally, several comments that we need to ensure that all stakeholders are involved, and that patients are a key stakeholder.

DR. C. GOODMAN: Excellent, thank you, Dr. Phurrough. If later in the day or even now you've got some thoughts about something Dr. Phurrough might have missed or something that you might contend might be a little different, we'll have a chance to speak about that later on in the day. At this point I would ask that you take a look at your watch, everyone, add 15

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minutes, and know that that's when we're going to get started again. I hope everybody will be back in the room seated just short of the 15 minutes. Thank you very much.

(Recess.)

DR. C. GOODMAN: It was brought to our attention that one person who did want to sign in for the public comments did not quite locate the sign-in sheet, he has since done so, and so

we're going to do this a little bit out of order, but we would like hear from our public commenter.

And Dr. Chris Castel, please, will approach the mic. If you'll give me one more moment, Dr. Castel, since this meeting has brought together a lot of folks who feel like talking about it, which I guess is a good thing, so we're still filing in.

As is always the case with public commenters, we need to just ask you to keep this within a minute, Dr. Castel. Dr. Castel is with Hanger Orthopedics and the Neurostimulation Alliance, I believe it is. Dr. Castel, welcome, sir. Thank you for your patience.

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DR. CASTEL: Thank you very much. I will keep my comments brief, and I do have, the only conflict I have is working with Hanger Orthopedics, who is a provider of various orthopedic products for artificial limbs, orthotics and other devices nationwide.

The two primary issues that I think also need to be thought through, and we appreciate that during the course of this discussion perhaps other people thought about, one is the question of when should a CED be invoked. In other words, should it be invoked on an existing coverage technology that has a long history or utilization that has, for example, may have a ten- or 15-year, or even a five-year coverage with no side effects. In other words, is this something that is supposed to be evoked for that, or was its purpose employed to allow another vehicle to take promising technologies and provide coverage, as opposed to denying them.

Secondly I would comment that rather than a binary model that you have been thinking about in terms of individual modalities or therapies, one of the challenges is many of

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these modalities and therapies are used together and within a clinical pathway for treatment of a patient. So what might not be effective, for example, might be effective when several things are used together based on the clinical judgment of the physicians that are taking care of these patients. So I think we should also try and do things that avoid conflict with the ability of a physician to be able to make the right medical judgment for the patients as well.

So, you know, when you're considering these issues, consider those types of things, especially the multimodal side, which is hard to study, but collaboratively and with transparency with CMS, the databases would be available to look at that, so thank you.

DR. C. GOODMAN: Excellent point, well taken, Dr. Castel, I'm glad you took the time to be with us today, we appreciate it.

Next on our agenda is an interlude between question one and question two, and we're going to hear from Dr. Mark McClellan. Dr. Mark McClellan is the director of the Engelberg Center for Health Care Reform and a

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senior fellow of economic studies and the Leonard D. Schaeffer Chair in health policy studies at the Brookings Institute. Also quite to the point is Dr. McClellan had, as you may know, a bit of a tenure here at this Agency running this Agency, also ran the Food and Drug Administration, so obviously these two agencies are quite relevant to our discussion today.

Dr. McClellan dutifully brought a swell set of Power Point slides, we're still having, as they say, connectivity issues in the trade, but Dr. McClellan, as gracious as he is, has agreed to start his remarks out without his Power Point, and we're pleased to do that, and once his Power Point comes on, he will switch effortlessly and seamlessly to that, I am sure.

Welcome, Dr. McClellan.

DR. MCCLELLAN: Thank you very much, and I would like to thank the MEDCAC for the opportunity to join you today. This is a very timely meeting, as I will talk about, and a very special privilege for me to be a part of it. We are going to try to get the slides up and running even while I speak here, so if I'm able to switch over to that, that will be

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great. If not, I may try to shorten my presentation a bit and make these slides available afterwards, and spend more time with discussion.

You know, the opportunity to talk about the coverage evidence development policy is a very special one for me because of the fact that it was an important part of our policy work while I was at CMS, and I know it continues to be a key part of CMS coverage decisions, not just from the standpoint of figuring out whether the evidence is there or not, but just because it's part of a lot of

fundamental themes for trying to get better care and avoiding unnecessary costs for Medicare beneficiaries, so that's kind of what I want to do today.

As you heard from Cliff, this is a bit of an interlude between the specific questions, it's really meant to be -- it looks like we're up and running, great, if I can just figure out how to start the slide show. This may be the best I'm able to do.

So, this is a good time to reexamine the CED policy. We've had a number of years of

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experience with it and a lot of people talk about how we did some new initiatives related to CED when I was the administrator in the 2004 to 2006 period, and there were a number of questions related to registries, related to CED with clinical trials, but it's important to remember that, as you all know, that CED has been around for longer than that and that's why I'm going to talk about some of the past examples, but now is the time to really look at whether it's possible to have a more systematic approach to CED, and that doesn't mean necessarily using it more often, it doesn't necessarily mean using it less often, it does mean using it more predictably, with a better relationship to some underlying infrastructure, and an ongoing predictable well-articulated strategy for evidence development. And so I want to talk a little bit about how the past has been a prelude to that, with some of the evidence that's emerged and some of the challenges, and where I see some of the opportunities for the future being different, being better in terms of increasing the benefits of CED, having CED activities

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conducted more effectively, more efficiently, and better in terms of reducing their costs so that when CED is applied, we can be more confident that benefits in terms of better evidence, better support for patient and clinician decision-making are far outweighing the cost in terms of both infrastructure and resources required to conduct CED and in terms of any potential impacts on patients.

So a little bit of background, this is from more of my personal perspective when we were seeking to apply CED in specific cases at CMS, as is still the case, the underlying goal is to provide beneficiaries with access to innovative treatments that they might not have

gotten otherwise given the evidentiary standards based on what existed, not what was feasible to develop. While developing better evidence they showed improves its use or improved decision-making in the future. In some cases CED has had an impact on future coverage decisions but in a lot of cases it's really been that learning that's helped to promote effective decision-making by doctors and patients that's been most important. So

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there's some potentially important benefits here when I see there's a potential way to provide more rapid and broad access to new interventions.

Also, as we're increasingly seeing, there are a lot of unanswered questions even when treatments have been approved under FDA standards for safety and effectiveness when they reach the market. And so better evidence in the postmarket setting is an important goal, and fortunately there's some new opportunities such as the progress in electronic records and research networks and other types of methodologies that I will describe in a little while, more opportunities for doing that. And again, this can lead to a better understanding of risks and benefits of the new interventions.

Although CED hasn't been used that widely, according to a recent Avalier analysis, 15 percent, about one in six national coverage decisions have incorporated CED evidence, so this is not an infrequent tool. And again, as these infrastructures for developing better evidence from actual medical practice become more widespread, there's the potential for them

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becoming an even more regular part of Medicare coverage.

I was going to just mention a few early experiences with CED just to illustrate some of the benefits and some of the challenges that have arisen, and again, remind everyone this is not a new or even in the last decade policy, you know, lung volume reduction surgery represented what many people still regard as a model of bringing together infrastructure support from the NIH and AHRQ with a very relevant question for Medicare beneficiaries about lung volume reduction surgery, that developed much more comprehensive evidence on this question than would have been the case in the absence of a coverage with evidence development policy, and that has led to more

insights and better treatment decisions for patients with respect to this technology. Some of the more recent examples I think also reflect the valuable new evidence. The implantable cardioverter defibrillator registry system was part of a CED for ICD coverage in 2005. That coverage was relatively broad compared to what clinical evidence had

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been conducted and in some ways compared to the FDA label, with the idea that this would help CMS and doctors and patients who were considering the treatment have a better understanding of the natural history of the use of ICDs, potential adverse incidents avoided, or many types of patients that weren't widely studied in the premarket evidence but what looked like a potentially very beneficial technology. That registry has to a large extent been continued, and you're hearing and have heard already about some of these specialty-supported registries like this one, some of the industry-supported registries, and I note interestingly, some of the evidence that has come out of this was not what was expected at the beginning, so the registry has been used for studies of, say volume variations and intensity variations in these devices providing insights about specific types of patients. But because it is an observational study and not a randomized trial like the ongoing reduction surgery study, as I stated earlier, there are some complications in reaching some conclusions about risks and

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benefits in particular patients, complications associated with patients who receive ICD where the benefits or avoided complications reflect the impact of the ICD or differences in the complication mix can be a bit challenging to sort out, and I'll come back to that. One of the other ICD applications that took place while I was at CMS was for off label use of some innovative new biologics that had been approved for certain labeled indications but had not yet been very widely studied elsewhere, and the idea was to try to get ahead of actual clinical practice with some better evidence. So CMS in general covers these drugs for not just approved indications but other routine uses in medical practice, and for cancer drugs in particular, if the drugs are mentioned in widely used drug compendia, then these indications will be covered. And the

idea was to get ahead of, you know, hopefully anticipating where medical practice might head where clinicians, oncologists, patients might think that many drugs with prior indications will also be beneficial in additional indications, and to determine whether, ahead of

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time before medical practice evolved, whether the evidence was really there or not. And this application I think illustrates some of the challenges in applying CED. CED comes in in the context of national coverage decisions, and so while that might seen like forever in terms of a 90-day process and comments, so forth, for patients who are waiting for the technology and for product developers involved in trying to get it to market and trying to get it paid for, it is not a very long time in terms of setting up an infrastructure for doing a clinical study. And so in this case what happened was some use of CED where CMS was covering the use of these biologics in clinical trials, but they were perhaps not the trials that you would design if you were thinking about this from the main standpoint of what would most benefit Medicare beneficiaries, what were the most important questions for them. Rather, I think some of the trials reflected areas where NCI or existing funding mechanisms at NIH already had some plans in place, already had study sections in place, and

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while they were moving forward, they weren't using CED to fit into a context that isn't really the most important set of questions necessarily for Medicare beneficiaries. And so I think that illustrates a challenge in trying to use CED to help with relevant clinical decisions for the Medicare population. CED has not been widely used outside of that clinical trial context for Part B covered drugs, even though this is an important source of variations in medical practice, and even though there is some important unanswered questions about physician-administered drugs for Medicare beneficiaries. A couple of other examples. Positron emission tomography and the so-called SAMMPRIS trial involving stenting versus aggressive medical management for preventing recurring strokes and intracranial stenosis. This is one that I think is kind of more widely regarded as

providing some more dependable information in a case where for these devices, it's kind of impossible to set up the studies, the clinical studies needed that are more directly on point

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for Medicare beneficiaries. But you know, these examples illustrate both the potential for CED to provide better evidence, but also some of the challenges with applying CED, and this is where I'm hoping that the next round of CED can, the policies can be helpful. When me move in the direction of a little more systematic approach for prioritizing the application of CED, this can be very important. This is challenging and we've talked some this morning about how it will be very difficult to develop specific evidentiary standards with specific modifications, but generalizable along the coherent overall policy, but I do think it's possible to make some progress in that direction. And this gets to the point I was mentioning earlier about CED generally being applied on a case-by-case basis within the time frame of national coverage decisions. It is a long time frame in terms of making decisions about coverage for patients for innovative technologies. It's not a very long time frame from the standpoint of designing and implementing an infrastructure

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for carrying out the evidence that would be desirable to obtain, and I gave some illustration of that with the case of off label use of biologics. Since that time, I don't see that policy as having that much of an impact on, that CED ending up having that much of an impact on coverage, both because the optimal studies couldn't be designed quickly enough within the CED-NCD time frame, and because medical practice continued to evolve outside, and so a lot of additional labeled, a lot of additional indications showed up in the drug compendia, and I'm not sure there was that much of an impact there. This illustrates some of the limitations in trying to apply CED on a case-by-case basis, and also the challenges of needing to apply it quickly, because you don't want to hold up coverage decisions. CED also has some significant costs associated with it, so Medicare pays for the cost of coverage of the technology involved in CED, but that's only the beginning of the costs of conducting CED effectively. There also are

resources needed for the infrastructure for collecting data, for compiling it, for

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analyzing it consistently and effectively, and because these costs are significant and because over these case-by-case applications there hasn't really been a systematic effort to evaluate whether the benefits in terms of better evidence, maybe faster access or broader access that would otherwise be the case, and better decision-making down the road for patients, but the benefits versus the cost of CED, including not just the cost of coverage per se but these infrastructure costs, I don't think we have as good a handle on that as we should, and that's something that I think is very important for the future.

And so, also unclear is whether the impact on access to technology that the CED has brought about, maybe sooner in some cases, maybe delayed or complicated in others, it's a little bit harder to judge whether that's been positive or negative for beneficiaries on that.

And again, there is no standing infrastructure for conducting these studies, so really facing the challenge on one hand of doing all this within the NCD, national coverage decision time frame, but on the other

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hand, trying to design studies and evidence development that is really effective.

So all that brings us to why it is so important to readdress these issues now, what's worked, what hasn't, and what are the opportunities for the future. And I really want to commend CMS for putting this set of issues on the table. It's inspired a lot of activity, obviously inspired everyone coming here today. We sponsored a roundtable meeting back in December bringing together a range of experts and people with different perspectives on what had worked and what hadn't in CED, and that informed some of the comments I've already made, but also made clear that there are some better opportunities for the future as well as important challenges ahead.

And just another light on why this is important, and I think Louis may have mentioned this earlier today in introductory comments, this has only been mentioned by the administration as a potentially important impact on the nation's bioeconomy, reports that with more predictable incentives for innovation with CED can certainly influence, both at the

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time of coverage and then creating more confidence that treatments that really do work but we don't know as much as we would like about the benefits versus the risks, will be, will have further evidence developed, and so can potentially have a greater impact. That could be a big benefit for valuable biomedical innovation. On the other hand, the flip side of that is that if these policies aren't articulated and implemented effectively, that can inhibit not only the bioeconomy, but more importantly, better health for Medicare beneficiaries.

So given that there's a lot at stake, I wanted to maybe spend a few minutes sketching out what might help with getting to a brighter future, and this reflects a lot of work that we're doing at Brookings, and also my role in chairing Institute of Medicine's efforts for supporting a learning healthcare system. I do want to be very clear that we need better evidence, especially for products that are, that get to the market and are going to be used in ways that are different from what was the case in the clinical studies that preceded

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approval.

There are lots of reasons that's true. I think the main reason is that we are hopefully headed towards a more individualized health care system, one where we have much better evidence on risks and benefits for particular patients, but developing that kind of evidence is very hard to do in free market clinical studies which, a refusal to focus on populations that aren't that large, meaning you're going to get a diverse group of patients or you're only going to get a narrow set of enriched patient population, but you're not going to get as comprehensive of a picture as you would like.

And that's okay, you know, we certainly have enough of a foundation for approving new technologies based on FDA regulatory approval on that basis. It just means that there is a lot more to learn, so there's an uncertainty about longer-term outcomes, we don't want to wait five, ten years for approvals, but many technologies, implanted devices, treatments that are intended to influence outcomes for earlier stage cancer

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have important, hopefully have important

benefits to go beyond ten years, and we want to characterize them as well as possible. There may be differences, as I mentioned, in different types of individuals. You know, I mention on the slide older individuals, people with multiple comorbidities, people who are underrepresented in clinical trials, many even more fundamentally than that, patients that may differ in other clinical characteristics and preferences, and genomic or metabolic features that could be predictors or risks and benefits, and also characteristics of the course of a disease. And how technologies are applied matters too. The experience of providers for using devices, the way in which a particular technology is combined with other supportive care, other medical technologies, all that matters, all that is very hard to study in a premarket setting. So hopefully we're going to have the potential to have a more personalized innovative health care system, a lot better capacity to develop evidence on all of these

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more individualized aspects of patient characteristics and health care delivery. The good news is there are more opportunities to fill in these postmarket evidence gaps, and that includes better evidence coming to market, so as treatments are developed with better predictors of patient response and more genomically labeled therapies, for example, better markers of when patients are responding so maybe you don't have to wait the full ten years, or indicators of both safety and beneficial effects earlier. That's increasingly the case with treatments that come to market today, and then once treatments are on the market, and you've heard about this some already and I'm sure we'll hear a lot more, there are more sophisticated registry capabilities, more sophisticated research networks using electronic data, using data analytic methods to develop better evidence in the postmarket setting, and CED should be definitely viewed as a piece of this set of overall trends in our health care system, that I think we need to reinforce and support.

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So there is a good deal of private and public support for these types of research and analysis already. I think more support is

coming from the payment system itself. This is coming through changes in payment policies away from being focused just on volume and intensity of treatment, and paying more for more complications. The payment systems are increasingly focused on seeing better results at a lower overall cost for patients.

CMS is in the midst of a number of bundled payment initiatives, the panel of care, organization reforms. The private sector is in some ways even farther ahead on these payment reforms as well as changes in benefit designs, and encourage patients to find better ways to meet their health care needs at a lower overall cost. Those kinds of payments, those kinds of financing reforms only work if we've got good evidence to back them up, so I do see more of a push for the kinds of evidence that CED could help develop from these more large scale global changes happening in our payment systems, and CED fits into that.

Also in the category of good

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opportunities is improvements in infrastructure for collecting data that's needed for evidence development. So, I mentioned earlier that I think a big challenge has been the kind of the one-off nature of many of these CED studies, and that's probably not the future in terms of evidence development more generally. There are a number of opportunities for CED potentially to partner with data collection infrastructure that are reasonable. There's an ongoing infrastructure that can be used for CED as well as many other postmarket evidence-related applications. This means finding ways for CED to get to more of these general policies to be matched up better with the kinds of existing and emerging data sources that draw from data in routine care, increasingly data from electronic records, claims data, data being submitted by patients through smart phones and the like, and relying on the infrastructures that are coming together to make use of those types of emerging sources.

These are typically, and I'll give you an illustration in just a minute, these are typically not just run by some particular

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research center or some agency, but are public-private partnerships that keep, that pull together the data that are needed for a relevant evidence question from the systems that are being used to support improvement in

routine care delivery, like that emphasis on those payment reform steps, improved outcomes and lower costs. All those payers involved in payment reforms are setting up their own registries for patient care purposes, so tracking their patients with diabetes, with heart disease, with other specific indications, and using those registries to take steps to identify known gaps in quality of care, and also taking steps to intervene early for patients who have complications. If you think about it, those are the same kinds of data sources that are relevant to CED analyses, data more clinically valid and relevant to the characteristics of patients and their clinical history, clinical development, and complications that can occur.

So one example that's a little bit afield, but hopefully won't be for too long is a network that FDA has been instrumental in

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getting off the ground for drug safety surveillance called the Sentinel initiative. It started out as a Mini-Sentinel, I don't think you can call it that anymore since it involves organizations that collectively have more than a hundred million covered lives. But the idea here is to have a network that can draw from real world clinical practice consistent data for questions about drug safety, not necessarily questions about CED, but for safety, and there is a contextual similarity.

And the way the Sentinel initiative works is that there's an overall collaborative effort for governance, for developing standards for data definitions across a wide range of participating organizations, and the participating organizations at this point include most of the large major health insurance companies, United, WellPoint and so on. Also, Medicare and some state Medicaid programs are participating in a parallel effort, again, trying to determine consistent data methods.

And the way the system works is

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because there's an infrastructure in place, when FDA has a question about a safety-related issue and wants to find out more about what's actually going on in real world practice, FDA with support from this network can query with questions about particular drugs, particular types of patients, what are the utilization

patterns of the drugs and what are any associated patterns of adverse events. So drugs that might be suspected in a premarket clinical study or in some smaller observational study that's reported as having an association between a serious adverse outcome, cardiovascular events or death, or a metabolic toxicity can be studied, you know, more comprehensively using closer to real time data, for more than a hundred million Americans. As the Sentinel network has evolved it's been incorporating more sophisticated clinical data from not just insurance claims, which are in the parties' consistent data model, but also electronic records, electronic lab results and maybe, hopefully soon, more patient-reported functional outcomes as well. So it's a network that doesn't necessarily

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answer all these evidence questions definitively, but it's a much more routine regular source, a timely source for information from real world practice related to risks and potentially related to benefits of medical technologies.

So just to highlight, that CED instead of being used sort as a one-off kind of separate effort, could help support and be reinforced by these kinds of other efforts to develop an ongoing, and sustain an ongoing postmarket data infrastructure. You've heard about some of these registries today, I mentioned the Sentinel initiative. FDA's device center is in the process of launching a standing MDEpiNet, which is based on a network of registries to be augmented by more of the claims data and electronic data from sources like in Sentinel.

There are a number of efforts underway at the state level and elsewhere involving multi-payer claims databases. I think, again, what most commonly these efforts have in common is that they find ways to use data that stays at home with, from health care providers and

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organizations that are delivering the care, but they have a common infrastructure so they can share summary information.

So like with safety studies, you don't need to send all the information on a hundred million Americans to some data warehouse somewhere, all you need is a querying system with consistent data rules to ask how many patients do you have with these particular

clinical characteristics. All that needs to be shared is consistent summary statistics, not identifiable patient information, and it's much more promising than one-off approaches to try to collect evidence on the fly for any particular NCD.

So, besides all these steps with data, I also want to emphasize the importance of methods development. Up until now, CED basically has fallen into a couple categories, broadly speaking. One is where CMS has supported randomized clinical trials, so a condition for coverage in the CED has to be enrollment in an appropriate clinical trial where patients are randomized and that obviously, it is much more, it is much easier

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to make causal inferences about the relationship between a treatment and the outcome compared to whatever the alternative treatments are. Another set of CED applications would involve larger epidemiologic studies involving registries and involve some of the networks like I described before. The future may actually end up being a combination of the two where it becomes easier to do some kinds of randomizations, maybe site level or coverage base, and we may have some discussions about between binary on or off coverage decisions, something intermediate, I can see that maybe fitting in with these networks in the future too.

But I think the point I want to make is that these research methods for interpreting the data in both the randomized context and certainly in the observational context for CED, you need a lot more development. There are a lot of things that influence the impacts of medical technology on patient outcomes, so that the effect of the technology can be compounded with different patient characteristics, how it's being applied, and finding ways to capture

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that effectively is a challenge.

Again, keeping with that FDA safety surveillance example that I described before, along with building that data network has been a partnership effort called the observational medical outcomes partnership which has been largely funded by the private sector, with a specific focus on developing better methods for understanding data, understanding whether the data that's being used in these studies from the real world are really valid for the

intended purpose, and also for determining whether the methods being applied really can avoid biases and can get to reliable conclusions.

This is the future, I think, of biostatistics as well as epidemiology, and is a different set, different scale of data, different way of putting data together, and I don't think we have the methods in place yet to develop that. Now that's not something that's really within the scope of CMS funding, for reasons I talked about before, but it is something that needs to be a part of developing future CED, that your methods have to be

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determinative whether doctors, patients view the findings of CED studies as conclusive and therefore pay any attention to that, is very important for CMS as we go forward in these areas.

You know, I emphasized the importance or significance of costs associated with CED earlier. Finding ways to address those costs is also important. There isn't really one in place or in general for supporting costs of conducting CED, and by that I mean the analytic infrastructure, the data collection and analysis, the things that kind of go beyond just paying for the technology used in the CED coverage. There have been a variety of sources for filling these gaps, typically on a one-off basis by the research agencies. Industry in the case of many of these registries that I described before, administered by specialty societies or other clinical experts, but the financial support comes from industry, and that may be one way to go, but again, I think the one-off approach is not that sufficient.

And I think there are some opportunities to combine ways of supporting

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this kind of infrastructure for CED with the support that's going into these emerging networks already. So a more systematic way to fund CED as part of the step back in overall policy and predictability is very important, and is for a partnership with other agencies, industry, private payers and the like on something other than a one-off basis, something that's more strategic might be helpful.

There are many other organizations, some of which have the ability to support these efforts financially, others have an ability to support them in kind through expertise and the

like. Many organizations have a better, have a vested interest in developing better overall postmarket evidence capacity.

So, I'm going to try to wrap up now, and I will emphasize that I haven't tried to provide answers to those specific questions, but I do think they are very important questions and they are questions that should hopefully be viewed in this larger context of where our health care system could be headed in supporting better evidence for personalized care decisions.

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And in this context, I did want to mention that proactive predictable priorities and predictable implementation of CED is important for both efficiency and for reinforcing these opportunities for an ongoing better evidence infrastructure, so making sure that we get to some best practices for data collection infrastructure and methods that go beyond each individual study and get to be more systematic insights about best practices, drawing on the experience of CED so far in CMS and the private sector is important.

I talked about the need for CED infrastructure funding that's not perhaps independent of all of these other opportunities and all these other financial support that's emerging for evidence-based infrastructure learned from actual medical practice. More work on consistent methods and effective methods, and included in those methods are cost-benefit analyses of CED itself.

I know you're going to talk some during the rest of the day about criteria for applying CED, I have a few thoughts on that here, and look forward to hearing more about

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that discussion during the course of the day.

I just would, again, emphasize the importance of gearing towards more individualized patient care, and evidence that really is being achieved by patients and doctors that is relevant to particular cases.

And in doing all this and particularly going forward in CED, I think it's important to review what's going on not just for purposes of whether or not CED decisions should be implemented or continued, but also for developing better evidence on costs and benefits of the overall CED program.

So I think, again, the reason I'm here is because I think this is a vitally important

aspect of Medicare policy even if it's not used that often, because it's only a piece of the many trends in the direction of supporting better evidence development from medical practice, but I think it's also important that we learn from the experience so far, to make sure, do a better job of making sure that the benefits of CED are outweighing its costs, and that CED is used part and parcel of this variety of fundamental trends towards payment

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reforms, benefit reforms, better data capabilities in medical practice that mean we can have the potential for a much brighter future. But in order to get to that future, it's not going to be automatic, CED policies and how we afford them is very important to determining whether we can actually have some of those technology benefits, avoid those additional costs and get to that better future for Medicare beneficiaries and all of us.

I thank you all very much for the opportunity to join you today, and thanks for bearing with me with the slide presentation.

DR. C. GOODMAN: Thank you very much, Dr. McClellan, very helpful.

(Applause.)

I appreciate your background -- and our first applause of the day, merited. I appreciate the background, and obviously you've got a career-vested interest in this, and we appreciate hearing straight from you as someone who was here at the important buildup of this important program. Dr. McClellan, if you would stay with us perhaps at the podium for just perhaps the next eight, ten or 12 minutes for

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some questions.

If you don't mind, I would like to start by asking you something that's relevant to our very next question, and our very next question is going to be, can an evidentiary threshold be defined to invoke or start CED? Can you help us bridge a couple of concepts, please? I know this is sort of on the fly, Doctor, but something that is perhaps up for CED may not have hit the standard of reasonable and necessary. So how do you get from not hitting the standard of reasonable and necessary to an evidentiary threshold that says it's time to do CED? How do we go from not getting reasonable and necessary to say aha, there's something missing or something needed that would trigger NCD? Have you had a chance

to think about that?
DR. MCCLELLAN: Well, I think the CMS staff who are here know this a lot better than I do, but over the years in trying to apply CED, there have been some real questions and a lot of involvement from the counsel's office about how this does fit in with the statutory authority of the Medicare program. And how

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this question has been answered over time I think has evolved, my own sense, and I'm not a lawyer, but I do think it would be good for MEDCAC and the rest of you involved in this to consult some of the legal experts who have worked on this over the years. My own sense is that while you're right, and there is this issue of kind of earlier access that was touched on before, there are some treatments that if you just apply the existing standards of evidence, it may not be there in terms of a traditional reasonable and necessary decision. On the other hand, the fact that you are collecting more evidence in particular cases may have two benefits. One is while this will help us learn more about whether treatment is really reasonable and necessary for future Medicare beneficiaries, and that's important, but remember, the statute really focuses on what's reasonable and necessary for a patient, and so some of the legal justification for CED is based on whether the additional information that's being collected could actually result in some proven outcomes for that patient. So if you're doing a better job of

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monitoring the clinical characteristics of the patient, that may be something that can help with that patient's ongoing decisions involving the technology, tracking whether it has any adverse associated events, and that is to illustrate that with the ICD coverage decision, that was a pretty broad coverage decision kind of going beyond some of the clear indications where in the clinical studies ICDs have been shown to be clearly beneficial and therefore reasonable and necessary. In cases where there's suspected benefit but in the absence of collecting additional evidence, CMS might not adopt this philosophy, and I think additional data collection may give the Agency confidence, the Agency's counsel confidence that this was the case, that now with CED, was reasonable and necessary.
DR. C. GOODMAN: Thank you very much.

Further questions for Dr. McClellan? We will start with Dr. Phurrough.
DR. PHURROUGH: Dr. McClellan, the Agency has yet to clearly define what the threshold is for reasonable and necessary. How can you define a threshold for something else

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that's not reasonable and necessary if you don't know what reasonable and necessary is?
DR. MCCLELLAN: So again, this is not, I mean as somebody said this morning, this is not clearly binary on or off, this is, you know, some things that we know are clearly reasonable and necessary, there are some treatments that clearly shouldn't be covered, and then there's a zone in between where there's a lot of room for interpretation. I guess one of the points of what I was saying earlier is that zone is likely to get bigger and not smaller unless we develop better mechanisms for postmarket evidence because these questions about effects in subgroups of patients, effects that may, where patient preferences may lead to differences, questions like that are not easy to address in traditional premarket clinical studies. So I think just because we don't have a complete and fully, you know, defined criteria here for when it needs to be applied, we don't have terrifically detailed focused criteria for reasonable and necessary either, but that does mean there is this big zone of

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areas where better evidence could be really helpful and could help lead to better results for patients. So maybe, you know, more of an outcome focus for the criteria would be helpful, and as I said earlier, I think CED could really be used at this point with some more formal evaluative criteria. So if you're going to do it, even if all the criteria aren't fully defined, you should at least have a way of answering the question of, you know, what do we expect to gain from this that we wouldn't otherwise, you know, what patients are going to get access that wouldn't under a traditional coverage decision, how do we expect to see an impact of CED, is it outcome-related, is it in terms of publications coming from this, but something, even if we don't have a very detailed criteria for exactly when it should be applied, to at least guide us to applications where the benefits are going to clearly

outweigh the costs. And again, I don't think you're going to get to, maybe not how exactly we were talking about the binary process earlier, and I

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don't think we will get into a completely binary and clear process here; instead it's getting more complex and not less. That doesn't mean that we don't need better evidence and it doesn't mean that CMS -- CMS really should be supporting all these kinds of efforts that I was talking about earlier in my remarks for developing better evidence in clinical practice, and those will be beneficial to our patients.

DR. C. GOODMAN: Thank you. I saw Dr. Neumann next.

DR. NEUMANN: Thanks, Mark, great comments. I was very intrigued by the reasonable data structure idea, not having one-off CEDs, and I guess my question is thinking about the CEDs in the past, you really need to have clinical detail in these databases, disease stage, medications, maybe variables tied to specific devices. So I guess one question, how practical will it be to anticipate those kinds of needs, and secondly, what kind of time frame will we need, are we talking three to five years, shorter than that, maybe longer?

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DR. MCCLELLAN: It's a moving target. I definitely would hope for something better and more systematic within three to five years, and maybe that's a reasonable goal. It's not going to happen overnight since we are in sort of a one-off framework here, but more clarity around when the one-off framework should be applied coupled with at least a pathway of thinking about when CED decisions are made, could they be made in a way that reflects and potentially reinforces some of these infrastructures will be helpful.

So with respect to devices in particular, the MDEpiNet effort around device safety that FDA is leading is getting up and running now, it's starting with orthopedic devices in a number of institutions, Columbia, and some researchers at Harvard have been very instrumental in that effort, and I know FDA expects that that can expand substantially within the next few years.

Also coming on devices, as you all know at some point, hopefully sooner rather

than later is a regulation from HHS via OMB that's going to implement a unique device

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identifier. I think industry has already been great about supporting that and about finding ways to get the UDI onto the device so that it's easier to track in these systems. The next step of course is getting that UDI information factored in to electronic record systems reliably and payment systems reliably. CMS has been having some discussions too. I don't know exactly when it's going to happen, I do really hope it's going to happen within the next several years, I think that's very feasible. And so the capacity for doing this kind of tracking on a larger scale is going to get better.

And you know, you don't know exactly what device questions are going to come in for an NCD three years from now, but you do know that it probably is going to involve data that will increasingly be factored in to electronic systems and these kinds of emerging surveillance networks, and that's something that I think should factor in, that's where you can get some more predictability, and maybe move away from the one-off framework without delaying, which we certainly don't want to do

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so, without delaying the CED.

DR. C. GOODMAN: Good, thank you. A few more questions, and I will ask for a concise Q&A here. Dr. McDonough?

DR. MCDONOUGH: I'm going to try to get in two questions.

DR. C. GOODMAN: Briefly.

DR. MCDONOUGH: One is, are there any kinds of, on this evidentiary threshold question, are there any kinds of questions or technologies that you think would be off limits? And what I'm hearing from is, some people saying that, well, if it's FDA-approved through a PMA that should be off limits, or if it's something that we cover now that we shouldn't go back to have conditional coverage, or if it's something with a life-threatening condition, that shouldn't be subject to coverage with evidence development. I mean, in my personal opinion also, I'm thinking if something is very early in the stage of development, you can't make a judgment about being promising, and it shouldn't be the subject. Do you have any feeling about where the boundaries are?

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And the second question is, and this is something I didn't understand, when you were talking about the legal analysis of the benefit to the member, the individual patient from getting this promising treatment, are you talking about the benefits from the experimental treatment itself, or the fact that they're in a clinical trial and being carefully monitored.

DR. MCCLELLAN: So, the answers may not be as specific as the questions, so let me take the second one first. I was talking about the benefits to the patient from the treatment, and in a system where we aren't collecting this additional kind of data, it may be harder to know whether the patient is having a benefit or harder to know whether there's a potential side effect emerging that could be harmful for the patient. And knowing and having that additional clinical data, you know, the same reason we want richer clinical registries for high quality patient care, to do a better job of tracking the patient, because this is a new or emerging technology. Now that has costs associated with it too, and that gets back to

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the cost-method analysis that I described. But I think that is the point, that there can be well-designed CED studies that focus on those items right then and there, not just better evidence in the future.

And I do want to, with respect to your first question, I guess with regard to anything off limits, you know, I always thought that FDA, and an FDA device as safe and effective, it's pretty strong evidence that it's reasonable and necessary, at least as an option available to patients. As you see, the payment system's evolving, though, with more attention to applying treatments effectively and preventing unnecessary costs. You know, I think there will be some interaction between CED and other payment reforms that are worth thinking through a bit, but again, I think it's not a binary set of questions.

If you weigh sort of the benefits against the costs, that's where I think some criteria could be really helpful, you know, how should we be thinking about the benefits of CED relative to not doing CED, and what are the costs of CED, both the financial and resource

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cost in terms of actually conducting the

evidence development, plus the potential costs in terms of impacts on patient help. That's where I think criteria will be useful, I mean, and could hopefully be applied to a whole lot of different contexts.

DR. C. GOODMAN: Thank you. We have a hard stop on this thing in five minutes. So Drs. Lasersohn, Sedrakyan and Goodman, if you can pull it off with Dr. McClellan's answers within five minutes, we'll do it. Otherwise, we do have a hard stop in five minutes. Dr. Lasersohn first.

MR. LASERSOHN: I wish I was a doctor.

DR. C. GOODMAN: Oh, Mr. Lasersohn. You might be better off.

MR. LASERSOHN: Mark, I'm very interested in the cost-benefit analysis that you're proposing, and specifically, clearly one of the costs that we've talked about in the first session is the uncertainty that the non-binary type of approach creates, that is particularly in the minds of innovators, that is, what happens when we have the answers, do we get to the marketplace. That's a clear cost

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in addition to some of the costs of information.

One way to offset that cost is to have highly constrained, very very predictable, and maybe not as flexible criteria for moving forward. For example, it may be ultimately perfect to say that PMA devices should be presumed not to fall into the CED. Maybe for the sake of certainty and lowering that cost, that would be a reasonable place to start, a kind of precautionary principle, right, let's not do anything until we really understand this better. What do you think of that, is it worth being maybe a little less flexible and having a little more certainty, at the expense of perfection?

DR. MCCLELLAN: I think the more predictability is definitely good, and I just want to be very clear, I'm talking about costs and benefits here, I'm not talking about CMS making some judgment about the cost effectiveness of a technology or the cost-benefits of a technology itself. I'm talking about the CED process and making sure that we're not applying a process that is

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having financial and health costs that outweigh any benefits for the patients affected and for further evidence development.

And, you know, I think to the extent that we can make that more predictable would be good. My own hope is that for these manufacturers that are involved in these very costly and difficult technologies, very hard to bring to market, been through clinical trials in the PMA case before they get to market, we need to do more to reduce that time, reduce that uncertainty to get those beneficial treatments to patients faster. I think maybe the best way there are some of the steps I'm describing in really bringing down the costs of doing CEDs so it isn't a big holdup, there can be time, there's this kind of more a routine part.

You know, for many providers today, an increasing number of manufacturers today, they are reporting on outcomes not as part of CED but as part of the payment contracts. You know, they get paid more if they prevent more complications, they get paid less if they don't, or if the costs are higher. So, you

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know, that's getting built more into the routine of clinical practice, and to the extent that CED policy steps could bring down that cost side, that may be a way to both give the manufacturers both predictability and more confidence that they're not going to be held up with additional resource costs, additional delays with CED, because, you know, the evidence can be collected as a more routine part of clinical practice.

DR. C. GOODMAN: Great, thanks. Let's have a one-minute Q&A, Dr. Sedrakyan, and then we will break, we will go to the next section.

DR. SEDRAKYAN: I will try to be short.

DR. C. GOODMAN: Go right ahead.

DR. SEDRAKYAN: So, Dr. McClellan, I agree with the position that you have, but maybe a few questions regarding the clarification that I need.

DR. C. GOODMAN: Maybe just one question.

DR. SEDRAKYAN: So, the evidence as yo said is often not complete, particularly after FDA decisions, and you also said that rapid

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access to technologies that are reasonable and necessary will help develop better evidence to improve the care and make better decisions. So that in my head means a lower threshold for initiating CED, delaying for a moment the cost

of initiating the CED. So it means the threshold to start CED should be lower because most of the technologies we don't know much about, particularly at patient-level decision-making.

And the second concept you have is that you said CEDs might need to rely upon data infrastructure elsewhere developed. It can be, essentially it can be the data registries that are out there, but for many technologies that are important and we don't know much about, then CED is the first step to initiate that infrastructure, which later on may make the conduct of CEDs less expensive and easier to do.

DR. MCCLELLAN: Yeah, on the second point, clearly there is not infrastructure in place to do everything we would like to do and that's the reason for, you know, the CED on a case-by-case basis is still going to be

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important and challenging with the additional costs and so forth of setting up these new systems, but we would like to see us find a way to move away from that over time.

With respect to the first question about threshold, I'm not necessarily arguing we should be doing this more, I'm arguing we should be doing it better and we should be more clearly justifying the cases of, when CED is applied, where there is an articulated set of reasons, hopefully a more standard set of reasons applied if this is going to be beneficial for Medicare beneficiaries and for evidence development, and the costs don't outweigh that. So yeah, we live with a lot of uncertainty in medical decision-making today, that's not going to change overnight. That doesn't mean we shouldn't provide, you know, access to innovative treatment, it doesn't necessarily mean we should apply very costly evidence development structures. It means we should be thinking about ways of improving those benefits and reducing those costs as technology grows and we learn more about how to apply CED.

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DR. C. GOODMAN: Great. Dr. McClellan, thank you very very much for this great exposition here and your willingness to take some Q&A off the cuff here. We appreciated your viewpoint, your history with the program, and your forward thinking. Thanks a lot.

DR. MCCLELLAN: Good luck with all this. It's very important.

DR. C. GOODMAN: Thank you very much. What I'm going to do now is ask Sean Tunis, who is already at the foot of the stairs, to present his expert view on question two. And when Dr. Tunis does that, we will break for lunch and then adjust this afternoon's agenda accordingly. Welcome, Dr. Tunis. This is question two.

DR. TUNIS: Well, thanks, Cliff, thanks to the panel and the CMS folks for inviting me to make some comments. I will focus on this question number two of the evidentiary threshold to invoke CED, and then later observations they said I could make on other subjects that were not in the questions, so that's what the other part will be.

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So, you know, I would say that we have heard already this morning that Medicare's experience with CED to date, there's been some encouraging successes but some challenges with past implementation. You know, challenges may be an understatement depending on what your views of this are, but I think Dr. McClellan did a very nice job of summarizing what some of those challenges are.

I was thinking as Dr. McClellan was talking about the early stage of consideration of CED, and I left CMS in 2005 and Mark left in 2006, and I was kind of reminded of that Southwest Airlines commercial where the elderly couple shows up at the door and a younger couple sort of opens the door, hands them two crying babies and jumps in a cab and heads off, and the guy is saying don't leave us with the babies, and that's I think how Louis and Tamara felt when Mark and I left, so hopefully the babies will stop crying.

But anyway, what I'm going to actually do today is propose a very, you know, what I think is a fairly specific concrete proposal for moving CED forward from the point of view

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of a threshold to initiate it, and this is based on some work that we had done reviewing Medicare's experience with CED for the Medicare Payment Advisory Commission and a whole bunch of workshops and expert interviews we've done over the past few years with some funding from the California HealthCare Foundation, so all of that went into -- I'm not going to give you a summary of lessons learned, what I'm going to

give you is a proposed approach that is based on the insights from that work. And, you know, as we all know, one of the reasons you don't hear very specific proposals in presidential campaigns is that it gives people something to object to, I think everyone will hear a lot to object to today, but it's done in the spirit of trying to move the conversation forward as much as possible. Be prepared to be annoyed, but what I'm hoping to do is kind of annoy the different stakeholder groups equally, which I think is the mark of a good policy perspective. So first of all, we've heard this already, that the core policy objective of why does CED exist, rapid access to promising

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technologies and promoting innovation, particularly for the Medicare population, generating evidence to address important uncertainties, and being aligned with Medicare's programmatic aims of improving health outcomes and using resources wisely. And what I want to be very clear about is that any version of CED that doesn't almost equally meet all three objectives simultaneously is not going to work. If it's too innovation weighted it's not going to work because it won't be sufficiently focused on generating useful evidence. If it's not mindful of the need to use resources wisely and address kind of issues of resource consumption and costs, it also won't work because there's key stakeholders, you know, that won't be supportive. So the approach that I think needs to be envisioned is one that simultaneously and equally addresses all three of these policy objectives, and if it fails to do that, it ultimately won't get traction and be able to move forward. So with that in mind, that premise that we have to meet all three of these kind of

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key policy objectives, the first point I want to put out there is that there needs to be minimum mandatory requirements for at least the next stage of CED, and these have to be the following: The technology is to diagnose or treat a serious disease or condition, or for an unmet need in the Medicare population, so it's got to be meaningful, important, unmet need. Otherwise, it's not worth bothering with it. This is the part that's going to annoy some number of folks. The intervention can be

plausibly anticipated either to substantially improve health outcomes with the same or lower level of aggregate health spending, or produce comparable health outcomes at a substantially reduced aggregate spending. So you don't even pass step one unless the technology can plausibly make the case that health outcomes will be improved at no increase in cost or potentially lower cost, or that you get the same health outcomes at substantially lower costs. Otherwise, no CED should be considered. Obviously there would be some exceptions, and in fact some of the important past episodes of CED are examples, have been

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around cost increase and quality improving technologies, but I think for purposes of meeting those three policy objectives of CED, if we focus mostly on quality improving/cost increasing, again, it won't gain traction, and so I think we need to satisfy these criteria. And for quality improving/cost increasing technologies, they can be addressed through the binary coverage process as usual, but for the next phase of trying to get support for CED and put it in place, we need to be focusing on early access to technologies that meet these two critical criteria in terms of improving outcomes at lower or the same costs, or the same outcomes at lower costs. And it's a tremendously important signal, if you will, to the innovation community that this is what the Medicare program and the health care sytem generally needs to be looking for and will need to facilitate an access associated with CED for technologies that meet those criteria. So understanding that we don't go forward unless those criteria are met, let me shift to what is the evidentiary threshold for invoking CED. So first, you know, just as a

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brief comment about the sort of the binary or traditional coverage, currently coverage is defined as something's reasonable and necessary are covered if there's adequate evidence that health outcomes are improved. Well, we all know that evidence and the sort of knowledge, knowledge increases over time with more research, as well as, by the way, there's increased costs to create that knowledge, but generally knowledge or the level of certainty increases over time, it's a continuous function, it's not a binary function. And so to stick a line in there and

say suddenly evidence is adequate, we just have to understand that that's a subjective judgment, it's not a scientific principle. At some point someone made the determination that that level of certainty is adequate, but it's a socially constructed notion, it's not a scientific concept. So there's some natural wariness to what, you know, this sort of binary mechanism.

And then the sort of CED or non-binary approach, again, just to sort of make it very clear, initial reimbursement or coverage, you

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know, at a lower level of certainty and a lower level of investment, so the purported advantage from sort of an innovator and investor point of view is less investment necessary to get additional reimbursement and you get to it faster but at a lower level of certainty, and the quid pro quo is a commitment to generate additional evidence to erase that level of uncertainty over time until you get to the second blue bar, that's the reasonable and necessary end of CED bar in this new paradigm.

So now the question is well, what defines the bar to the far left, you know, and what I would propose is, and again, the wording is, this is not fully wordsmithed, but again, this is just sort of a straw man for sake of the committee to consider. The evidence threshold to initiate CED, a moderate level of confidence based on available evidence that the item or service will improve health outcomes. Moderate level of confidence obviously needs to be defined, but I would say something like benefits considered more likely than not to exceed the risks. A preponderance of the evidence, if you have a higher level of

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confidence then CED should not be applied. And then there would be two mechanisms by which the determination would be made whether the moderate level of confidence threshold has been met. So we're talking now about CEDs invoked when there is a moderate level of confidence, and there are two mechanisms that would allow you to determine that the moderate level is met. One is what I'm calling deemed categories, which are essentially other mechanisms outside of CMS that are presumed to meet the moderate threshold, and then there would be a CMS determination that would be kind of an internal agency judgment about whether a moderate level

of confidence has been met.
And here are moderate confidence, the deemed categories, and again, these are, you know, sort of a straw man for purposes of consideration. But any intervention being evaluated in a prospective comparative effectiveness or patient-centered outcomes research study funded by NIH, AHRQ or PCORI. So if there's a drug, device, diagnostic, et cetera, if there's a funded study, any

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intervention that's being studied in that study would automatically be deemed to meet this moderate level of certainty and would be eligible for CED.
Second, drugs and biologics granted accelerated approval by the FDA would be deemed to meet this moderate level of certainty.
Medical devices approved through the 510(k) process when additional clinical data has been provided, this is not a 510(k) without clinical data, and research diagnostics approved or cleared by the FDA based on clinical utility would meet this threshold. And then the notion would be, even if this is sort of a starter set to get you thinking or to get the panel thinking, but I actually would suggest that these categories of what would be deemed to be qualified for CED could be refined and augmented through an NCD process, a national coverage determination process, much like the clinical trials policy that was developed and revised so that there would be kind of a public iterative process and a master NCD for the coverage process that would define what constitutes a moderate level of certainty and

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which would be the deemed categories that would be presumed to meet a moderate level of certainty.
So the second mechanism whereby something would meet this evidentiary threshold for CED would be the moderate level of confidence of improved health outcomes as determined by CMS. And again these are just suggested for purposes of consideration, but for all interventions, at least one high quality study showing improvement in intermediate or surrogate outcomes. High quality studies demonstrating effectiveness but for patient population setting that's not representative of the Medicare population, so it's a study of younger individuals or, you know, only in tertiary care settings, so that

would qualify as moderate confidence. Drugs and devices approved by the FDA with significant post-approval study requirements, so they are approved but for those where there is clearly a fundamentally important question that is going to be addressed in a post-approval study, that might be considered a situation where there's a moderate level of

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certainty and it would qualify for CED. For diagnostic tests when there's clinical validity, I sort of said this one earlier, but for the ones that are not reviewed by the FDA and are only under a CLIA certification mechanism, all they would have to do is demonstrate clinical validity, and then the CED mechanism would be used to demonstrate evidence of clinical utility. And then surgical procedures for which one high quality observational study demonstrates effectiveness, but there clearly is a need for a higher quality comparative study to generate sort of a reasonable and necessary high level of confidence of improved outcomes. I'm sure everyone could come up with a whole bunch of additional criteria, and again, my point here was just to put some things out there that might look like, at least at first blush, that we moved beyond the view that every situation is different and we can't possibly define a threshold for initiating CED in any kind of explicit way. I think there probably are some ways with criteria like these or

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modifications of these that we could use to start having a conversation about what would be deemed to meet this moderate level of certainty, or what CMS might consider to be a moderate level of certainty. And then very quickly, because I think I'm running out of time, so these additional requirements or considerations really go to what has been pointed out by others here and elsewhere as sort of recurring kind of defects in the CED process that would have to be addressed in order for it to work successfully. The point is, there needs to be a study protocol that's approved that will address the specified key uncertainties, so we can't be implementing CED unless we've agreed in advance to a study protocol that really has the potential to address the uncertainties in a meaningful way.

Secondly, there's got to be sufficient funds identified to cover the clinical research costs, because if you don't have the money there is no point in doing it, so somewhere you've got to have a plan for having those resources, whether from a public funding

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agency, whether from industry or elsewhere. And I think the study results have to be available in a reasonable time frame. Five years might be wrong, but I think ten years probably doesn't make a lot of sense for CEDs, so I think there ought to be a time limit. And then of course the whole process for doing this CED has to be as transparent and predictable and consistent as the NCD process has been designed to be to date. And perhaps the most controversial thing which will, you know, probably require further discussion, but basically I'm proposing that the only thing done at the national coverage level are CED decisions, and that all binary coverage policies are done by the regional contractors rather than the NCD process. There's limited impact from the current NCD process over the past decade, most product developers are avoiding it anyway because it's viewed as too stringent and they choose to go to the local contractors. The number of NCDs is declining over the years. I think that most binary coverage decisions can easily be made through the

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regional contractor mechanism and perhaps that's a better way to accommodate those kinds of approaches, but the national coverage process should be primarily focused on implementation of CED to promote access to evidence for a promising technology, and the idea here really is that we use the regulatory and reimbursement authority of CMS in a proactive way to try to promote and facilitate the development and adoption of technologies that are important to the Medicare program, to sort of be in a proactive mode rather than to play kind of the defensive mode of trying to protect the beneficiaries from, you know, harmful or ineffective technologies, which tends to be politically challenging, resource intensive, and is probably best delegated to the local contractors. The NCD process should really be focused on getting CED right, figuring out how to get these promising important technologies

that meet those requirements that I said at the beginning, which is quality improving, cost decreasing, or comparable results at a lower cost, really focusing on getting those into the
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system faster, evaluated quickly, and then for the ones that are demonstrated to work, deployed widely to Medicare beneficiaries. Thanks very much.
DR. C. GOODMAN: Thanks very much, Dr. Tunis, and thanks in particular for doing what we asked you to do. You did provide an on-point response to the question about evidentiary thresholds being defined, you addressed those very clearly and we appreciate that.
When we come back from lunch, and this is a note to Charlie, who I know is listening. Charlie, when we come back from lunch, I would ask that you show slide six from Dr. Tunis's presentation. That may be a good point of departure when we continue our discussion. Sean's points gave us a lot of food for thought but it may not be enough food to get you through to one o'clock, so lunch would be well taken at this point. Just a note of advice. This is a big building with a lot of folks, we are a large group today, and there's only one cafeteria, so you may want to be prompt about getting down and through the line.
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We will see you at one o'clock sharp to continue. So take my advice, come back in an hour, but get down there soon. Thanks a lot. See you at one.
(Luncheon recess.)
DR. C. GOODMAN: Let's reconvene, please. Dr. Tunis, if you would be so good as to join us, thank you, sir. Let's come to order now. Before lunch we broke after the initial presentation of question two by Dr. Tunis, and we will proceed to the rest of the questions this afternoon. What we would like to do now is take, if there are any questions from the panel for Dr. Tunis first, we will take a few, or several of those as appropriate. We're also going to ask Drs. Sandy and Kuntz to make some comments as well on the matter of question two. And I took the liberty of asking to have Dr. Tunis's slide number six put back up there, because remember, this question is about thresholds, and there's some interesting information on this slide about thresholds as there is on slide seven and

a few of the following slides.
So keeping in mind the purpose of this
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question, which is to answer the following, can an evidentiary threshold be defined to invoke CED, can we define some evidentiary threshold, and I will entertain questions from the panel at this point for Dr. Tunis. I will start with Dr. Goodman, who was so kind as to be patient over lunch. Dr. Goodman.
DR. S. GOODMAN: Well, it's good, because the question you put off is the same question I'm going to ask Sean, but now it's more appropriate. I have two, actually no, he said it, so I won't have to ask you, but I have two questions. One may be more for clarification, but the second goes to the foundational issues.
The first, which may be the clarification question, is how would he propose that we deal with a new extremely promising therapy like Avastin, approved by the FDA on the basis of highly suggestive but certainly not definitive evidence, that in fact is more expensive, so there's huge pressure on CMS to approve that, and you might not want to provide a binary coverage decision for the same reasons that the FDA wanted to follow up. So that's
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the first question.
The second relates very directly to this notion of an evidentiary threshold, and I think we have to define what we mean by that. Because Sean defined it by saying more likely than not or a moderate level of confidence, and I would say actually, those are not the same thing. 51 percent is not necessarily a moderate level of confidence, that language might be more like a 70 percent, so we have to be careful what language we use. But that is an evidentiary threshold.
The deemed categories themselves are not evidentiary thresholds. The deemed categories are actions taken, even though I think they are extraordinarily appropriate and arguably the only actionable criteria we can use, so I'm not saying we shouldn't use them, but we have to be clear about what this is. Because someone else has decided to fund a clinical trial for accelerated approval, we're in a sense putting off the evidentiary assessment on them, we're saying that another group has deemed this to be promising enough. So if we use the deemed category we will

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essentially be saying if someone else has taken an action in which they think that there is some degree of confidence, we will agree with them. That's not the same as us setting an evidentiary threshold.
So we have to be very clear. I think they're very important, I think they want to be accepted operationally, and we may want to say those are surrogates for a moderate level of confidence as measured societally. So that's sort of a question for us, but I will pass the first question on to Sean and whatever he wants to respond to when he's talking.
DR. C. GOODMAN: Thanks, Dr. Goodman. There are at least two questions there, Dr. Tunis.
DR. TUNIS: For the first question about whether there should be circumstances under which, you know, quality improving/cost increasing technology as approved by, say the FDA, would be eligible for CED at the national level, I guess there's sort of three possible answers.
One is you could say all right, we'll add to the, you know, the list of minimum
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requirements, that in addition to be quality improving, cost reducing, you know, the ones that I mentioned, the same outcome at a lower cost, with certain exceptions. You know, on a case-by-case basis CMS can decide they're going to do CED for really breakthrough, uniquely breakthrough technology that dramatically improves quality even though they increase costs. So that's one way to deal with it, just say okay, the threshold criteria that I proposed are too narrow and we should add that.
But probably, I would suggest that it would really need to be in sort of unique, infrequent kind of breakthrough situations.
The other possible answer is, you know, those get dealt with at the regional contractor level through the ordinary processes and whatever additional uncertainties need to be addressed are addressed through FDA-mandated post-approval studies, and maybe CMS kind of weighs in and says, talks to the FDA and says while you're doing the post-approval studies, we would really like this additional question answered. But it just works through the existing regional coverage, you know, binary.
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And the third one, like some

presidential candidates, I forgot what the third answer was, but it might occur to me later. Education, Department of Education, thank you.
(Laughter.)
On the second question, you know, the only thing I would say, I think that truly is a question for the panel. I will take your point that perhaps moderate level of confidence is the wrong word to go with a preponderance of evidence, but it can't be a low level of confidence because no one is going to agree with that.
DR. S. GOODMAN: My question was on preponderance of evidence, you know, that's a legal criteria too, more likely than not or a preponderance.
DR. TUNIS: Yeah. So perhaps instead of using the word deemed it would be more sensible to use a word like presumed, the list on the next slide would be presumed to meet that standard, but it still has to be reviewed and sort of endorsed by CMS, as opposed to just a delegated authority essentially, which would

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probably have to happen anyway.
DR. S. GOODMAN: I just want to add one thing. In the new legislation, and I don't know exactly what will survive and what we've asked, but there is a proposed new formal category for breakthrough categories at the FDA, to be distinguished from other things for accelerated approval. So if that survives, it corresponds exactly with your own designation.
DR. S. GOODMAN: Thank you, Dr. Goodman and Dr. Tunis. Did I see another hand? Dr. McDonough is next.
DR. MCDONOUGH: Two questions, Sean. I loved your presentation. Could we switch to slide five? I thought it was kind of interesting, and maybe I'm reading too much into it. It looks like with the binary coverage decision when you look at the point at which full coverage occurs, it includes both a much earlier time and lower level of evidence than if you invoke for the same technology in a non-binary decision. And I'm thinking, is it possible that actually, if that was the intent, then maybe this non-binary coverage could actually delay access to technologies for the

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broader population.
And I guess my second question, everyone tries to get in two questions, you

talked about having study results within five years. I'm just wondering how at a practical level when you don't know how quickly you can accrue people, and that may be a great limiting step in a lot of these studies, to say it's going to be ended in five years. You know, we may not have enough people, enough statistical power to answer any questions.

DR. TUNIS: Yeah. I think it's a good point about, you know, the point you made about slide five if I understood it, clearly the most important part is the non-binary initial coverage, the CED, occurs earlier and with less evidence than sort of the existing what's considered, you know, adequate evidence, in which there would be an initial reasonable and necessary path.

I guess the second blue line to the right, you're saying if that becomes the point at which, you know, broad access is available and until then all you would have is access under CED and isn't that a, you know, a

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significant delay in broad access compared to what the yellow line is.

DR. MCDONOUGH: That's what I'm saying, you may have a higher evidence threshold involved than if you were doing the binary evidence.

DR. TUNIS: Right. So I guess, you know, there's really no way to avoid that, I think, in the CED model with earlier access and some study that has to be completed until access outside the study was, you know, became available. I guess the only way that that's dealt with is strictly in the case of registries, you essentially allow for universal access in the context of a study, but in the case of, say a randomized trial like the NETT trial or any other RCT where the service is only going to be provided to patients in the trial, like the CREST trial, the SAMMPRIS trial, et cetera, I guess what you're saying in that case is that yellow bar really should be moved to the right because until that trial is done, we don't have adequate evidence to make a high level of confidence that benefits exceed risks. So I guess your point is yes, you know,

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the earlier access is also going along with the recognition that there will be some delay until sort of universal access because it's a registry where everyone gets it anyway as long as they're in the registry.

The second question?
DR. MCDONOUGH: The question about five years.
DR. TUNIS: I think that's right, you know. The whole premise of this proposal was to kind of offer an approach to CED at least as the next phase where we're trying to get it right, has a high chance of showing itself to be successful and feasible, and if we allow sort of studies at any length in there, we won't have any way of really being able to judge its success in the short-term. So the whole premise of offering the criteria of focusing on quality improving/cost reducing technology is not because necessarily that's where CED should be perpetually, but just we want to take the next step, you know, let's try to focus the effort on technologies that were really needed to be expedited in the Medicare program because they have potentially high

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value, and let's try to apply it to studies that can actually be done in a reasonable amount of time.
DR. MCDONOUGH: So it's not hard and fast at this time.
DR. TUNIS: No.
DR. C. GOODMAN: We have several more questions. I would ask the panel to do as well as you can to focus say down on a single question or point, and let's keep it on question two, which has to do with the definition of evidentiary threshold. With that, Juhn, Schwartz and Lasersohn in that order, and we will proceed.
DR. JUHN: This is a question for Dr. Tunis as well as the CMS staff, and it has to do with setting clear evidentiary standards for when you invoke CED, and my question has to do with, can this be a two-way street. So instead of this being a CMS decision, can you foresee instances where the manufacturer would actually create or have trial data that would meet some of these evidentiary thresholds and actually come to CMS and actually ask for a decision to actually invoke CED?

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DR. TUNIS: So it's basically they would come in with studies that would meet this preponderance of evidence standard and they would come in and be proactively -- well, I would think that is the preferable way for it to work, would be to actually not have this, not have the onus on CMS to be prioritizing

what gets, you know, to what CED gets applied, but as much as possible, at least my notion would be that it should be a turnkey operation where, you know, either you meet one of the deemed categories in which case you would have to go through the NCD process. But it could be sort of a shortened version because now you've got, you're presumed to have met this preponderance of evidence threshold, and hopefully it could be a shorter process that says okay, CED is in place, you've met these other criteria, there's funding, et cetera. I would think if the CED is really going to meet the policy objectives of promoting important innovation, it really should be initiated from the technology developers, not from the CMS side.

DR. C. GOODMAN: Thank you.

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Dr. Schwartz.

DR. SCHWARTZ: I just have more comment to follow up on the time frame issues. I want to just remind people of something Rick said earlier today, and that is there's an armamentarium of approaches and tools that we have for doing this, and the question for an evidentiary approach for CMS, I think, would be where does CED fit best, where is it the best tool to deal with this type of question. And when you start getting into long time frames, again, assuming that -- because I think realistically at least in the near future, most of these things are going to be devices and procedures, they change quickly anyhow, they are always evolving. And if the time frame gets too long, you end up with continued coverage with inadequate evidence. You know, if this is going on for seven or ten years and you're covering it, in a sense you've made a decision.

So I think that having a short time frame doesn't mean that you've made a decision that this may not be the right approach to this. Maybe CMS has somewhat of a different

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approach, but I think for the reasons Sean said originally, focusing on this, I might even pick a shorter time frame, something like three years or four years, something that really can get done.

DR. C. GOODMAN: Dr. Schwartz, your point is well taken, I think especially in light of the comments that Dr. McClellan made with regard to the environment for data

generation has changed since the inception of this program a decade or more ago, in that there are other data sources and types, multi-payer claims databases in Sentinel, and registries and so forth that might be as good or better than CED in some instances. So your point about making sure CED is the best fit is very well taken, so thank you.

DR. SCHWARTZ: You know, given the whole issue that Mark was also making about efficiency and driving down the cost, we want to get the most of what we can do.

DR. S. GOODMAN: Thank you, Dr. Schwartz. Mr. Lasersohn.

MR. LASERSOHN: So, Sean, a clarification on the question. Just for

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clarification, your idea of cost is a very broad idea of cost, it's an aggregate health care impact, right, not like an episodic cost?

DR. TUNIS: Right. You know, I didn't spend a lot of time sort of unpacking these and as I thought about it, but I think the notion is it's not just whether or not the acute episode of care is more expensive to manage with a new technology, but whether there are offset downstream costs such as rehabilitation, institutionalization. And I kind of chose the word carefully that said you have to be able to make a plausible argument. You know, I don't know what the definition of plausible is, it requires some further discussion about the definition, but you know, some reasonable expectation that in fact the additional cost of the service itself in the short term would be compensated by some kind of reduced, by savings, and you could say either the Medicare program or you could say more broadly to the health care system in some respect.

MR. LASERSOHN: Great. And then again, clarification. As I understand this, your view is that this sort of combination of a

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set of objective criteria, deemed criteria, plus the flexibility to call things into CED, your goal is actually to expand the coverage with CED to things which might not in fact be covered now, make it applicable to things that might not be applicable now. Is that right, that's your goal with this definition?

DR. TUNIS: Yeah. I think the intent is to create a framework within which CED can be applied much more frequently but, you know, with a focus on the technologies that have

plausible potential to improve quality and reduce costs, and, you know, that should to some degree be aligned with the report on the bioeconomy which talked about CED as a way of promoting innovation. My view is the only way that's going to fly is if it has sort of a quid pro quo piece which is it's promoting innovation that is contributing to the sustainability of the health care system broadly, and if you're just going to try to have a CED mechanism that is all about innovation and not mindful of resource issues, it's sort of a fantasy, and I don't see that that's going to play in Medicare or certainly

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with the private payers. So yes, it's intended to expand it, but it's sort of trying to, and you'd know better than anybody here, to send a signal to the innovator and investor community to say let's be working on innovations that really have the potential to take costs out of the system if at all possible or at least, you know, be cost neutral and really add something of value.

DR. C. GOODMAN: Good, thank you. Briefly, Drs. Min, Normand and Rich. Dr. Min.

DR. MIN: I was just curious about your graph, I think it's a good model, but the question at hand is whether or not we can, can an evidentiary threshold be defined, and I think before it's defined we could apply a lot of adverbs, and one of them I think is constantly or statically. So as an example, Dr. Mack this morning talked about transcatheter heart valves, so there's another transcatheter heart valve that's in development and there's at least seven companies that are developing different kinds of valves. And so I'm just curious, in your opinion, if you do an

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observational registry with one type of valve, then do you anticipate you would have to do another CED for every iteration of technology, and if you do, or if you don't, does that somehow affect the innovative process?

DR. TUNIS: Well, I don't know the details of how the NCD was written, but I would assume that it would allow for other companies' transcatheter valves to be covered under the existing CED as long as they're included in the registry. So, does that answer your question, or did I miss it?

DR. MIN: Yeah. I guess I'm curious

if the CED ends up getting closed and then a new valve comes about, does that mean that we have to reopen a CED every time there is a new iteration of the technology?

DR. TUNIS: Right. So if it comes into play after sort of the CED is done, the hope would be that if it worked, then now you have a coverage decision without any requirement for ongoing data collection, so, you know, new technologies that would fit under the current coverage decision would actually be covered without any CED requirement.

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DR. MIN: Would they be looked at within the CED to comparative effectiveness to say well, those might be covered, but those wouldn't, or is there a class effect?

DR. TUNIS: I think there's a lot of details to this, and again, probably a better question for the folks who wrote the NCD, but I think, my understanding is it was written to sort of cover the class of technologies. And there's always the, you know, CMS always has the authority to decide that a certain technology within the same class represents significant differences in terms of risks and benefits of CED considered outside the boundaries of the NCD but they're generally, NCDs are generally written to be broad enough to include reasonably similar technologies in the same class.

DR. C. GOODMAN: Thank you. Dr. Normand.

DR. NORMAND: My question is along the same lines, and first of all, I really thank you, because having some concrete ideas is I think very helpful to us, and so it's been very special for you to pull those points together

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and looking at them, and of course at these questions, which is the fun part.

My question is related to the evidence of threshold to initiate CED, which is your slide six, and it's a related question to my colleagues, because often benefits are considered more likely than not to exceed risk.

So what I wanted to ask was to get your sense of when one thing's a benefit, one thing, that is what I think of a comparator, I personally feel that you can't measure benefit unless you have a comparator, so I wanted to get your take on that. Now we heard about technology changing over time, that's not necessarily my question. My question is when you say benefit,

did you have that in mind, that there needs to be a comparator, is it the standard of care, if you were thinking about that.

DR. TUNIS: Well, in most cases there is going to be a defined comparator, so I was assuming there was a defined comparator. And for the deemed or the known categories the comparator is whatever, you know, went into the FDA approval or whatever is included in the PCORI or AHRQ or NIH-funded trial. The

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comparator --

DR. NORMAND: Excuse me, I was not interested in all FDA comparators, I'm just asking you explicitly, would you want a comparator?

DR. TUNIS: Yeah, and the comparator could be standard of care or placebo or whatever it is, so I think it is whatever the comparator was, whether it's placebo or standard of care for the deemed categories, and then in the case where it's a CMS determination, CMS would determine what the appropriate comparator should have been, to determine what the incremental benefits are.

DR. NORMAND: This isn't really a question, I just wanted to get it straight out in public that one is thinking of a benefit relative to something else.

DR. TUNIS: Right.

DR. C. GOODMAN: Good point to be made, thank you, Dr. Normand. Dr. Rich.

DR. RICH: I was going to ask a question about the transcatheter aortic valve replacement, but I will switch because it was already asked. If you create a constellation

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of deemed categories, are you saying that anything that falls into one of those deemed categories automatically must be covered under CED?

DR. TUNIS: It probably would be more sensible to call them presumed to qualify, you know, as, presumed to qualify for CED subject to CMS review, because I think it's a CMS decision. Well, I guess there's sort of an AHRQ authority thrown in there depending on whether it's A or E, but it's somebody's decision that's not the decision of the deemed body. So NIH and AHRQ and PCORI have no authority to make national coverage decisions directly or indirectly, so that can't technically be delegated. So CMS has to hone sort of the final decision about whether a kind

of presumed qualified technology, you know, actually then would be, have CED applied. Does that make sense?
DR. C. GOODMAN: Thank you. Charlie, would you go to slide seven just for reference here. I should have passed through this a minute ago, but these were the deemed categories, just for the panel's edification at
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this point. Mindful of time, we do need, this question calls for a yes or no, as did one of the earlier ones, and I'm giving a little warning to Drs. Kuntz and Sandy, because we want to get their views on question two. So if you could pull out your yes-no sheets, and remember, this is a pretty straightforward question, can an evidentiary threshold be defined to invoke CED. It doesn't mean that one has to be defined in all cases, and it's just saying is it possible, can this be done? So can I get a yes or no starting with Dr. Phurrough on can an evidentiary threshold be defined to invoke CED.
DR. PHURROUGH: Steve Phurrough, yes.
MS. CABRAL-DANIELS: Rene' Cabral-Daniels, yes.
DR. GRANT: Mark Grant, yes, with a little bit of no.
DR. MCDONOUGH: Bob McDonough, yes.
DR. MIN: Yes, but not universally.
DR. NORMAND: Sharon-Lise Normand, yes.
DR. RICH: Jeff Rich, yes.
DR. SAADI: Ryan Saadi, yes.
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DR. SCHWARTZ: Sandy Schwartz, no.
DR. SEDRAKYAN: Art Sedrakyan, yes.
DR. JUHN: Peter Juhn, yes.
DR. S. GOODMAN: Steve Goodman, yes.
MR. LASERSOHN: Jack Lasersohn, yes.
DR. NEUMANN: Peter Neumann, yes.
DR. C. GOODMAN: Thank you all. Ms. Ellis, that's all of them, correct?
MS. ELLIS: Yes.
DR. C. GOODMAN: Thank you, Ms. Ellis. We're now, speaking of warnings, after we get Dr. Sandy's and/or Dr. Kuntz's input to question two, we're going to go back to you, the panel, and we're going to actually ask you to say something specific about evidentiary threshold definition, okay? So pick out something that matters to you, it could be therapeutic, diagnostic, what sort of criteria, but one with concrete input from you on this

issue. But first, Dr. Sandy is going to comment on question two. Dr. Sandy, thank you for your patience.

DR. SANDY: I was intrigued by Sean's proposal and I guess what I think I've heard through the morning and the afternoon is that

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the need for CED to have more clarity and more predictability and some kind of prioritization scheme in order to administer the program, and I think his proposal has a lot of those advantages. Having said that, in addressing this particular question, I think what I heard him say, and I guess my interpretation relating to evidence threshold is he's kind of commingled an evidentiary threshold with a prioritization, which in a sense says that the stuff that needs to be prioritized is the stuff that is kind of double arrow up relating to value, either in terms of cost effectiveness or clinical efficacy, and I think this addresses Dr. Goodman's question.

It seems to me that's a little different than saying we need to support clinical innovation. There's a lot of clinical innovations along the lines of what you said that is incrementally advantageous clinically but it's going to be expensive. And so I think the prioritization question is different than the evidentiary standard question. My answer to the question of what should be the way to think about an evidentiary threshold is much

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more around the contextual variables of the population, the service and the comparator, what is usual care, and then I think that has to be contextualized for the Medicare population.

And I guess relating to kind of the, can you develop a defined evidentiary standard, it seems to me there's some other way to think about it in addition to just the way that he described it. I would describe it in qualitative terms, that in fact the evidentiary standard can be higher or lower depending, again, on the contextual variables and the comparator, and when actually I get to questions three and four, I will give some examples of that.

DR. C. GOODMAN: That's great, thanks, Dr. Sandy, very helpful. Dr. Kuntz.

DR. KUNTZ: With respect to can an evidentiary threshold be determined, I don't think it can from a general perspective, that

is a general definition, that can be very hard to arrive at. But there is a special pathway that one could achieve an evidentiary threshold, and that would be to use a working

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definition like any stakeholders involved. So I want to expand a little bit more on what I talked about earlier. There are two levels of stakeholder involvement. The first is when CMS has made a decision that they're considering a national coverage decision. There should be an assembly of stakeholders which should include the industry in addition to all the relevant stakeholders and patients, to come in and look at all the remedies. The remedies will be CED and other solutions we talked about. If we can define what are the evidentiary needs, they may be satisfied by other remedies other than CED. The second level of stakeholder involvement is when the decision to do the CED is drawn, a reassembly has to be done. The current use of a 30-day response period is too haphazard and results in studies that I think are very quickly designed and could be more formally developed. So to get the stakeholders back involved at that level to make an appropriate CED after the decision is made is also critical, and through those processes I think we can define a workable definition of

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evidentiary threshold going forward. At Medtronic we spend a lot of our time working with the Food and Drug Administration and have a very familiar understanding about what evidence is in that arena, and the PMA process is a very robust system, probably the best in the world, for determining what's safe and effective. What is it further that CMS wants to get evidence for, that has to be articulated; that has direct implications on exactly what study would be done. Do you want to look at cost effectiveness? Do you want to look at long-term outcomes? Do you want to look at real world applications, including average doctors that weren't in the studies in the premarket, for example, or average health systems? Do you want to look at broadening the application, the utility analysis? All of these would have direct implications on how the evidence would be defined and what the effort would be in the CED and/or another alternative.

DR. C. GOODMAN: Thank you very much,

Dr. Kuntz, also very helpful to the point. I would like to look now to the panel,

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we won't go down the table from one end to another, but we do want to hear concrete observations or findings regarding defining an evidentiary threshold across technologies, for a particular type, what have you. I see Dr. Grant first, and we will proceed. I see a few more hands. Go ahead, Dr. Grant.

DR. GRANT: Just a few comments from my wavering about yes or no. I think the first thing, the notion of a threshold implies to me one has to have a metric, a metric that people understand, some sort of scale, and I think in the case of evaluating risks and benefits, you know, how people add things up, how they weigh them, how they consider what the preferences are, and all these different groups are very different, sometimes vastly different. And so for that reason I think, and also their calculus is just different, and I think that it is potentially very problematic to say that we in fact have some sort of bargain once you get over it and in fact it is more complicated than that.

DR. C. GOODMAN: Thanks, Dr. Grant. I believe Dr. Goodman's hand was next.

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Dr. Goodman.

DR. S. GOODMAN: I just wanted to expand a brief comment I made before, which is, you know, we have a system in this country that deals with evidentiary thresholds and yet individual decisions, which is the legal system. So we have to be very clear on what we mean. For the legal system in a criminal case you have preponderance of evidence, you have clear and convincing evidence, and you have evidence beyond a reasonable doubt. Those are evidentiary thresholds.

However, they are subject to interpretation and individual application for every single case, that's why we have trials and hearings, et cetera. So one could say in that case we have an evidentiary threshold, but at the same time you could say we don't know in fact how to apply them generally, we have to have trials and hearings, like we do here. So it's not inconsistent to say we have evidentiary thresholds and yet we have to make individual determinations, but that means you have to have a very general statement of what an evidentiary threshold is.

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And in fact, the operationalization of that threshold can be extremely complex for exactly the reasons that you say, we don't know how to weigh eyewitness evidence versus, I won't say DNA evidence, versus flawed fingerprint evidence or all these sort of flawed sorts of evidence. So we might want to distinguish between the operationalization of these very broad concepts which are extraordinarily difficult, versus the evidentiary threshold, which sometimes can be so general as to be useless, but we can define them.
DR. C. GOODMAN: Thanks, points well made, Dr. Goodman, and the interface of kind of the legal and scientific, that point is not lost, because it does ultimately return at some point to the phrase reasonable and necessary in the statute, which is a legal concept. Point well made, thank you. I saw Dr. Neumann's hand next, and then Dr. McDonough.
DR. NEUMANN: I voted yes on this question, but thinking about a flexible standard and thinking about Dr. Sandy's point, I think, again, by kind of contextualizing
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individual cases and at some level at least being qualitative, even as we want a standard. The other point, going back to Sean's very nice presentation, it struck me, Sean, in I think slide six, is that benefits are considered more likely to exceed risks. At some level that sounds right, but I think what we really need is potential benefits are somehow worth the risks involved. And one way to think about this is going back to something Dr. Kuntz said, value of information framework, and in a sense it is maybe an economist's framework. If we collect more evidence and we think the potential benefits of collecting the evidence exceed the costs of collecting the evidence, it might be worth bringing that framework somewhere into these definitions, even as we try to quantify those costs and benefits, I think it's the right way to think about this.
The other point is, it may be worth putting that into the process, putting into the early engagement process a formal step where we try, or CMS tries to think about the costs and the benefits of collecting additional evidence
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as a way of thinking about the evidentiary

standard.
DR. C. GOODMAN: Excellent points, thank you, Dr. Neumann. Dr. McDonough.
DR. MCDONOUGH: A couple points. I think one of the things that I think is implicit in terms of this evidence threshold is that we're looking at things that are in late stages in development, not early stage, and all those deemed categories I think would fall in that.
But the other point is, I think there are factors other than the evidence threshold that would go into making a decision about whether a technology would be eligible, and Sean pointed out, one is, is there a potential cost neutrality or cost savings with, cost neutrality with improved health outcomes. In my mind another thing would be that if there's some important barrier to clinical trial that the insurance coverage would provide, such as for surgical procedures where there's really no sponsor, or where there are multiple manufacturers of PET scanners. I don't think it's wise that this program would end up being

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sort of a wholesale subsidization of the development of products for the pharmaceutical medical device industry.
DR. C. GOODMAN: Thank you for that point, Dr. McDonough, it's the first time we've heard that. Mr. Lasersohn.
MR. LASERSOHN: I think one of the things we haven't talked about, at least from the point of view of the innovation ecosystem, is that knowing what's in CED is, that's very important, but even more important is to know what's not in CED, and whether the goals of any of these thresholds is to exclude cases that should not be covered by CED, and I find that to be extremely important. For example, under Sean's scenario, I'm not saying this is the right scenario, but under Sean's scenario PMAs by definition would in fact not be in CED, it would be in the normal coverage process. And being able to define that in advance for the innovator is just incredibly important, it's as important as knowing that something is a 510(k) or a de novo or a PMA. Just being able to put these things into those categories, put these things into different

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buckets at CMS would be predictably, consistently and predictably, would be enormously important.

DR. C. GOODMAN: Great, thank you for that, Mr. Lasersohn, point well made. Dr. Schwartz.

DR. SCHWARTZ: As the only no vote, let me explain my vote. It's largely along the lines of really what Rick and Louis said. I think we have, I feel comfortable with what Steve said about a generalized flexible approach, but being unable to operationalize it and not being a lawyer, and you can't underestimate my knowledge of the law as my criminal record demonstrates, but I feel that what we have is some general guidelines of prioritization of criteria, or we have studies that are pathways to get there, but you know, I think it's sort of like what the Supreme Court said about pornography, I know it when I see it but it's hard to define it. And so I would say qualitative terms, yes, but an evidentiary threshold, no.

And along those lines, just a couple things I just note is, one, I agree with the

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comment about failure of information, I think it should be a formal aspect of it, especially in light of what Mark was talking about, making sure there's efficiency, making sure it's worth it, so we don't go on putting limited resources into an area that's not going to be worth the information.

The other thing where coverage with evidence development might be particularly useful, I'm surprised Sean didn't say it since he wrote the landmark article on it, but it's in areas where the concerns are such about the evidence that finding how, and concerns about how it performs for the safety in more real life pragmatic settings would be particularly important. So there might be some narrow advocacy evidence, but there are real concerns about how this translates into wider practice.

So, the last thing I would say is I agree, and Sean may be shocked to hear me say this as an economist, but I just don't think that Medicare politically in the environment we have right now can go quite as far as I would like to have them go into putting costs as a criteria, so I think that might be a goal

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rather than a target.

DR. C. GOODMAN: Thank you, Dr. Schwartz, excellent. Dr. Saadi, and then Dr. Rich.

DR. SAADI: A couple observations.

First of all, I think it's obvious from the discussion and Dr. Tunis's presentation that it all comes back to the payment for it. We all are struggling with how do you fund for all of this, we need to find a way to fund for this research, and it's not really that difficult to do.

The second thing is that the industry folks are investors, they want some possibility of reimbursement if they're participating in a registry, which is true, but I think if we can actually bring some discipline in the process into the mix, so we have to come up with a matrix, if not today or tomorrow, you have to come up with a matrix, what is the evidence, how do you plan to find that. I think in my mind you have to, they have to come up with a matrix which the industry people can quantify and can calculate before they actually make the significant investments.

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Now a couple of things, and I think Peter and Sean are pretty familiar with that, it was some, probably not the quality of adjusted life there, which is something we all know. The second thing is that it has to encompass effectiveness and safety and all of this, and it seems that the definitions and the goals for the technology should be expressly stated, and this all can be done.

And the last thing is that in the mix, I think the patient factor and the industry factor and the discipline has to be there; otherwise it's not going to work.

DR. C. GOODMAN: Thank you very much, Dr. Saadi. Dr. Rich.

DR. RICH: That was a nice segue into some of my thoughts. I think that for me the biggest example was transcatheter aortic valve replacement, and that was a good learning experience on how you take the technology and design a randomized clinical trial with the primary endpoint of that, and you can get FDA approval based on safety and efficacy for that, but when you look at the other results that are happening, the other outcomes for those

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patients in those trials, strokes, major vascular events and quality of life, you would have looked at the primary endpoint and say here's a mortality benefit in inoperable patients, whatever, but when you add together that a number of them are having strokes, a number of them were having major vascular

complications, and their quality of life wasn't good.

I think CMS raised an excellent question, would you want to be 86 years old and have a stroke, at least your breathing is better but now you're antipyretic, is that a good outcome? So that brought together in my mind the thinking that CMS had on the need for CED with that device, that you want to know over time whether the collection, as you say, the composite is really truly beneficial to the health outcomes of that population.

DR. C. GOODMAN: Great, thanks, Dr. Rich. In a moment we're going to ask Dr. Phurrough to give us some kind of competent bullet points representing what we've heard thus far. I would just add that it sounds as though, yes, evidentiary thresholds can be

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defined, and in fact the deemed list that Dr. Tunis put up has in it some of the kinds of categories or types of technology for which respective sets of different criteria could be defined to invoke CED. Excellent point about distinguishing among moderate evidence available as opposed to a higher level. If there's high evidence available, probably not CED. If there's just low evidence available, we don't seem to be going very far, probably not CED. But moderate evidence sounds like something where we ought to go after it, and CED might be feasible here.

The availability comparator, as Dr. Normand pointed out, it might be a very useful consideration as a potential criterion for invoking CED, to what do you expect to compare this thing.

Another one, it sounds like, is it feasible to gather data at all? Are we in a position where there are existing data sources? If yes, that's helpful. If not, what are we going to be able to do about it insofar as gathering those data?

Another important consideration was

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timeline, over what period of time might we be able to practically gather these data from existing or not yet existing data sources, that's an important aspect of go, no go.

And finally, as I think Dr. Kuntz made quite clear, at some point along the way, and earlier rather than later, input from stakeholders is essential.

So if we could turn to Dr. Phurrough,

if he's ready to give us some summary bullet points, Dr. Phurrough.

DR. PHURROUGH: Well, I will try to make these summaries about what we talked about, and I will, I'm attempting to summarize panel comments and not the general discussion that we've heard, since that is what CMS needs. First of all, the panel generally believes that there is the ability to establish a threshold, but in general that threshold is a fairly general threshold and will require additional work and specificity around each particular technology. Even a general threshold may be difficult to do. There is a clear view from a number of panel members that the benefits of collecting additional evidence

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should outweigh the cost of collecting that evidence, so the value of the particular CED needs to be considered. Other factors may need to be considered other than evidence itself. Cost was mentioned, barriers to process participation was mentioned. Potentially a composite score similar to Qual-8, since Congress in its wisdom said we have to think about quality of life in the program, and that the applicants also need to clearly look at the quality of life outcomes that may go beyond the hard endpoints of survival. Deciding on thresholds and deciding on prioritization of CED should occur after some determination of what the end needs are, and we have to clearly define what those are prior to deciding what particular technologies fit into the CED group. And then finally, it would be quite helpful as CMS defines what the threshold is, to clearly elucidate what's not included, so that industry has a very clear picture of those areas where they can proceed without having to be concerned about a CED.

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DR. C. GOODMAN: That's great, thank you very much, Dr. Phurrough. So, did he pretty much capture it, panel? It looks like he did. Thank you. We are next going to move to question three, and indeed question four, we'll take these together. Dr. Lew Sandy has been kind enough to agree to provide a presentation covering both questions three and four. Both of them deal with what factors might influence evidentiary thresholds to invoke CED and they

are set up, question three is set up A through F, and in question four we have a set of other types of factors one through three.

So Dr. Sandy is going to give us a consolidated presentation first which will cover both of these questions. Then we will proceed as we have before with panel discussion and input from our other expert speakers.

Thank you, and welcome again, Dr. Sandy.

DR. SANDY: Well, thank you, and good afternoon. I appreciate the opportunity to participate today and address these questions. What I thought I would do is just respond to these questions, outline the questions that

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we've been asked to address, provide an overview of UnitedHealthCare's approach to evidence review, coverage benefit design, and our programs to promote high quality cost effective care and support clinical innovation. And then also, as others have done, to kind of give just general perspectives on Medicare CED policy and programs.

These are the questions. I guess I kind of lumped them together even before I knew I was going to address both of them. Essentially question three are a set of things that could influence an evidentiary threshold, and question four, more things that could influence an evidentiary threshold, so I guess I kind of lumped them together and said what are the things that I think could actually impact the evidentiary threshold for the CED program.

Just by way of context, I mentioned earlier today that I'm with UnitedHealth Group, the parent company of both UnitedHealthCare and Optum. Most of my comments are going to be focused from the UnitedHealthCare side as a payer. I was the chief medical officer of

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UnitedHealthCare, but they've also been informed by our work at Optum, which is a diversified health services company that is actually very active in the whole realm of sophisticated analytics of large data sets, observational data, and many of the things that Dr. McClellan talked about we are already doing, including things like incorporating patient-reported outcomes. So I think it's informed by that, but most of my perspective is from the payer point of view.

As a payer, we are a large national payer, and I think one of the key points that I

guess I would start with is that when we think about these things we think about a comprehensive integrated program that is based on the most advanced clinical science and informed guidance, and we have a kind of flexible evolving toolbox. It's not just coverage, but it includes benefit design, network configurations, care facilitation, consumer engagement and activation, transparent performance assessment and feedback, shared accountability with physicians and hospitals. We're building, for example,

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performance-based contracts throughout our network. And even as we're strong supporters of clinical innovation as advancements in the art of science and medicine, we think you need to kind of have a full toolbox if you really want to advance clinical innovation and get people the care they need, it's not just coverage, or even coverage with evidence development.

So, how do we think about CED? Well, the first thing we do is when we think about it, we think about really what should Medicare beneficiaries receive, what are the ideal characteristics of health service available to Medicare beneficiaries? We actually start with safety, and this has been mentioned in passing, but the services if they're new, they ought to be at least as safe as the other services available to treat the condition. They ought to be effective, at least as effective in the real world as any other services treating the condition. They ought to be appropriate to the subpopulation, in particular I think Medicare rightly is and should be sensitive to the issue of multiple comorbidities and the unique

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attributes of the Medicare population. We believe the services ought to be cost effective and we typically look at is as an episode basis, not the unit cost so much, as what's the aggregate cost for treating the episode of care relative to other treatments.

And as part of that, again, part of our emphasis on quality is that it ought to be performed by the right people and in the right facilities, and there ought to be ongoing measurement of clinical quality and cost effectiveness, this kind of learning health system that I mentioned and Dr. McClellan mentioned as well.

These are just a few examples, I won't

go into the detail, we all know that the medical technologies offer both opportunities and challenges. And we also think about what is the issue, what's wrong with the current state, and there are a whole host of issues that go beyond CED having to do with the basic infrastructure for understanding what works and what doesn't in the right populations. I won't go into all of these details, just a few examples that I'd highlight, I guess.

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One is there is a lack of clinical evidence for some very important areas to treat Medicare beneficiaries that are outside the scope of CED because there's no device or technology that's at issue. To give you one example, treatment of chronic wounds, very common, very expensive, wide variations, very little evidence, just one example. And these are some of the others that I think have already been mentioned.

The other thing has to do with the issue of comparators. We know, there's a typo there, FDA does not have a requirement to provide information regarding comparative effectiveness in device labels. Well, should the labels be adjusted to state that there is no evidence? So the point we bring is not, this is a bit out of scope today, but essentially we need to be mindful of the need for comparative information outside of the scope of the Medicare program as well, and the other regulators and stakeholders have important considerations.

So coming to UnitedHealthCare, how do we address these issues? We look at scientific

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evidence, clinical appropriateness, and it has to be appropriate for our members in terms of type, frequency, expense and duration, and we believe in cost effectiveness. This may be some distinction between CMS and the private sector, but we also believe services should not be more costly than the alternatives at least as likely to produce therapeutic and diagnostic results, and that goes to what Sean talked about in his comments as well.

We believe in defining really the procedure and the processes that we use to make coverage decisions. This is our assessment of hierarchy of -- we use a defined specified hierarchy of evidence that starts with our CTs at the top and has expert opinion at the bottom, but we also have the flexibility

depending on what we believe then is using the best available evidence, which may not be an RCT, it might be a single site study or it might just be a guideline. So we have this hierarchy, but it allows us the flexibility to assess the best available evidence given the circumstances that we see.

The other thing, and this is an

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important point, is that we cover investigational and unproven services under certain circumstances, and this is part of the contextual idea that I wanted to introduce. As part of well-designed and appropriately sponsored clinical trials for treatment of life-threatening illnesses likely to cause demise within one year, and we have some evidentiary thresholds, I guess, in our -- this is a defined policy that we have, and so I guess this is an example of a flexible evidentiary standard contextualized in the case of life-threatening illnesses.

We have a similar kind of an approach for treatment of serious and rare diseases that occur so infrequently that it's unlikely to produce a body of evidence, and we have a process to basically qualify those kinds of conditions. And the point I'm making here is in addition to showing that we cover things Dr. Korn mentioned, that traditionally health insurers don't cover investigational or unproven services, but we have mechanisms to do it that don't require a CED, they're a different way of approaching the problem, and

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so there's other ways around it as well.

So, that's by way of context. Let me now try and answer some of the questions about kind of what are the issues that could impact the evidence threshold. We believe that the threshold of clinical evidence should be high for diagnostic tests and we believe, I think one of the speakers said the criteria ought to influence decision-making.

We think that's important but actually it's not enough to just impact decision-making, it actually has to impact health outcomes and improve health outcomes. If all it does is change physician decision-making but the ultimate outcome to the patient doesn't change, what difference does it make, why is it really worth coverage.

So an example, PET scans for various cancers, you actually have to have, and this

gets to the issue of comparator, compared to what? And in fact there are many new technologies that are coming on the floor, and I would think that one of the issues is that these things need to be compared with one another to essentially demonstrate where the

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value is.
Another example is PET scan for dementia. How can that impact physician decision-making when no effective treatment, or very limited treatments actually exist? That's an important question.
The example you often hear in the personalized medicine space is pharmacological testing to predict warfarin responsiveness.
There are all these issues of the analytic and clinical validity, but what about the clinical utility? Again, what difference does it make compared to usual care, and actually why do we need to do a prospective RCT when we have retrospective observational data to give us, and this is the kind of thing I think Dr. McClellan was talking about, to help inform our policies in this area.
I come back to safety. Clinical evidence must be sufficient to conclude that the treatment is safe relative to other available treatments. And I think one of the critical comments, Dr. Korn mentioned this in his remarks, and we know from clinical studies that the level of evidence sometimes just to

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show that something is effective, the sample sizes, the duration of the study, are insufficient to actually assess safety. That's why you need to do longer observational studies, postmarketing surveillance, and so a higher priority needs to be thought of on the other side of the equation, not just is this going to be a potential benefit, but what about the harms?
Now, what about lowering the threshold of clinical evidence in addition to the kind of specific examples I gave on investigational or unproven treatments? These are the other kinds of conjectural variable that ought to be worthy of consideration. The thresholds ought to be lowered when other effective treatments are not available, when it's a new treatment, when the condition is life-threatening, when the prevalence is too low for the development of a body of clinical evidence or the treatment doesn't lend itself to a randomized controlled

trial. Or it looks like it's not marginally cost effective but highly cost effective, and I think that kind of a 10-X, you know, something that's 10-X times more cost effective,

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something like that, again, one ought to be thinking about lower thresholds for clinical evidence for a threshold, evidentiary threshold.

Additional issues. As I mentioned, coming to the idea of a totality, a total program, that coverages for certain services should be limited to physicians at facilities with demonstrated experience and expertise. We have a centers of excellence program that we've operated for several decades in congenital heart disease, transplants and so on.

The threshold for evidence for new indications of existing technology should be high, and the threshold of evidence for safety and effectiveness of existing technologies in new sites of service should be high, again, really driven by the issue of understanding this is a different population, this may be a different site of service, and with a paramount focus on safety as well. And we've seen examples where a technology has been extended to a site of service, say a local outpatient surgicenter where the quality and safety have not been demonstrated, and in fact have been

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shown to cause more harm.

So what are the implications, then, for Medicare coverage policy? As I said, insuring appropriate access to clinical innovation is not just a coverage issue, it is important to have programs that manage the introduction and spread of clinical innovation. We want those, we need those to advance science and prevent stasis by also generating knowledge and advancing science. These kinds of programs should be a comprehensive initiative with multiple components and tools that work in concert with defined accountabilities, timelines and measures of success. The evidentiary thresholds may vary under these conditions, other effective treatment not available, conditions are life-threatening, prevalence of condition is too low to develop evidence, treatment doesn't lend itself to an RCT, or cost effectiveness data is strongly supportive of a new technology.

Some other issues linking coverage to evidence development, I think some of these

have already come up today. I think it's really critical to actually have the research
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questions fully specified. I think there's a bit too much evidence on the coverage of CED and not enough on the evidence development. Is there a protocol that is likely to answer the question in a reasonable time frame? Are the accountabilities explicit regarding the role of the sponsor of coverage, the deliverer of the service, the recipient of the service and the developer proponent. I think it's easy to develop policy in the abstract, that CMS would actually have to implement such a program, and the expectations regarding the scope, timeline, budget and success measures, I would strongly encourage this program as a program to have defined performance measures so at a few years out we can actually assess whether in fact the program is a success by whatever those criteria of success actually mean. As many have commented, there needs to be a consideration of the perspectives of various regulatory bodies, payers, other stakeholders in such a program. A few other additional considerations in developing evidence, and these are really more issued relating to designing studies. How
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do you address the issue of whether you do an active comparator trial versus a placebo trial when there's effective treatments already available? How do you do blinding when it's an invasive procedure? One of the key questions, I think, has to do with the definition of a target population, particularly for CMS and for Medicare, given that the tightly specified population needed to assess efficacy is not the population that's actually going to get the service should there be coverage in the Medicare program, and issues of generalizability from a study population to the real world, another reason to have a strong emphasis on large-scale analysis of observational data and a feedback loop to create learning. Coming back to question one, this idea that I think, my opinion is of binary/non-binary, is that all coverage decisions ought to have a period, a trigger for review. That might be a routine trigger because the policy is above X number of years old, it could be a review triggered by the new evidence in

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the literature, a naturalistic surveillance of the literature, a new experience comes out, or it could be triggered by the answer to the question that was invoked to invoke a CED program. So I tend to view that all coverage decisions ought to have a trigger for review as part of the learning health system.
So in summary, it is possible to develop and deploy evidence review coverage and medical management programs that promote appropriate access to new clinical innovations. We think we don't have all the answers, but we think we have a workable way to introduce clinical innovation in an appropriate way to our population, the 35 million people that we cover. Such programs today, and I would argue should, have some varying evidentiary thresholds based on a number of factors such as the ones that I've outlined. Optimal care for individuals and populations require a multicomponent program with coverage as only one element, and critical elements of a coverage with evidence development program include clear specification of the questions, clear accountability to ensure the answers, and
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realistic scope and performance expectations.
So with that, it was intended to springboard a conversation, so I will come down.
DR. C. GOODMAN: Thank you very much, Dr. Sandy. If Dr. Sandy would come back to the floor front and center for questions, and Charlie, if you could go back to about slide 14, it starts out acceptable threshold of clinical evidence must be high for diagnostics, I believe it's 14, the slides aren't numbered.
And Dr. Sandy, thank you very much. You covered a lot of territory and as you were doing so, I was looking to questions three and four trying to check off whether or not you covered these points, and I have checkmarks next to all of them. Thank you. So I did see that question three was raised in all of A through F, at least from your standpoint, and for question four you answered the lower case Roman numerals i through iii, so we appreciate very much your thoroughness here.
And just to get the Q&A started here, on this slide with regard to diagnostic tests, I just want to make sure. When you talk about
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acceptable thresholds of clinical evidence,

you're suggesting that these be the acceptable thresholds for Medicare, they may or may not be for UnitedHealth Group perhaps, but you're proposing these for Medicare, yes, no?
DR. SANDY: Yes, but these are also the thresholds that when we review evidence related to diagnostic tests, these are the criteria that we use in the commercial population as well.
DR. C. GOODMAN: Excellent. And I just wanted to confirm, this is an example where we talked about a combination of factors that must be present, you talk about must directly impact physician decision-making, not or improve health outcomes, but both. Did I understand that correctly?
DR. SANDY: Yes, that is correct. I think as a minimal threshold that the fact, if it doesn't impact physician decision-making it's unlikely to impact outcomes, so that's necessary but not sufficient. You have to actually then measure what is the effect on clinical care of the patients.
DR. C. GOODMAN: And you're not just,

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shall I say, just foisting this on the Medicare program, you do this or try to do this at your outfit; is that correct?
DR. SANDY: Uh-huh.
DR. C. GOODMAN: Okay, thank you very much. We may come back to this, but I would like to take questions from our panel, starting with Dr. Phurrough.
DR. PHURROUGH: Dr. Sandy, in these particular slides, 14 and 15, you're discussing factors that affect coverage decisions in your particular arena and perhaps in the Medicare arena also. Can we assume based upon that, that those factors also played a role in determining CED, what the evidentiary thresholds may be in CED, which is really what we're trying to answer for CMS today?
DR. SANDY: Yes, I think, Dr. Phurrough, that's sort of what I was referring to, that I would have to speak about different levels of evidentiary thresholds, and I was showing that in fact we use different thresholds for clinical evidence, we go lower on the hierarchy of evidence that I outlined in these kind of particular conditions. So it's a

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schema that if you were thinking about, well, how does this then apply to CED, that in fact a CED paradigm also could incorporate a similar

kind of flexing of the evidentiary threshold.
DR. C. GOODMAN: Good, thank you.
Dr. Phurrough and then Dr. Sedrakyan. Excuse me, Dr. Goodman and then Dr. Sedrakyan, pardon me.
DR. S. GOODMAN: I think we're getting very very confused about what evidence thresholds are and how to measure the, what it is that we measure, the net. I would say, accepting all the factors that you have put forth, that none of those affect the evidentiary threshold, and let me explain. If we say the evidentiary threshold is that something should exceed the more likely than not, that something could be the net utility. The net utility would take into account the degree of benefit, which would take into account, and by the way, degree of benefit is not on this slide, the seriousness or potential seriousness of the disease, and the side effects and how rare it is, and all those things.

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What you're talking about when you say the evidentiary threshold should go up and down, and this is very very common language, so it's when you're just simply measuring benefit or simply measuring one piece of the net utility or quality construct. And then absolutely what you want, because we want to maximize utility for the population we will say when it's more beneficial or potentially more beneficial, or more serious, we drop the evidentiary threshold, that is, we'll accept it when there's less evidence about the possibility of affecting survival versus affecting duration of the headache. So we have to talk, be very very careful about what it is that we're measuring and what it is that we're setting the threshold for. If you say that what we're about is measuring the net impact, which is sort of what Sean was getting at when he talked about benefits exceeding the risks, although the explicit nature of the benefit wasn't articulated there, then you can be consistent about evidentiary thresholds and the language you use about evidentiary thresholds changes.

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If you're only going to use one piece of whatever we call it, quality or utility construct, then indeed to maximize benefit we have to move up and down the scale and talk about different evidentiary thresholds. So

given that the questions to us are how do you construct evidentiary thresholds and can you be consistent, it's very important that we have in mind what is it we're measuring. Are we just measuring probability of success offset by the risk of harms, not offset by harms, and how do we take into account all the offsetting factors.

So I basically agree with you if the only thing we're measuring is one piece of that. I disagree if we say we have some sort of construct about the net potential health impact of using this technology, in which case we could be very very consistent about the threshold but we'll have lots and lots of debate about what that health impact would be.

DR. C. GOODMAN: So Dr. Goodman, just to make sure that I understand you, one of the important points you just made was that whether we are able to float up or float down some

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threshold on an evidence hierarchy, shall we say, is of note here. In addition to defining some threshold to undertake CED, you're talking about, as the question does as well, how will we know we can push up the threshold on the hierarchy or allow it to drop.

DR. S. GOODMAN: Well, we have to be clear about the evidence for what.

DR. C. GOODMAN: Yes.

DR. S. GOODMAN: So if it's for a composite index about which there could be a lot of debate, then we could probably agree on an evidentiary threshold. If we can't agree on what that is, then those disagreements will be manifest in determining an evidentiary threshold.

DR. C. GOODMAN: Understood, thank you. Glad you made your point. Dr. Sandy.

DR. SANDY: Yeah, I think your comments are really related to what I struggled with, which is, I guess I struggled with kind of a nomenclature challenge, basically how you actually answer a question about what might impact an evidentiary threshold without understanding what an evidentiary threshold

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actually is. Your comments on the earlier question, actually, using the legal kind of definitions I thought were very interesting because in some ways, and I'm not a lawyer either, but my understanding is those relate to legal standards, so basically it's kind of a standard that is used. And to your point, that

standard then is applied in the context of an individual set of facts and circumstances and the standard may vary.

What I was trying to describe, as you pointed out rightly, I think, is one aspect of it, which is kind of the rigor on which the evidentiary base exists. But I take your point to mean there needs to be greater clarity about what it is that we're talking about, and I agree with that.

DR. C. GOODMAN: Thank you very much. Dr. Sedrakyan.

DR. SEDRAKYAN: So in examples like diagnostics where the clinical evidentiary threshold is high, which means that to invoke the CED you would have a lower threshold because most technologies wouldn't meet that clinical evidence threshold, so you would lower

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your threshold to invoke a CED. But I'm having a hard time talking about threshold for clinical evidence needs to be lower when all of those conditions are met, which is other therapies are not available, the condition is life-threatening, because it might mean that if the threshold of evidence is lower for those situations, it can somehow also affect the threshold to invoke a CED. Can you comment on that?

DR. SANDY: Yeah. Thanks for giving me an opportunity to clarify. What I was laying out was what the level of evidence, the threshold for the evidence should be, regardless of whether it's what CMS calls a binary versus non-binary decision-making, it's independent of whether it's a CED or not.

My take on your question is that would, if I were running a CED program, I would think a lot harder actually, I would take the opposite point of view than you were describing. I would probably take a much tougher look at a CED relating to diagnostics, precisely because the evidentiary threshold is high, that means it's going to be more time,

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effort, money, resources needed to actually get the answer to the question.

Basically if you go back to Sean's, or Dr. Jacques' schema of kind of what gets you over the hurdle, my point is that the hurdle for a diagnostic test ought to be high in terms of the level of evidence. So therefore, you're going to have a fairly sizable hurdle to overcome as opposed to a therapy, for example,

and they would tend to basically look at prioritizing CEDs around treatments versus diagnostics. That would be my inference, but others might have a different point of view.

DR. C. GOODMAN: Good, thank you. In order, Ms. Cabral-Daniels, Dr. Grant, Dr. Normand and Dr. Min. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: Thank you again, I thought you had a lot of really good information. My question has to do with the sensitivity of the technology and the data that you get when you're looking at this, and that has to do, if we're going to make a legal analogy to case law, when we're looking at evidence, there may be certain cases that say in such and such an instance we're going to

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disregard this evidence for whatever reason, maybe a person wasn't given their Miranda rights, whatever, and so for whatever reason it makes sense. On the clinical side, does evidence that may be, is the touchstone for when evidence is considered only if it benefits the general population, or if evidence is particular to a certain subpopulation, how would evidence of that nature be considered, or does it get considered?

DR. SANDY: That's a very important question and I think this gets to the well-known issue in the current literature, the recognition that there is typically heterogeneity of treatment effects, and if you want to have a much more personalized delivery of care you need to account for the fact that different subpopulations may respond differently. Our sense is this is exactly where the science is taking us in this kind of personalized medicine role, and you need to incorporate those kinds of differences into your analysis as well. And so I think it's a really critical point, I may not have emphasized it enough.

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One of the important contextual things to consider is whether on average this has a modest effect, but is it possible to define a subpopulation with a significant effect, and how can you identify a program to identify that. We actually have a number, this goes to the fact that we use multiple tools in our toolbox to help manage quality of care and promote it. We have other programs in coverage that seek in fact to address the underuse of effective therapies in high impact

subpopulations.
DR. C. GOODMAN: Thank you very much, good question from Ms. Cabral-Daniels. Dr. Grant.
DR. GRANT: I'm just going to rephrase maybe my understanding of what you said, and if we assume for a moment that, I will call it diagnostic technologies, that we have some sort of metric we all agree upon, it's going to be what we use, and there's a couple issues here. One is, what is, how much evidence, you know, is it the preponderance, is it more likely than not to the patient's benefit? I don't think it's any different for diagnostic

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technologies. What's different about diagnostic technologies is the certainty because of the difficult nature of piecing together typically a chain of evidence. So I think that those two, certainty and then benefit greater than harm, I mean, it's clear, I think to everybody, but I think sometimes they get conflated here.
DR. SANDY: Dr. Grant, I agree with part and disagree with another part. What I agree with you is that it's harder to study and there's more uncertainty typically around diagnostic tests, and one of the public speakers this morning gave a very nice overview of some of the challenges relating to actually doing studies in diagnostic tests. It's a real conundrum, I think, that we all face. What I don't agree with is the fact that diagnostic tests don't treat the patient basically, and so diagnostic tests are, their impact is only mediated through a therapeutic, some kind of therapeutic intervention, I guess, unless you attribute some value of the information dependent on the therapeutic intervention.

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DR. GRANT: Just very quickly, I agree with you in part, but the difference is what you're measuring in the end, you're still measuring benefits and harms, it's the downstream, it's hard to get your hands on that, that's really what you're saying.
DR. SANDY: Yeah, if that's your point, if you're sort of doing a calculus of the net benefits and harms, I would agree with that. There is nothing unique about diagnostic tests in that regard, so I would agree with that.
DR. C. GOODMAN: Thank you.

Dr. Normand.
DR. NORMAND: I want to follow up on that comment because I find myself hopelessly confused now by what is meant by threshold and what is meant by going up and down. And back to Dr. Jacques' figure this morning in terms of not having the X and Y axes labeled precisely, I find utterly confusing, and so let me say the following.
When someone says a threshold to me, to me it doesn't matter if it's a diagnostic test, it doesn't matter if it's a diagnostic

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test, you have to have outcomes measured benefit, and if you're insisting that a diagnostic test improves outcomes, that has to be in there, that's fine. But I find it troubling, in my understanding of what a threshold is, to say that you can have different thresholds depending on whether it's a diagnostic or a pharmaceutical or whatever. So I actually think it would be very beneficial if we all came to an agreement on what we mean by a threshold. It just seems to me that we're talking around things and using different words, and if we send the message that the curve is different depending on if it's a diagnostic or a device or if it's a pharmaceutical, I think that's the wrong message.
DR. SANDY: My only comment comes back to, I think you're also raising the issue to clarify the nomenclature of what we're talking about. What I meant when I said thresholds for clinical evidence, what I meant, which may not be appropriate for CMS or for MEDCAC, but what I meant was that we will go lower on our hierarchy of evidence and say that level of

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evidence is sufficient for us in these conditions to justify a coverage decision that otherwise would be considered investigational. That's what I meant. Whether that's appropriate for this, that's another question.
DR. NORMAND: Can you clarify what is meant by --
DR. C. GOODMAN: Let me take a try. I hope we're converging on something similar if not identical. One could consider an evidentiary threshold is a vertical linear concept, one dimension, it would be vertical as opposed to horizontal, you got that, right, up and down, high and low. So if it's only a linear concept, that means just simply going up

or down on one dimension, and that single dimension comprises let's say the internal validity of various kinds of studies. I think what we're hearing, though, is that the evidentiary threshold is about that but not just about that, it's not just about a single linear dimension of evidentiary strength, it also comprises factors and descriptors and conditions pertaining to different types of technology and different

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types of circumstances. So while the linear evidentiary threshold is useful here, it may be necessary for this discussion, it's not sufficient for describing a threshold having to do with evidence that would say let's start a CED, it's not as simple as one line, if that helps. I'm seeing nods and shakes, I'm getting both here. Dr. Min is next. Do you have a comment on this aspect of it or something else? Dr. Normand, what else, what other help do we need here?

DR. NORMAND: I'm sorry. Other people should chime in on this instead of only me doing this, because it's my first meeting, and I have a feeling I will never be invited back. (Laughter.) But here's the thing. I'll tell you why I was confused about the linear and whatnot. We said there's a net benefit, and somehow we're defining the benefit as -- what goes into that benefit is a whole bunch of things. So the threshold at which we say, you know, it's substantially beneficial, the risks substantially outweigh -- the benefits

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substantially outweigh the risks, to me that's one thing. That's very different than talking about the factors that go into what measures a benefit or a risk.

DR. C. GOODMAN: Thank you very much. Just a moment, Charlie, if you could go back to slide 12, and then we will come back to Dr. Schwartz. It starts with statistically -- yeah, there it is. So there is one example of an evidence hierarchy and stronger stuff is at the top and weaker stuff is at the bottom. This happens to be what, I guess what UnitedHealth Group happens to use. So when we talk about moving up or down this kind of linear hierarchy, this is the kind of thing to which folks are referring. And when Dr. Sandy talked about

lowering the threshold in certain circumstances or raising a threshold in certain circumstances, he was referring at least in part to a hierarchy that looks like this. I think that what we're saying is that this is an important component of defining an evidentiary threshold but it may be all of the defining an evidentiary threshold, which could

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comprise some other things about which you and others have spoken. With that, Dr. Schwartz, you really wanted to weigh in on this.

DR. SCHWARTZ: I think, I want to get back to something Sharon said earlier that I think related to the comparators.

DR. C. GOODMAN: Is it relevant to the evidence definition or hierarchy definition?

DR. SCHWARTZ: Well, it's related to the question she just asked about what the evidence standard is and comparators, and I think the way to operationalize this, and gets around some of this and actually makes me feel more comfortable with some of this, is really the evidence threshold is, I think as other people said earlier, and I don't know if it was Sean or not in one of the slides, or maybe it was Louis, as good or better than what we have now.

So for example, to take one of Louis' slides, to go after one of his other slides, you know, for diagnostic tests if the test we have now is as good or better, or the new test is as good or better than what you have now,

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and/or is less expensive or no more expensive, you don't necessarily have to show improvement in outcomes because it's already better than what you have.

So an evidentiary standard might, one way to deal with this in part might be, the simplest identifier might be as good or better than what we have, and then when it isn't, go to these other more complex structures.

DR. C. GOODMAN: That's actually very helpful and it's a good example of kind of the other considerations that apply here concerning whether or not we have such a threshold to make a decision to go with CED or not. Point well made.

Anything else on this aspect that Dr. Normand raised for further clarification? I know we won't satisfy her curiosity about this entirely for the definition, but we're

trying to get a little closer. On this point, Mr. Lasersohn.
MR. LASERSOHN: So, at least my understanding is that we're talking about degrees of certainty, confidence, we're not talking about degrees of benefit, we're talking
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about changing the evidentiary standard, right? I mean, we're talking about how confident are we in a conclusion, for example, that a benefit is of a certain degree. If that's the sense in which we mean it, then I think it's perfectly rational in fact to change the evidentiary standard depending on the circumstances. And I think the analogy in the law is actually perfect. When you have a civil case where nobody's life is at stake, the outcome is just money, the standard is preponderance of the evidence, it's a low level of confidence where you just barely believe one side is right, the other side is wrong. In a case, though, where somebody is facing the death penalty, the standard is completely different, it's beyond any reasonable doubt, you're extremely confident that that person is guilty, because the consequences of being wrong are so enormous. And that is certainly the way I understand your paradigm here. So if you're dealing with life-threatening diseases for which, for example, there is no other treatment, it would be completely rational to lower the certainty
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standard, the threshold evidentiary standard. Not to lower the benefit, i.e., it actually does something, but your degree of confidence in its ability to do that.
DR. C. GOODMAN: That's a good point, Mr. Lasersohn. And by the way, and we don't have to go to it now, but Dr. Sandy's slide 13 that mentioned for treatment of life-threatening illness and another for treatment of serious rare diseases.
MR. LASERSOHN: I'm agreeing with him.
DR. C. GOODMAN: Yeah, those are the examples with which you would agree that would affect such a threshold. Point well made, thank you. Dr. Neumann.
DR. NEUMANN: I said this before but I hope it's relevant again, because I really think what we talk about and what we should be talking about is the value of information kind of framework. That is, we collect additional evidence when we think the benefits of

collecting that evidence exceed the costs and if we think the costs of that evidence, additional evidence exceeds the benefits, we make a decision. It's hard to operationalize

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that so we have kind of evolved into these contextual variables like diagnostics and severity of the disease and consequences of making a bad decision, but all of those factors really go into these cost and benefit calculations.

So Sharon, you talk about net benefit, but I think what we're really talking about is this implicit cost-benefit calculation. But again, it's hard to quantify that, it's hard to operationalize that, even if it's useful to think that way, but because of those difficulties we talk about these qualitative variables. But I will just put forward, we should put that value of information framework somewhere in here explicitly.

DR. C. GOODMAN: Great point, what's it worth for us to go and find this information, and is it worth it to find out about that potential delta. Thank you very much. Dr. Min is next.

DR. MIN: Thank you very much for the presentation, I thought it was great. I just wanted to clarify this whole issue between diagnostics and therapeutics, because I think

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that the notion that you espouse is one that typically the majority of people do employ, that diagnostics should improve net health outcomes. But I guess I've always been confused by that because the diagnostics by its very definition simply diagnose, and one might argue or contend that, you know, there should be downstream, you know, salutary treatment that should affect net health outcomes.

But what do you do in a situation where you have, say a randomized trial? One example was FDG-PET looking at myocardial viability. They did a randomized trial, it was a negative trial, but when they looked at the as-treated rather than the intention to treat population, those people really benefitted. So there's just so many factors that go into it, maybe when they get the diagnostic test they have a bad doctor, or maybe they are a nonadherent patient, or maybe they can't afford the medications.

There's so many factors between the diagnosis and the ultimate net health outcome,

how do you tease that out? And if you have a diagnostic test that improves the life of some
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but doesn't harm the lives of others, is that a test that should be covered?
DR. SANDY: Yeah, I think you have a lot of questions in that question and I think that, a couple of things. One is, going back to Dr. Neumann's comment, the whole construct of value of information is also a construct that can be applied to actually the clinical research in diagnostic testing, it has a kind of intellectual schema to actually address some of those issues, in addition to what he was talking about, which is using that framework for purposes of a CED kind of a thing. And I think that, I would come back, the other piece of it, I think, is that diagnostics often are kind of thought of as it can't hurt my health, but there's an evidence base that they hurt, they actually do as well. So I do think that, and we've seen this in many of the controversies around some of the common preventive services to date that have been occurring around certain aspects of the new Coverage and Affordable Care Act. So one of the issues I think is important to tease out is although the points
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are well taken, what that means is there really should be a much more robust research effort, and those that will be supporting comparative effectiveness and surgeons in PCORI, this will be an important area to invest in, it would seem to me, for all the reasons that you said. The other place I think they could elucidate, given the long causal change that you outlined, which is true, it's another reason to look and to see if you can detect signals from large linked observational databases of the kind that Dr. McClellan talked about as well.
DR. C. GOODMAN: Good, thank you. Dr. Rich, and before Dr. Rich asks his question, just a little heads up to Drs. Tunis and Kuntz. We will want to hear if you have any comments on questions three and/or four very shortly. Dr. Rich.
DR. RICH: Thank you. I will also use my question to switch topics here to cost effectiveness. A number of times you spoke about cost effectiveness on an episodic basis, and when we're talking about some of the technologies you pointed out like valves and heart transplantation, you can't really look at

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the episodes in order to come up with a cost effective treatment plan for a patient, it's very possible you could do it on an episode but not over long-term management. So, do you see CED as having a role in chronic disease management and figuring out which therapies are actually more cost effective and beneficial to Medicare patients?
DR. SANDY: Well, I think it's a point well taken. It comes back to the learning health system. When you do our kind of analysis, the point I was trying to make was we don't look in a very narrow slice of what is the unit cost of the service or device or what have you, we look at what is the all-in episode cost, and we use a variety of analytic techniques from essentially longitudinal tracking of patients to the use of episode group or technologies and things like that to actually do our own internal analytics around what is happening to the episode cost of invasive cardiac care, for example, over time. But part of your question, I take it meaning sometimes the benefit, you can't actually see it until two years out, three
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years out, five years out. That's part of the reason, and I would agree with that, and that's why you need to have really a learning health system, where in fact you can continue to attract those kinds of outcomes over time and incorporate that. We have had cases in our medical policy where we actually haven't had the evidence but there's a plausible scenario where the aggregate cost may be less, and that would be enough for us to offer coverage, so it's in agreement with your point.
DR. C. GOODMAN: Great, thanks for making that point. What we're going to do now is if we could hear from Drs. Tunis and/or Kuntz, and if you want to address question three and/or four, that's fine. After we hear from them, I'm going to try to give you a little assignment before a short break, and then we will wrap on these questions just after the break. Dr. Tunis and Dr. Kuntz on questions three or four. Dr. Tunis first.
DR. TUNIS: I'm going to throw in my lot with Sharon-Lise and admit to some level of confusion, even though I confidently answered this question earlier and suggested I had no
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confusion, but I think it's a good confusion to

have, or it's the right question, which is what do we really mean by evidentiary threshold? So just as I did earlier to offer a specific concrete and potentially incorrect, you know, definition, because I do think we are all struggling with taxonomy and nomenclature to some degree. At least earlier I offered the notion that a moderate level of confidence that benefits exceed risks based on evidence, or a preponderance of evidence, was an evidentiary threshold. In this framing for a rare disease, one might accept the lower level of evidence on this hierarchy as meeting that threshold, so that may be clear and incorrect, but at least one could think about whether, if you want to propose a different definition of a threshold, you know, we should just debate that and figure out is that right, is that wrong, or how should you do that, and maybe Dr. Goodman is planning to do that right away.

But the only other comments I want to make, two other comments. One is having sat along with Steve Phurrough and Louis Jacques and others in the seat at Medicare, in order to

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implement a program you need, you know, something fairly concrete, so some concrete guidelines or sort of principles to apply. And so coming away from a discussion like this with it all depends on contextual factors and case by case, it isn't going to be executable as a policy framework. So we can't leave them with that, or if we do leave them with that they're not going to be able to do anything with it, they'll have to come up with their own things.

So if you think about it, the FDA, the regulatory process has all kinds of, you know, I don't know whether they're thresholds or standards, but the notion of reasonable assurance of clinically important results is a regulatory, I don't know, threshold, I guess, you know, you all will decide whether that's a threshold or something else, but it seems like a threshold. And then, you know, they apply that in individual cases.

So it's important that they have that, it means something, and then it's kind of further defined in guidance and then it's applied in case-by-case settings, but it's still worthwhile to have the statement. And

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the fact that the FDA has it suggests that it's not impossible to do, you know, it can be done, all of this has been done in the regulatory

context, it's just that we're not that far along in the reimbursement context. And the last thing I would say, it was, you know, the point that United pays for experimental and unproven technologies in the context of well-designed clinical trials is CED, it's just kind of a bad version of CED, which is as long as it's in a clinical trial we will pay for it. That does nothing to advance programmatic aims of high value innovation, so you know, if the NIH decides to fund the clinical trial and it's well designed, United is going to pay for the experimental service. I don't think that makes any sense. That's the wrong framework. It's got to be, you know, is it potentially important and, you know, some other criteria should apply. Just the fact that it's being offered in the context of a high context clinical trial to me seems like a version of CED that is not as good as should possibly be put in place.

DR. C. GOODMAN: Good, thank you,

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Dr. Tunis, Dr. Kuntz.

DR. KUNTZ: Thank you. I will try to be brief, and given the comments about the evidence per se, limit my comments to discussion. Of all the factors that would look like they might influence the threshold discussion, I think that the effort to understand the alternative is really critical. So when new therapies are available, if there are no alternatives, that would be less of a criteria to use CED to see how it performs and how alternatives might come out. On the other hand, with respect to understanding, to set these general evidentiary definitions that will lead us to a threshold, I still get back to the fact that we have to have a customized approach towards each of the therapies when they come up, and that does involve stakeholder involvement, so again, a plea towards getting everybody together in a transparent way to address these issues, and I think after a few rounds we will start to get the general aspects worked out, but we have to start with a specific therapy.

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With respect to how to work on the generalizability of strong but narrow data on out, there's no question that starting with strong and narrow data, I think is a basis for coverage, but I would like to improvise some of

Dr. Rich's comments about the TAVR trial. In the case of TAVR, it was a very good randomized controlled setting published in a top tier journal where there was no alternative, that is the Cohort B, the extreme risk patients with aortic stenosis who were not subjects for surgery based on the evaluation of two surgeons, that demonstrated a clear-cut mortality benefit. If that is the answer only, then that becomes strong evidence for application of a payment for that group. Dr. Rich raises a very important question, though. There are other factors associated with that that might be worth studying. What about the secondary characteristics of stroke and others? If that's raised that should be part of the CED studies, and so when it's put together we should say are we addressing these questions that have been raised. And there should be

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patients involved in this because if they want to look at the effect of what stroke means on someone who has passed the survival time for aortic stenosis, we should do some kind of basic animal or some kind of tradeoff to understand what it is so those patients can understand that, and a study should be designed to address those issues, so I think that's an example of the kind of narrow but deep evidence.

On the other hand, if we want to look at that, then CED is very appropriate, so then the study can be customized. And we have to remember that Medicare has other measures available, including the category deemed investigational device exception which applies to marketed devices which follow, and we'll look at these, and a level of analysis that will be useful is now available to look at expansion beyond the basic component. So in many ways we have to look at the curtailment of the use of therapies and diagnostic solutions for patients with this kind of coverage policing effort, but let's not forget the fact that medical societies and the

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way we practice medicine offer another way to curtail how we practice medicine, and I think in the cardiovascular arena we have a lot of examples of what has or hasn't worked. In the interventional cardiology arena there have been several paid for devices that have gone by the wayside because the evidence

was overwhelming that they didn't work, and we didn't have to have a coverage decision to get rid of them, it came up because the evidence was very very strong. We are seeing that now with the treatment with stents of nonfunctional but narrow coronary lesions, this is being pushed by societies, so it's sort of driving the notion that the evidence is there, and we're starting to see a reduction in stent sales, for example, as a result of that, and in response to the medical societies providing good data. So it's a two-edged sword. We have to understand that there is a role for the societies themselves, both to provide the evidence, and curtail the behavior of doctors, in addition to being a stakeholder in connection with coverage.

DR. C. GOODMAN: Thanks, Dr. Kuntz,

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that actually helps to emphasize the point that there can be, there is a market response to this kind of evidence, and often can be, and that's an example of it.

Panel, let's, if you don't mind, let's do the following. We're going to take a break now, a short break, but when you come back, please come back with a statement, a single statement that addresses by your choice, either from question three or question four, how an evidentiary threshold to invoke CED would be influenced by at least one of those factors.

So take a look at question three, A through F, question four you've got i through iii, there might be another factor, but come back with a succinct statement about how an evidentiary threshold to invoke CED could be influenced by one of those following factors.

And in this instance, I will ask for a statement from each panelist. Having heard that, Dr. Phurrough will give us a concise kind of consolidation or summary of that, and we will do that before you move on to the next question. So we will see you in 12 minutes with an answer. Thank you very much.

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(Recess.)

DR. C. GOODMAN: So, that was a very helpful lively informative discussion on questions three and four, it was kicked off very nicely by the presentation made by Dr. Sandy, we very much appreciate that. So this time we're going to start with Dr. Neumann, we're going to sweep across the table from Dr. Neumann all the way through Ms.

Cabral-Daniels to Dr. Phurrough. And as I kind of requested before we broke, if you wouldn't mind, panel, if each panelist could give a statement or a viewpoint or perspective as concrete as possible that addresses at least one aspect of question three or four, that would help. We know we can't cover everybody and all these issues, but I want to get one concise sentence from each person that will help kind of put into the record and help Dr. Phurrough come up with sort of a consolidated set.

So Dr. Neumann, considering question three or four, what do you have to say about how an evidentiary threshold to invoke CED might be influenced by one of those following

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factors?

DR. NEUMANN: Okay. Well, I was hoping you would start at that end, actually.

DR. C. GOODMAN: This end lobbied against it, you lost the vote.

DR. NEUMANN: I will do my best. I'm still thinking about the information framework and thinking about the willingness to accept risks to achieve benefits and the costs of benefits to additional information, but I wrote down that you could invoke an evidentiary threshold in cases, two examples, severity of diseases you would accept a lower threshold, and in a case where you have no alternative, both cases where you probably would be willing to accept a lower evidentiary standard to achieve potential benefits.

DR. C. GOODMAN: That's great, thank you, Dr. Neumann. Mr. Lasersohn.

MR. LASERSOHN: I certainly agree with that, but in addition I wanted to address the question raised in question four, having to do with something that has come up two or three times, which is the whole issue of sort of applicability of results to subgroups, you

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know, which drives a lot of the CED process, is the Medicare subgroup statistically benefitted or not, for example.

And the problem of course with that is to do a study where every subgroup is powered on its own behalf is as a practical matter impossible, and if the test is that you have to do every subgroup or even a particular subgroup like over 65 has to be statistically powered to show significance, it becomes an impossibility.

So I think that we have to consider being able

to lower evidentiary standards on the basis of, for example in this case, a pattern of behavior, statistical behavior among subgroups. So if it's the case that a single subgroup in a population drives everything, well then, you might be very suspicious about its applicability across the entire population. If on the other hand there are at least trends of efficacy among various subgroups, then I think you might want to lower the standard for any particular other subgroup.

DR. C. GOODMAN: Good, thank you, Mr. Lasersohn, point very well made. Dr. Goodman, and we'll try to be concise about our

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statements.

DR. S. GOODMAN: I knew you would say that.

DR. C. GOODMAN: The value of information is great, however.

DR. S. GOODMAN: I will say that I'm going to define the issue here as, the evidentiary threshold is related to degree of certainty, period. It's not those things. Those things are how you operationalize it; if you get evidence from a randomized controlled trial for a given result you will be more certain, but it is not, RCT is not a degree of evidence, it's not an evidentiary threshold, it's simply a source of confidence. And I'm also saying it's degree of certainty about net health benefit. So net health benefit, tremendous debate about how to measure it, but if you state that as the definition of evidentiary threshold and state that as what you're measuring, then you can be very very consistent, and as soon as you start deviating from either of those you're at great risk. So all of these things are relevant, but they affect the net health benefit.

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So if there's no alternative, you know a lot more impact, potential impact of the new technology. It the outcome is serious, potentially much more net health benefit. Diagnostic versus therapeutic, for the same reasons as before. So everything listed here affects the net health benefit, and I think we should be consistent about saying a certain degree of certainty about that net health benefit, and then let us discuss how best to measure the net health benefit with stakeholders and all the things that have been raised today.

DR. C. GOODMAN: Excellent, thank you very much, Dr. Neumann, point very well made. Dr. Juhn.

DR. JUHN: So, I think this has been said a couple times, but I think the important consideration here in adjusting the threshold level, the evidence threshold level is really going to be this concept of unmet medical needs, and the way that it's stated here in the question is really the availability of alternatives, to determine the availability of proven alternatives that actually have that net

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health benefit, it's not just having another way of treating patients, but it's actually another way of treating the patient to get to kind of the delta improvement in the outcomes.

DR. C. GOODMAN: Got it, point well made, and complements most of the earlier points, thank you. Dr. Sedrakyan.

DR. SEDRAKYAN: My point would be that once there's an FDA request in terms of evidentiary standard for approval, that certainly will have impact on what percentage of technologies would meet the criteria we set up for evidence confidence if we have that particular evidence. So with that in mind, it will influence the threshold that we will set for invoking CED, but that's a general comment about these issues. If the majority of the technologies with the criteria that was set with FDA approval would end up as low confidence for us, then the threshold for invoking CED would be low, because most technologies will need to be studied and we don't have enough evidence to act on it or provide coverage decisions.

That being said, if the concept were

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adopted as the confidence, how confident are you that a particular technology meets the criteria for coverage, then my comment would be that additional settings and additional practitioners, particularly in the context of a device evaluation, would be critically important when you could have evidence for narrow but strong, narrow evidence base for a particular technology. So these will certainly affect the threshold for invoking CED.

DR. C. GOODMAN: Good. And one of the reasons that we raise this point, among others, is that this is not a decision about evidence or thresholds made in a vacuum, we're going to have to deal with part of the evidence that has

been generated prior to this, and in the case of regulated products, that is largely what the FDA has sought or acquired, or at least what's been presented to the FDA, so that's an important point of departure. Thank you, sir. Dr. Schwartz.

DR. SCHWARTZ: If this was a threshold, I'd agree with Steve and say that we're talking about, certainly about net health benefits. And if this was about trying to

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determine criteria or under what circumstances we decide to undertake a CED, I would say value of information is the tool we'd want to look at.

But I think we're asking the wrong question here, because I think it's more than that, and Steve made a nice distinction before between confidence and level of confidence. We want to look at things like, you know, distribution of potential benefits and harms, the nature and severity of those patient harms. You could have two mean values, but, you know, there's a small percentage of people who would be killed as opposed to a larger number of people who have a minor benefit, you still may end up with the same number but the implications are very different. So I think, you know, it becomes about probabilities and events and distributions.

And also, I went into quality and utilities, and you may actually talk more about this, but I think what we have to remember is this is about the patients, you know, they are the beneficiaries, they're the ones assuming the risks, they're the ones who are in the

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trials, either the formal trials or the informal trials like a CED, and they're the ones who are increasingly going to pay part of the costs. So we have to look at this from the patient perspective and, you know, if the old model is a hammer and everything looks like a nail, you know, we could say all models are wrong but some are useful, but we ultimately have to come out with some sort of approach that takes into account the different types of information and the different types of outcomes and different sources of information and puts it together to make sense. Otherwise, we'll get a very precise and accurate answer that won't be of value to the people we're trying to serve.

DR. C. GOODMAN: So Dr. Schwartz,

you're asserting, then, that this is a highly multifactorial consideration. You've brought in a bunch of perspectives.
DR. SCHWARTZ: I think that's what you said in your dissertation, as I remember.
DR. C. GOODMAN: It worked for me, sir. Thank you. That's very helpful, Dr. Schwartz. Dr. Saadi.

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DR. SAADI: Question number three, sub-question F is a combination of the factors, I think they are B, C and D, they are related. In terms of the severity of the disease threshold, the threshold has to be brought down or compromised if the disease or condition is serious. In terms of the safety profile, I think the same concept applies, but this is a different question, because if the severity of the condition is extremely high, then you can actually have to compromise on the safety to obtain the patient benefit. In terms of the available alternatives, if there are other options for this condition the evidentiary need is not there, so the evidentiary requirement would be high.
DR. C. GOODMAN: Good point, good tradeoff consideration, thank you. Dr. Rich.
DR. RICH: So, I think I'm hooked on transcatheter aortic valve replacement, but let's pretend there's no CED for it but we want to go to a population that's younger and has a very viable alternative to an open aortic valve replacement. For me, the moment you said that I would want to invoke a CED, and I don't know

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if that changes what my threshold would be for invoking the CED, which way it went, up or down, but I would think that would be, so broadening clinical indications for technologies, and particularly some of the abuses we've seen with off label use would make me want to invoke a CED.
DR. C. GOODMAN: So broader indications as sort of a trigger or a prompt to say wait a minute, where is that strength of evidence here, we don't have it yet.
DR. RICH: Beyond the label.
DR. C. GOODMAN: Beyond the label. Thank you very much, Dr. Rich, point well made. Dr. Normand.
DR. NORMAND: So, I'm looking at question three and I, my answer would be F as a combination or a tradeoff, and I think it's a tradeoff involving both the elements listed in

question three as well as those in question four. I think all of those impacts would set off in my mind how that would impact the net benefit as well as my overall certainty in the net benefit.

DR. C. GOODMAN: So it's really a full

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diverse set of factors once again.

DR. NORMAND: Yes.

DR. C. GOODMAN: Thank you very much, Dr. Normand. Dr. Min.

DR. MIN: I'm addressing question 3.A and B, I guess, and I have one comment about diagnostics and one comment about therapeutics. It seems that there should probably be an evidentiary threshold partition for diagnostics and therapeutics given that they have different clinical intentions that are very multifactorial between the diagnosis and ultimate treatment, and the difficulty to link to inaction, so oftentimes a diagnostic test will result in cessation of care, such as a woman who feels a breast mass and she gets a mammogram and it's negative, it's a benign lesion, and she can go home and she has peace of mind.

I think diagnostics can also potentially cause the avoidance of very expensive technology, so were there a diagnostic test that would effectively reduce ICDs, that would be a very useful diagnostic test but it wouldn't improve net health

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outcomes.

And then for therapeutics, I think that the number B was the severity of disease. Going back to this analogy of transcatheter heart valves, I think that the trials did in a very controlled fashion demonstrate efficacy, but I think that there has been no emphasis on education or this learning curve that is necessary to ensure that the effectiveness will be useful for the efficacy. So I think if CMS could partner with societal partners and try to make sure that that learning curve is achieved before widespread use, that that might be a useful model for coverage with evidence development.

DR. C. GOODMAN: Good, thank you, Dr. Min. So once again, what you're saying is that once we kind of depart from that at least firmer ground of labeled indications, for example, going on to other indications, other populations, other settings, people may not be

trained the same way and so forth, then you're starting to say I'm starting to think more about the potential for CED. Thank you very much. Dr. McDonough.

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DR. MCDONOUGH: Two different points. First, I think we should get rid of the term evidentiary threshold, because when I read that question I was thinking exactly what Ms. Manning was thinking, you know, the evidence hierarchy. But then it dawned on me that we were talking about level of confidence, which is more analogous to sort of a legal aspect. And I also liked Steve Goodman's concept of the net health benefit, and in fact Steve Pearson from ISER has a little graph that probably many of you have seen where on one axis is the level of confidence and on the other axis the net health benefit.

And then I want to pick out on question four specifically, there's this question of how in the context of where you have generalizability of a strong but narrower evidence base to the broader clinical indications for related and unrelated diseases, if it's a related disease that goes to the net health benefit if you're confident about the net health benefit because you have both evidence about the safety and the effectiveness for the indication even though it's in a

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narrower group, whereas if it's an unrelated disease you have information about safety that would be applicable, but since it's an unrelated disease you would have no information, reliable information about what the benefit would be for the other diseases. I don't know if that's very clear, but I wanted to pick that out for how that might work.

DR. C. GOODMAN: It actually is clear and may not be achieving unanimity on the viewpoint, but it does sound like we're converging in an area of some agreement where this notion of threshold, unless there's a better term for it, embraces something about strength of evidence in the traditional sense as well as the matter of confidence about the evidence that you've got, as well as trying to assess the net health benefit of the consideration. Your comments are most appreciated. Dr. Grant.

DR. GRANT: A couple things. First, I concur with the definition, although I tend to use the term net clinical benefit because net

health benefit sometimes has an economic connotation and we don't usually go there.

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I think from a health policy perspective, I think it's important to be predictable. And from a health policy-maker side not necessarily including all stakeholders, but just where this sits to start with is to have a well-defined threshold for the degree of certainty.

I think, I just, reaction to Sandy's comments, which are as always, he's correct, but at the same time I think from a decision-making perspective, you still have to use expected values. And I think it's very hard to, and Sandy doesn't agree, whatever, but it's hard to go all over, to meet everybody's needs.

And I just want to make another point. We heard a number of times about rare diseases, and rare diseases really don't fit here because you can't study them, so they're things, that's a one-off, and in those cases I think it's critically important to rely on expert opinion to supplement the usual evidence base for decision-making purposes.

DR. C. GOODMAN: Great, that pulls together several important points. Thank you,

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Dr. Grant. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: I'd like to focus on question three, focus on C, the safety profile of the technology, and Dr. Schwartz actually read my mind, because I will focus on the legal term, and that is assumption of the risk. But I think when we're looking at the safety profile it has to be prospectively determined, but patient community willingness to assume risk should be integrated into the safety profile. And that's, to further expand on that, patients shouldn't be relegated to a limited partner status in the patient-provider partnership, but this approach should be less paternalistic or maternalistic as the case may be.

DR. GOODMAN: Ah, another original point, thank you. While Dr. Phurrough is dotting a couple I's and crossing some T's, I just want to make sure that -- oh, he's ready -- that Dr. Kuntz's slides are going to be cued up momentarily, and that Dr. Kuntz will slowly make his way to the podium. And now, Dr. Phurrough, a difficult challenge, but let's see if you're up to it.

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DR. PHURROUGH: No, I quit listening around Sharon-Lise so I could at least write something down.
One of the real key points is that CMS needs to clearly define what they mean by evidentiary threshold. When you have the option of making it a fairly narrow term focused around level of evidence or a much broader term focusing more on degree of certainty as Steve mentioned, both focusing around health benefit in one case, net health benefits. So I think that's the key message from the panel, you need to clarify what you mean by evidence threshold.
And whether you are using one more narrow definition or a longer definition, the factors in both questions three and four play a role. They play a role in defining net health benefit or degree of certainty, or they play a factor in determining what is the threshold at which you apply the level of evidence, and the factors that were mentioned most often I believe by the panel, at least in question three, safety was a real key issue, severity of disease was also mentioned, and alternatives to
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a lesser extent was also mentioned.
In question four, the key factor there was the discussion of new indications for technologies that are currently available, as a key factor to take into account.
There was also some concerns that there were other factors that are important factors to consider in determining threshold of CED that weren't listed and may not necessarily be in either definition, unmet needs or the need for a definition that will somehow fit into the decision around whether CED is done or not.
And then Sandy had a couple on, I think for the distribution of benefits within a particular population was important area to consider, it may be difficult to assess within that particular degree of certainty or net health benefit calculation.
And then finally, again, whatever the decisions are and whatever the definitions used, you should get broad input, and some general consensus around the appropriate way to use it.
DR. C. GOODMAN: Thank you very much,
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Dr. Phurrough, for that summary, and I think

that our discussion of these two questions has given CMS plenty to work with, a lot of grist for this mill, and we very much appreciate the input from all of you, thank you.

Now we're going to move to question five, and Dr. Kuntz is going to take the lead on that. We will use a similar format, Dr. Kuntz will speak about this for 12 or 15 minutes, we will move to panel questions for him, comments from our other expert speakers, further discussion, and then final points on it. Dr. Kuntz, thanks for your patience, and you're the last person standing toward the end of the afternoon, so we appreciate your fortitude.

DR. KUNTZ: Thank you. So, I'm going to address the question, as you know, can the evidentiary threshold be defined to trigger an evidentiary review to determine if CED should cease, continue or be modified.

So let me first start out from the perspective because I answered the question, and I work in a medical device company, a little bit about how we view CED as a

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background to answer this question. Some of this stuff could be generalized but it's not necessarily so. We're committed to obviously developing clinical evidence, we spend a lot of money on that, we do a lot of work in the pre and postmarket to develop evidence with very specific tools, and it supports CMS's interest to ensure adequate evidence on the clinical benefit of technology for the Medicare population. Most of the devices that we make in our company do go to the Medicare population and so the vast majority of our research is driven towards the questions that we've talked about today.

The real question is as I raised before, is the CED the proper tool in a large or small portion of answering those questions, and we would take a general view that it should be somewhat restrictive. And I just want to point out, because I don't think we've made this clear at this discussion today, but CED by its very nature has to be done on every patient that receives the therapy or the diagnostic treatment. It by definition has to have a somewhat parsimonious element in order to make

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it to be easy to use. If we make it too complicated it will restrict access to care. Also, the cost or burden by the

hospital, so one has to understand that the view of CED is going to be a somewhat parsimonious program, and it has more of a general registry than anything else, and the past would suggest that that's actually true, that these were general registries without much prior hypotheses, that didn't address specific questions. If we have a really formal and wide stakeholder meeting early on about the needs, we would come up with more specific tools to answer questions, rather one that goes to every single patient in a very parsimonious set of patients, and they could be generalized. So therefore, given the stated goal of CED, which is to increase access to medical advancement, we think that it should be applied more rarely in its current form, that may change after this discussion, and one threshold is the decision to consider a national non-coverage decision, that would be a great threshold to say okay, that's the point as an alternative, it really should generate the need

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to start a CED. So it's a very very rough measure of how to initiate a CED, but we felt that the viewpoint that we would have, given the pantheon of different tools available to answer that question, and our interests as well as I think other people in the industry too, provide a lot of resources to answer questions. The objective of CED should be to generate evidence and information that will be directly applicable to the key open issues in determining whether an item of service is reasonable and necessary, which is really the job of CMS, for the Medicare population, and therefore fully coverable with no continuing CED requirements. So again, we'd like to be able to say what question needs to be answered for reasonable and necessary, and how is it going to be answered, and when will it be closed. Several changes in the process are necessary, therefore, to assure that CED most appropriately achieves its goals in a defined time, and does so in a very transparent and inclusive manner, again, with the idea of bringing more stakeholders in early on. So, the proposals we would have for

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CED are that the CMS intent to consider CDE be stated at the onset of an NCA if not sooner, so when the national coverage decision, or national coverage assessment is started, right away get the stakeholders together, start to

address the issues that are open, what needs to be answered, and can they be solved by conventional tools and clinical research, and put the burden on industry to be able to pay for those and do them in an effective manner. When you do a clinical study you don't do it in every patient that gets the therapy, you do it at clinical sites, you do it at places that have research commitment so you can ask more detailed questions, you can get better instruments of care. And you can also, using those research tools, answer specific questions I think better than general registries or even small randomized studies that would be applied to every patient who gets the therapy. Research questions, therefore, need to be very specifically addressed in advance. CMS implementation should use a steering committee with full stakeholder role. The role of industry is very helpful because

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they understand the device better, they can come up with a lot of engineering and technical aspects that may not be considered by other individuals who are concerned about the societal benefit or the roles of those stakeholders who designed the study. This doesn't mean necessarily that industry has to make the final design decisions or even the major design decisions, but they should be there to address issues that might fall through the cracks if they're not there. And we shouldn't design this quickly in a 30-day response period, this needs to be done like other clinical studies. There should be some time, and it doesn't necessarily have to be a long time, but it should be longer than 30 days, it should be enough time for the steering committee to get together. So therefore, there should be some gap policy to provide coverage while this is being determined, and I think because of the lack of this gap policy is one of the reasons that there's this sense of urgency to get it done very quickly, and when we get things done very quickly there's more likely the CED will be

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general and not specific. And clearly one has to identify timelines for the CED, so we know what we're measuring, what questions are going to be answered, when is it reasonable to expect those questions to be answered, to drive enrollment, to drive analysis and drive reporting, so that

one can button this up and be able to effectively let all the stakeholders know when the questions will be answered. An evidentiary threshold should be defined to trigger an evidentiary review to determine if CED should cease.

So, we've all heard the nuances of evidence and what factors go into them, and I think as we start to crystallize some general rules for what evidence is, we still have to be somewhat specific about the technologies. So I think it's impossible to have just a general uniform approach, but I think we can have a combination of more crystallization about the standards, but still specificity associated with each therapy going forward, and those address the issue or the need for stakeholders to come together on each of these CED

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considerations.

The reconsideration timeline must be technology or service-specific. We didn't talk much about this before, but there is a cycle time of devices which is different than drugs. To make it reasonable, to be able to keep patients having access to promising new technologies, one has to understand this whole outside life cycle of devices, which is a little bit different than drugs. And therefore, we should customize the CED to answer questions that fit that timeline as much as possible, so it doesn't delay the cycles of technology, and we don't have old technology given to patients when it could be newer.

It also goes on to say that we should kill fast as well. If our technology is not working, we should get a rapid understanding to get it off the market, so in most situations we have to understand that the timeline should model the iterations of the process or technology, to be able to be killed early or to promote.

The key factors that we will address in each individual case are listed here, I

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won't go through them all, and I think we've talked about them before, but we have to make these considerations in a formal meeting before CED is done to make sure that they will be covered as we go forward.

Absent a uniform evidentiary threshold, when should CED stop? Well, in order when to stop a CED, we really have to understand what the original research question

was. So this just reiterates our point, it's very difficult to determine when to stop if we don't know where we're going. So at the beginning it's really critical for us to say what was the goal of the CED, what do we really want to answer, that really helps us understand when we can stop.

Again, a steering committee is really critical to this, and like any clinical study, one should go through the checklist to utilize the talents on the committee to address research design. Access and ownership of data collection, which we talked a little about, again, we want this to be as transparent as possible, and we're strong proponents of transparent data and learning how to get that

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out into the public. We want to understand how to fund the data collection. If it's too burdensome for hospitals, we can share in those costs. And then the timeline for reconsideration, as I talked about earlier.

Evidentiary threshold, when should CED be stopped, and I will continue with this question. CMS should clearly outline timelines to reconsider coverage for the item or service under the CED in the final decision memo, that just has to be in writing.

As I said earlier, CMS should have a central role in this. We don't think that we should farm this out completely to outside groups. CMS is the one responsible for payment, it's the one responsible for getting together, I think, the questions, and should have a central role in this process. To work with other partners I think is really important, but we want to make sure that CMS stays in the central position.

CMS should continually monitor the data collection in some way, either through a data monitoring committee or through prespecified reports, to understand what

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they're collecting, how they're doing it, the quality of the data, and whether questions were answered before they thought they could be answered.

Integrated studies, we believe that CED should be integrated, and this is that we should not only look at the CED in isolation but if questions are being addressed by the design of the CED, we should have a complete understanding of the ecosystem of other studies that are being addressed throughout the world

that might be synergistic and leveraged to answer these question, and that probably is not done enough.

And once the research questions are addressed by CED, CMS should reconsider the decision based on the new evidence. So whether we want to take a more basic approach of updating our priors and understanding how to be more crystal in formalizing and reducing our confidence in something, we should have a formal process to understand what it means to look at new data and reassess where we stand.

So, my last slide is here. We know that previous CEDs need to be tuned up to some

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degree. For example, the CED on ICDs was mandated under an NCD. The federal essential detail data collection requirements really weren't established until about five years after registry launch, there were many fields that were still being added in, so we think that could have been better designed up front rather than as a general process that was kind of iterated going forward.

Even after we established the registry, no formal agreement between CMS and the registry was obtained on the protocol or what kind of well-designed questions were going to be addressed by the ICD registry in and of itself.

In addition, there is no time table for this to sunset, or to understand what would be the conditions on which this ICD CED would stop. If fact, we conducted a 3,000-patient registry that's just been finished and we're in the process of analyzing to address questions that were raised in the ICD CED, but with more specificity, because the design of the study that we put together did address the questions that couldn't be answered by the ICD CED, and

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we think some of those questions could have been assigned up front and probably been better positioned in the ICD registry to address those questions going forward.

So in summary, adopting a policy that would require the establishment of research questions and timelines at the outset of CED would greatly improve overall process for CED, and specific processes for determining when to reconsider the evidence and end the CED collection requirements for a sunsetting CED.

I will just stop there.

DR. C. GOODMAN: Thank you very much,

Dr. Kuntz, and if you would make your way back to the front row here. It was very helpful, among other things, the way you described sunset or stopping rules, or the need to revisit CED in terms of what the various roles of the parties should be in making that determination. I think you also made clear that stopping rules have a lot to do with whether you had enough to go on when you started in the first place, you know, don't get started unless you've got some things agreed with stakeholders, a point well made.

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So I think what I would like to do now is see if our panel has questions directly for Dr. Kuntz, and then in a few moments we will ask Drs. Tunis and Sandy to weigh in with their opinions on question five as well. So for starters, anything now for Dr. Kuntz to get started? Dr. Juhn is first.

DR. JUHN: So on this slide, when this agreement was made to actually create this registry, was there any discussion of endpoints or kind of when the project would sunset, was that discussed and there was no resolution, or was that not even discussed?

DR. KUNTZ: The ICD registry was well intended to understand the utility of the therapy, an expensive device, seemed to be working in a lot of populations from randomized studies, the potential for broad use was there, I think the motivations for the registry was good. But I think there wasn't enough specificity about what questions this registry could answer and how it could be designed, and in the end there were some important questions that came up during the study where the fields had to be changed, to be added on, and a

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parallel study even answered it more specifically.

Whether or not that would have happened anyway is very difficult to say, but it's our view that had we had a little more time in a more traditional way to design a study, to kind of identify some hypotheses of what would be addressed, the study might have been designed a little bit differently. But again, I think the intent was good, the decision to do one, there was a lot of rationale behind it, it's just that I think it could have been more rehearsed.

DR. JUHN: Thank you.

DR. C. GOODMAN: Thank you.

Dr. Schwartz.
DR. SCHWARTZ: Very nice, as usual. I want you to put your hat on before you were at Medtronic when you were still at Harvard and incorporate that into your answer too. Mark McClellan mentioned earlier, you know, the attraction of trying to take advantage of existing infrastructure and things like that. You identified a problem with using a registry that's not highly specific, and other people
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have mentioned aspects of that today. You know, my own experience has been when I've looked at people trying to use general registries for unanswered questions they come up later and it always seems that you're missing a piece or two of the information that you need, and you haven't thought about the questions clearly in advance.
So I just wanted to get your thoughts on that tradeoff between, you know, the efficiency and startup speed and all that of using existing data, as opposed to the need to get good technical data that's often needed to answer these very specific questions that have to do with confidence and net benefit.
DR. KUNTZ: Yeah, I think that's a great question, because I think it's timely that we're having this discussion in 2012 and not 2005. We all know that the holy grail of EHR is when will EHR have research grade data that we can actually surrogate, and I think most of us would agree we're not quite there yet, but we are much closer that we were in 2005.
So when looking at designing a network
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that might utilize existing electronic digital data and the addition of specific outcomes, it's easier to address more questions now with special outcomes attached to a broad base of electronic data than it was before, and that's something we should consider here. But it does require us to still go through the formal question of addressing what questions we want to know.
So we have a huge interest to develop a network for surveillance, for example, and when we look at surveillance we should mainly focus on our ability to detect the product performance and when it fails. There are highly specific technical questions we're asking, because our goal would be to be able to determine when a product fails before its

clinical events. That requires specialized endpoints that would not be available in the general electronic record database or general registry.
So we still need some specificity, but I am very optimistic about the fact that we're getting very close to the grade of EHRs being able to be hybrid and connected to a more
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reduced set of outcomes, but it still has to be specifically designed and set up, and I think the process of actually getting the stakeholders around the table and asking the research questions early on is still critical.
DR. GOODMAN: Thank you. Dr. Saadi.
DR. SAADI: This is more of an observation, I think. This morning we have heard multiple times of industry complaining that the CED is a binary process. This observation comes from my point of view. I think a lot of coverage decisions for the products might end up with the CED because it's not easy to generate enough data to begin with. So obviously I do agree that every CED has to have a predetermined objective and a timeline, and we should tie that to the time frame, but I cannot go more than five years or ten years, I think that would be enough time to produce those data, so I think it's more important to complete your sample size so you can go ahead and make those conclusions.
DR. KUNTZ: I think that's a very good point. I think that my comments about a never-ending registry is probably not exactly
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what I said. We intend to do forever registries on surveillance, that's very important. But we also have a selection size and a sample size that we utilize, we don't do it on everybody.
So the notion is that the idea of doing a pan registry on everybody who receives therapy, I don't think is an optimal way to do research. Number one, it does restrict access to some degree because some hospitals just don't have equipment for research and won't be doing CEDs. The second thing is by definition, the broader you make this, especially if you end at a hundred percent, you will have a parsimonious data set, there's no question about it. Third, it does reduce the compelling need to actually determine a sample size, because you're doing it on everybody.
So those are the things I think we

need to shift more towards, and I don't think that there is a patent need for us to get rid of the CED concept. It's just make it smarter for all of us so we can utilize those tools and address the questions quicker. So I do like the registry format, I do like observational

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studies, it's just that we should be more selective in the areas that are actually measured. For instance, if we look at instruments required to really measure outcomes, you're going to have a smaller set of hospitals that can do that than the overall group.

DR. C. GOODMAN: That's a very helpful answer and good question, because I think it speaks directly to what the practical considerations are in setting this whole thing up in the first place with regard to different data sources, and that's a good insight on that. Dr. Grant.

DR. GRANT: Just kind of maybe to react, but first of all, I really loved your presentation, and I think it did contrast somewhat with some of the directions, I think somebody coined the term omnimetrics for using registries. Because I think it emphasizes the use of research question goes to the point that to make decisions, there's a number of different parameters that are necessary to be informed and in the context of -- I mean, this is all just valuable information, but it

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addresses it head on specifically as opposed -- in particular, there's two pieces. One is the sort of, how strong is the evidence is sort of the rigor and all the validity parts and the comparative effectiveness pieces. And then the other piece is relevance, which is where the observational data really fit in quite nicely and are very very useful.

But I think that getting from out of the starting gate, lacking that specificity, one really can spin your wheels a lot. And just in the packet of reading we got from the Ontario Ministry of Health, I think their approach in the time to field studies, I think is very much along the lines of what you are advocating.

DR. C. GOODMAN: Good, thank you. Was it Dr. Min next? Dr. Min.

DR. MIN: I just wanted to follow up with just a methods question. I think, unless I missed it, I don't think it was in your

presentation but you said it a couple of times today, which was this kind of multi-stakeholder steering committee that would help advise Medicare on these coverage with evidence development decisions. So I was just wondering if you have any vision of how the structure of that committee would be. Would that be a one-off committee per indication, would it be a standing committee or rotating committee, and if you have given any thought to what the makeup of that committee would be. Would another function of that committee be to maybe create a dynamic prioritization of which CED should come first, et cetera, et cetera, so I was just wondering if you could elaborate on that.

DR. KUNTZ: We had a little bit of discussion about exactly that point and it would be a mix. If we were to look at this function occurring at CMS, then we would probably have standing members appointed by CMS to be a general CED steering committee that would get the experience with, efficiency associated with doing it over and over again, but there would have to be rotating chairs, obviously, through the technology side, so we can bring those individuals in. And when I talk about stakeholders, I don't necessarily mean that we have to have equal roles or weighting on how a study will be designed, because I think at the end of the day we need to have objective and dispassionate individuals designing studies so they can have the desired effects on patients and society.

But the one thing that is often asked in steering committees, does industry ever benefit patients. It's represented because one feels like there's a special conflict of interest and they're not needed, but in fact the knowledge about how a device is designed and how it affects patients and so on is very valuable, especially if you get more technical, and we want to relate how data derived from this device is used, especially in the medical device arena. And then on the patient side it's critical, because we don't address issues of patient preference and values as much as we should.

So to answer your question, I think the ideal might be a standing committee in CMS that has a few statisticians, a couple trialists, members of a group of 10 or 12

maybe, basic monitoring of chairs that may have a longer rotation cycle, and then other chairs would have specific attendance only for that study.

DR. C. GOODMAN: Good, thank you. Dr. Normand and then Dr. Phurrough.

DR. NORMAND: Thanks, Rick. I had a question that relates to coverage with evidence development, which is today's topic obviously, but we're focusing on this in terms of, you're talking about CED and talking about not having the question specified and having stakeholder groups with all these people, that I totally agree with. What my question is, are we asking for different information than we would ask for if, without having to go down this route? I'm not being very clear about this, so I'll use two specific examples and then you can let me know.

So for example, if you're thinking of your hypothesis test, I think you mean look at the questions that aren't specified. Because presumably there's information available already and so you need more evidence, or developing more evidence, that's why we're going down this route. Have you put any thought into, and perhaps I shouldn't raise the question that way, but how have you thought about how that affects your designs in terms of, I don't know, affect size power, and things such as that? Do you think about it differently because there's already existing evidence and you just need to build more, or how do you weigh those things, as opposed to a de novo PMA?

DR. KUNTZ: Well, I think those are great questions. I don't know whether we're going to put specific hypothesis testing in the formal sense for observational studies, but I think we need to have questions about what the observational study is going to define, even if we're trying to basically just improve a prior with new data, to understand how we can get better confidence around a variety of different estimators. We have to know what those questions are so we have those fields in the study.

I think there's a lot of opportunity for a variety of different methods, Bayesian methods and others to be able to, that we can leverage on observational studies to refine even without understanding what the question is

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specifically. But we just have to know, is this registry going to look at broader utility of the indication? Is it going to look at elements of economic value? Is it going to look at the real world usage parts? And then I think we can respond to field requirements based on a few hypotheses, but it's not limited to those hypotheses.
DR. C. GOODMAN: Great, thank you. Dr. Phurrough.
DR. PHURROUGH: My focus is mainly on registries. CED has in fact extended trials for specific RCTs or RCTs that may have been determined at a subsequent time, and in both circumstances a challenge that Medicare has always had is the lack of ability in its current legal framework to have different levels of coverage. So if you're going to require a registry in general, you have to have a registry that everybody is involved in, which then sort of challenges your concern about having a pan registry. If you have a specific RCT, then you really are limiting access to people who in general are in academic settings where most of the studies are done. So how do
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we resolve that, or do we not resolve it, what are the issues?
DR. KUNTZ: It's a really good social question, and the question is if there is the possibility of a modern evidence device or drug that's going to be available for access and one feels uncomfortable about that, the first decision is should that be available to patients. The second question should be how can we get evidence over that time period where we're comfortable with the risk we're taking in letting that device or drug out in the market. They may be mutually exclusive. For example, the population that actually gets the therapy doesn't necessarily have to be the research population, because they're still going to be exposed for the time period to do the actual research study.
So I'm not completely sure why the urgency to get information, even in a risky subset or a new technology, has to be applied to every patient who receives it, unless there is a safety monitoring component, which would make sense, and then that could be a reasonable data set. So somehow we've linked the notion
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that if we're going to get into this risky zone

of getting evidence for therapies that we are allowing the public, they have to all be researched, and in many ways that constrains you because of the limited data sets that you have, and maybe it will be faster if we had a subset that actually had a more formal registry randomized study performed during the time period, and then the exposure to everybody is actually shorter. So I don't know the answers to it, but these are questions that we need to think about.

DR. C. GOODMAN: Good, thank you. Before we move on, I've got a couple more questions, I see. This is one of those questions worded that calls for a yes or no, and so I think we've talked enough about this so far to render a Y or N on this one, and then we'll return to the questions. And I see Dr. Rich and Dr. Neumann and others are lined up for questions.

So if you would pull out a yes or no sheet of paper, and we still need to do this for the record given the way the question is worded. Dr. Phurrough, this is a yes or no.

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DR. PHURROUGH: Steve Phurrough, yes.

MS. CABRAL-DANIELS: Rene' Cabral-Daniels, yes.

DR. GRANT: Mark Grant, yes.

DR. MCDONOUGH: Bob McDonough, yes.

DR. MIN: James Min, yes.

DR. NORMAND: Sharon-Lise Normand, yes.

DR. RICH: Jeff Rich, yes.

DR. SAADI: Ryan Saadi, yes.

DR. SCHWARTZ: Sandy Schwartz, yes.

DR. SEDRAKYAN: Art Sedrakyan, yes.

DR. JUHN: Peter Juhn, yes.

DR. S. GOODMAN: Steve Goodman, yes.

MR. LASERSOHN: Jack Lasersohn, yes.

DR. NEUMANN: Peter Neumann, yes.

DR. C. GOODMAN: Thank you very much, it sounds like yes is a good one for this one. Before we move on, I just want to make sure, and we will get to folks who are lined up for questions. Starting with Dr. Tunis, and then Dr. Sandy, do you have any points to be made on this question five, which has to do with circumstances for ceasing, continuing or modifying CED. So once CED is on the move,

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what about these rules?

DR. TUNIS: A couple very brief comments, and I apologize, I have to leave in a

few minutes.
So you know, I think it's a great notion that Dr. Kuntz has proposed about this kind of stakeholder committee that would help establish both study design as well as stopping rules, so I think that sort of process would be useful. And then I'm sure everyone knows that this is the Medicare Evidence Development and Coverage Advisory Committee, so there's already a stakeholder committee that might be deployed to serve some of the functions perhaps with some additional members, but one wouldn't have to create a new FACA committee, it's possible that some variation of this committee could actually serve that function.
DR. C. GOODMAN: Good.
DR. TUNIS: And the second point is that, you know, for some of these aspects of specifying the research question and informing the study design as well as the stopping rules in a multi-stakeholder process, that wouldn't necessarily have to be done as a one-off for

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every kind of new potential CED or new technology, because much as the FDA has guidance documents that sort of articulate what are the evidence expectations around categories of technologies, it's possible that for major categories of technologies that might in the future be the subject of CED, it would be possible to work out a whole lot of these features of study design, comparators and outcomes and settings through a multi-stakeholder process without having to begin that when there is actually a technology in front of you.
DR. C. GOODMAN: Point well made, thank you, with regard to timing and preparation. Thank you, Dr. Tunis. Dr. Sandy, on question five.
DR. SANDY: Thanks. I really do largely agree with Dr. Kuntz, I think he did a very nice job outlining, I had said similar things.
The two points I would make on question five are, first, the stopping rules should be driven by the question. The question, as you pointed out, should be

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specified, or questions, a priori, and the decision should be revisited when the protocol has the answer. So the design of the protocol should be driving and the question should be driving the data collection strategy and the

timeline and things like that. The only other comment I would add, I think it was sort of implicit in his comments but I'll just make it explicit. Participation in a registry is not research. It is a means to an end but is not an end in and of itself. I guess I would emphasize, and I'm a strong proponent of research, I'm actually cochairing a group called the NQRN, with Dr. Dave Shahian from STS to promote the broader use of registries for all kinds of purposes. But I think for this purpose it is important to point out that just participation is not sufficient, you really do need to do what Dr. Kuntz suggested, which is specify the questions in a multi-stakeholder format and then have that drive the process.

DR. C. GOODMAN: Good, thanks, Dr. Sandy. We want to move back now to Drs. Rich

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and Neumann and then after -- and Dr. Sedrakyan, after which I'm going to ask the panelists for a weigh-in statement, a concrete statement for question five. Dr. Rich.

DR. RICH: Thanks. I think I had a similar point of clarification, because I thought I heard you say hospitals may not participate because they don't participate in research and therefore wouldn't be involved in the CED, I don't consider the CED to be a research tool, I think it's really just a way to monitor real life applications of the new technology. So, I think it was clarified in the last statement as well. Do you agree?

DR. KUNTZ: Having never participated in a CED, I don't know what the burden is. I know the hospitals have to pay for the therapies and the question would be, are there hospitals who aren't doing it because CED exists that otherwise would be serving patients if the burden for CED is so low. I don't agree with you a hundred percent. I think, though, what I was saying is if you make that burden low enough, you might not have the rigor of a tough study.

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DR. RICH: And I just want to make a comment, that the challenge is to CMS in creating the stopping rules up front because with the new technologies you will never know what the adoption will be or how fast enrollment will be, or use of the technology, so it may take years to accumulate enough

patients within a registry to do a reasonable analysis.

DR. KUNTZ: Right, and I think that is a really important question that maybe will be answered by using claims-based data linked to other outcome databases more efficiently than to do a CED if we're looking at utility, for example. If it in effect can be done, obviously something like this would be very very valuable, but have they been exhaustive with other methods for looking at things like utilities.

DR. C. GOODMAN: Good. Thank you, Dr. Rich, thank you for your response, Dr. Kuntz. Dr. Neumann.

DR. NEUMANN: I also really liked this presentation. As you were talking, Rick, about steering committees and data monitoring boards

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and such, it just emphasized to me that doing CED really puts CMS and the coverage group in particular into the research business, and maybe that's obvious, but I just say it, want to observe that it's hard to do research with high stakes sort of research in real time to try to come up with decisions at the end. But also as CMS sort of rethinks its CED policy, it may well be, and I know that CMS has a lot of talented people including researchers, it may well be that it needs to rethink and beef up its research enterprise to do these early engagement decisions right. So looking at question five, but just generally thinking about the day, part of this is getting the framework right, but part of it too is just going to be the issue of managing that framework with researchers.

DR. C. GOODMAN: Point well made. It's about designing, implementing, reporting on, interpreting research. Good point, Dr. Neumann, thank you. Dr. Sedrakyan.

DR. SEDRAKYAN: I join my colleagues in commending you for a very nice talk. I have concern that a hypothesis treatment with CED

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potentially can be a problem if you think CED treatment is a registry. With registry we know clinicians get more engaged and provide better care, the outcomes of the technology look better. So over time, I'm concerned that after the end of the registry the technology's profile might change because of the engagement of the clinicians during the CED, and if we don't have an ongoing data collection in place

to understand what happens to the technology, that is potentially of concern. So an example, we don't have a registry of hip and knee replacements in our country, and let's say in the beginning for a new technology we start a CED and then through 510(k) modifications we end up with metal on metal products that potentially cause a lot of harms and cost billions of dollars to CMS because we don't have that infrastructure in place. So knowing for some of these technologies there would be more companies joining in, say percutaneous heart surgery, seven other companies are lined up to potentially bring these kinds of products to

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the market, so that one manufacturer would be bearing the cost, but all of the manufacturers potentially interested in this issue might share the cost. And providers have the benefit also of having this ongoing registry in place that will answer a lot of questions for CMS. What are your thoughts about that whole concept?

DR. KUNTZ: I think your point, you make a really good example of surveillance studies that I think should go on, and we agree that when we're looking for things where surveillance is necessary, a change in patient population, rapidly changing technology, interest in long-term performance, those are studies that would be long, but they actually have their designs addressing those issues specifically and the studies are designed to answer those questions. It seems that some of the other questions that have been asked under the CED framework were discrete questions that could be answered in a prescribed study, that were just addressing the general process of the registry and it having sunset.

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So I think you're right, there are clearly questions that have to be addressed by perennial research methods that may go on forever, especially rapidly changing technologies. As you know, when we started to understand the impact of implantable joints, it has had more consequences to be interpreted, so for a while we're going to be measuring this stuff in everybody for a long time, there's no question. I just think what we'd like to see is

just more robust and rigor at the beginning to say what's the goal of this so we can design it. Some will have an end to it and some will continue forever. What we don't want to have is just a basic general registry that needs to be done everywhere that really doesn't have any specificity toward answering the questions.

DR. C. GOODMAN: Dr. Kuntz, one more question, I think, and then a wrap-up question. Can you explain how the following should go with regard to stopping or modifying? This kind of thing crops up. We've got some sort of promising technology that has not yet hit the standard of reasonable and necessary, it's

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promising but it hasn't been judged reasonable and necessary. So with some stakeholder involvement we design, plan and so forth some kind of evidence collection for coverage with evidence development. We set this up and we push it forward, whether it's a registry or other sort of data collection mechanism or mechanisms. And then over time data don't come in as rapidly as we might have anticipated, for any number of reasons, and over this period of time there's not enough data coming in to answer the question and we look even further around us, other data sources still don't seem to provide enough evidence to achieve the reasonable and necessary standard. Now what? Is the burden on CMS to say well, we couldn't get enough evidence, I guess we'll cover it, or is the burden on a technology sponsor to go and work harder to get that evidence? What do we do in a circumstance such as that?

DR. KUNTZ: So, I think what you're talking about is, have you converged to certainty around that demand that you want to establish, but they're not coming in.

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DR. C. GOODMAN: Correct.

DR. KUNTZ: And if we had at least another standard in the beginning, what are we trying to estimate, either as a scalar outcome or the difference between two therapies, for example, that would help define whether or not we reached that, to continue. If we get to the situation, and again, I'm talking a little bit extemporaneously here, I haven't focused on that specifically. But I would imagine that if we have critical questions that we need to answer that address patient issues specifically, then we own that burden, the

technology companies. And so when we haven't achieved the understanding of value to the patients on the clinical side, even the economic side, and reasonable studies that have been designed have not answered them have to be extended, then I think the burden is on industry.

DR. C. GOODMAN: Okay, good, thank you. That helps, because that kind of thing has cropped up and may in the future, despite the best planning. Thank you.

We're going to close question five

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soon, but I want to make sure that we've heard from the panel insofar as any particular aspect of defining this threshold or other conditions or criteria that might influence a decision to cease, continue or modify an ongoing CED process. Have we missed anything with regard to those conditions' criteria or thresholds that anyone can hit? Dr. Schwartz.

DR. SCHWARTZ: Cliff, I'm not sure about this, but I think the only thing might be to the degree that there's some rapid evolution or substantial changes in the technology over time could confound this. Otherwise I think, you know, this is a lot more tractable to me because if you've done what Rick suggests, which I agree is define the problem, identify the questions, you know, that's pretty straightforward research. With hypothesis testing and design, you know, you can make sure you have the power and are measuring the right thing. But if there's some change along the way, that would be the only thing, and I, you know, it will happen. That's what Louis gets paid the big bucks for, to handle those things. But you know, that probably has to be

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broadened at some time, and that's an area where industry and the key clinical users can be particularly helpful, because they have a much better sense of what's coming down the road than the rest of us.

DR. C. GOODMAN: Great point, it's a moving target, has multiple dimensions, and that's one of them. Excellent, Dr. Schwartz. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: I would like to just build on that, and I think that maybe there could even be a hierarchy where we first try to modify, and the last event continue, and only cease in the most egregious of cases, especially in regard to safety. But even in

the decision to cease an activity, the decision must first invite the patient community to identify how the item might be modified in a way that might be useful.

DR. C. GOODMAN: That's a very good construct to think about, these conditions for stopping. Thanks, Ms. Cabral-Daniels. Dr. Phurrough is approaching being ready to provide some comments. I will give him a little pause here. Does anybody else

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want to add anything that Dr. Phurrough, for which he must account at this point? And by the way, panel, I'm going to ask you for one last final word from each of you in a moment, we're going to have a closing question for all of you. Dr. Phurrough, would you venture a couple summary points on question five? And while he's dotting that last I, I do want to for the record note that part of the sub-question here was to discuss whether the factors identified in questions three and four are relevant to five, and Dr. Kuntz, I might mention, you mentioned several in your presentation that would reflect back on three and four, and several of our panelists' points also reflected back on items discussed in three and four, so I think we have discussed that item quite specifically.

Dr. Phurrough, any wrap-up comments on question five in particular?

DR. PHURROUGH: It seems to be the general conclusion was that while we answered the question that yes, there are, there is the ability to establish stopping rules, we did not define what those were but did define the

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process, or recommended a process where a steering group is formed, several recommendations for who that might be, to include this group, to define that early in the development of the CED process so it's very clear from the outset what those stopping rules are. It should include a bit of flexibility to allow for changes in technology that may occur during that particular process, but the flexibility should not be such that it engenders a CED that continues forever. Another point is that there are different types of CED that require different kinds of study design, one is more focused around a particular question and one is more surveillance. So there may be different types of study design, different kinds of data

collection based on what that particular goal is, and those should be defined up front. The stopping rules also ought to include a consideration for the next steps when you reach a particular point in time and make a determination as to whether the stopping rules have or have not been met. So if the stopping rules have been met, then CMS has options that

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it should be required to follow. If stopping rules have not been met, then industry has some role in making some determinations as to the next steps for that.

One last comment that we, a personal comment that we didn't discuss. It seems rather obvious to me and maybe obvious to everyone else that if you can clearly define a stopping rule for CED, that once you have done that, you have defined for that particular technology what in fact is reasonable and necessary. And if you can define what's reasonable and necessary for a CED, you should be able to define what's reasonable and necessary broadly.

DR. C. GOODMAN: Point very well made, and it is as someone said earlier on today, philosophical, theological, but it is right on point. Thank you, it helps close the loop. Thank you.

Dr. Kuntz, thank you. As was the case with Dr. Sandy's presentation and the presentations by Drs. Korn and Tunis, your presentation in and of itself stood upon its own very very well, it was quite substantive, I

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think you've heard reflections on that, and we appreciate that.

Panel, a last question for all of you before we go, and I know this is kind of on the fly here, and we'll start with Ms. Cabral-Daniels, go across, and finish with Dr. Phurrough, is this. We have been at this since eight o'clock this morning, and a lot of you have been reading about the material for quite some time. If you wanted to say to CMS, listen, since eight o'clock this morning we've gone through all this information. If there's one thing that was said today that you must not overlook, what is it? When it comes to revisiting the coverage with evidence development program, if you are going to take home one thing from our discussion today, CMS, that will be of use in an objective, systematic, fair and transparent approach for

improving CED for the betterment of Medicare beneficiaries, it is what. And I will ask you to do that in a sentence or a bullet point, no dittos, original comments. Ms. Cabral-Daniels.
MS. CABRAL-DANIELS: Okay. Well, it certainly will be original since I'm first, but

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I think the one thing I would say is to always remember that at the end of the day this represents an opportunity for access to care that would otherwise be unavailable to the patient population.
DR. C. GOODMAN: Great, thank you, access to care. Dr. Grant.
DR. GRANT: One of the most important -- well, before you get started with CED, make sure you define what the most important questions or parameters are that in fact determine the decision or net clinical benefits.
DR. C. GOODMAN: Thank you, sir. Dr. McDonough.
DR. MCDONOUGH: I had a couple points.
DR. C. GOODMAN: As long as they're in a sentence.
DR. MCDONOUGH: Okay. I think the most important thing, I think, is that in designing any type of coverage with evidence development that you have to be very practical in terms of timelines, what can be accomplished. Otherwise, it's just not going to work.

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DR. C. GOODMAN: Thank you. Dr. Min.
DR. MIN: I think I would just emphasize what Rick Kuntz said, that a multi-stakeholder group of individuals who can help design, prioritize and represent the overall Medicare beneficiaries.
DR. C. GOODMAN: Excellent, thank you. Dr. Normand.
DR. NORMAND: I would emphasize that we leave here knowing that this type of study is not for surveillance, it is to answer a particular question, and to do that we need a comparison, at least one comparison.
DR. C. GOODMAN: Excellent, it's not surveillance, it's asking a particular question. Dr. Rich.
DR. RICH: I would say that having a credible data source is the sine qua non of success here. Without good data you won't have good results in the CED.
DR. C. GOODMAN: Thank you. Dr.

Saadi.
DR. SAADI: I'm trying to pick one from everything that was said. It's important that CMS afford a positive opportunity for the
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industry and the financial community, and the second point I would make here is I think it is important for CMS to reach out and to qualify that point, that we really should have innovation.
DR. C. GOODMAN: Excellent, thank you, Dr. Schwartz.
DR. SCHWARTZ: Next time I will sit at the front so I don't need to keep changing my answer. I would say it's important to assess that it's worth doing, you know, the value of it and the conditions under which the -- the question's well designed so it can be answered in a time frame in a well-specified manner.
DR. C. GOODMAN: Thank you, sir. Dr. Sedrakyan.
DR. SEDRAKYAN: I think that payment is in part an incentive for getting the structural development, and I do believe that CED can help us to develop data in a structure for looking at the effectiveness of the therapeutics in the long term, so there are benefits other than answering questions within CED which improve quality of care and a better provision of care that CMS should consider as
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well in addition to answering the particular question and the payment, so investing in maintaining that kind of system I think would be of benefit.
DR. C. GOODMAN: Excellent point, data construction. Dr. Juhn.
DR. JUHN: So, I would really just focus on something we really didn't speak to very much today, which is not to forget the operational challenges and costs of actually conducting a CED program. So I think it's very important that you take that into account, and to do this right is not, there is no kind of fast and easy way to do it right now.
DR. C. GOODMAN: Thank you. Dr. -- or Mr. Lasersohn.
MR. LASERSOHN: I'd say that it's extremely important in developing the CED paradigm that we really focus clearly on what's not included in the CED and try to really make that a clear distinction, between that which will be looked at by CED, covered under CED, and that which will be covered through the

normal course.
DR. C. GOODMAN: Great, thank you.

Dr. Neumann.
DR. NEUMANN: I think the challenge is to come up with a framework that's at once simple and predictable and flexible, and that will not be easy, but I think it's doable. I mentioned FDA coming up with their plan, so I think it's doable, and I think it will be made easier by some of these new databases that Mark McClellan talked about.
DR. C. GOODMAN: Excellent, thank you.
Dr. Phurrough.
DR. PHURROUGH: Similar to Jack's comments, I think we did not spend a lot of time on this, but I think it's above the definitions of thresholds and inclusion-exclusion criteria, inclusion-exclusion criteria are quite important. We need to define what are the eligibility criteria for CED, we talked about that a bit, particularly in Dr. Tunis's presentations, but I think that's critical to sort of narrow the work that may need to be done in defining the program and how we're going to define threshold criteria.
DR. C. GOODMAN: Great, thanks, Dr. Phurrough. Just a couple comments before I

turn it back to Tamara Syrek Jensen.
First of all, coverage with evidence development is not a new concept, it has been at least 20 years in the making. I happened to notice that one of the authors of a seminal article on this, Bill McGiffney is here today, wrote an article 20 years ago about this, and what's changed since then is that we have a lot more reasons now to look for better evidence, and evidence that can help us learn and adapt as we go. There are a lot more reasons why we need more, better, more specific evidence to help subgroups, different facilities, different providers, broader indications that are patient-centered, all of those things are much more important than they were 20 years ago, so we need to keep on doing this.
Even today, whether it's clinicians, patients, payers or other decision-makers, we still don't know everything that we would like to know about many technologies at the time that they're approved or cleared for market entry or when they're initially up for coverage. This is a problem or a challenge that is not going to go away.

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The good news is that we are much much better equipped to start answering this kind of question, what with the new methods, data sources, and a lot of perspective on what's worked and what hasn't worked so well with CED in the past. We could also even look abroad to other models around for the world for what's worked and there may be some opportunities to learn there.

I want to say that I'm very impressed today by the level of preparation, the superb preparation that was done on the part of all the participants today. Starting with CMS and the careful thought with the questions, and staff work as is always the case here. But I would add that our nine scheduled presenters obviously spent a lot of time and careful thought thinking through the questions and particular perspectives, all of which have been useful today. I also want to thank our single public commenter; in his minute he was superb in providing a couple of very useful points.

I thank in particular Drs. Allan Korn, Mark McClellan, Sean Tunis, Lew Sandy and Rick Kuntz, all of whom clearly spent a lot of time

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thinking through the five questions, not just from the standpoint of their particular stakeholder institutions, their home offices as it were, they also brought perspective in much of a global societal nature, and I think every one of them made comments that reflected their interests in the well-being of the Medicare beneficiary population, and we certainly do appreciate that very very much.

And panel, great appreciation to you for traveling, reading the material. I think, I have rarely been in a -- I probably haven't been in a MEDCAC meeting where so many panelists were able to weigh in on point with substance on all of our question, so much appreciation to each of you for your commitment to this and your great insights. With that --

DR. SCHWARTZ: And we want to thank you for your leadership of the panel and of the group for the last however many years.

DR. C. GOODMAN: Thank you, Dr. Schwartz, thank you, sir. Well said by my dissertation advisor, I might add.

Ms. Syrek Jensen, back to you for the Agency.

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MS. SYREK JENSEN: I was told by Maria

that I have five minutes, so I will make this very short.

I think this was an excellent meeting and there is a lot for us to take back. I think what I heard loud and clear is we need to have stakeholder involvement, and I can say that we will have stakeholder involvement.

I've also heard about an open and transparent process. I think that coverage has always strived to have an open and transparent process, and we can commit that we will be doing that as well.

There are a lot of steps in front of us that we plan on taking back. One of the immediate goals is to write the guidance document, so we hope to have that done in the near future.

But most importantly, what I wanted to do once again is thank the panelists, the guest panelists and the speakers. And I especially want to thank Dr. Cliff Goodman, this is his last MEDCAC. He has had a tenure here for two years as the chairman, oh, three years as the chairman, I'm sorry, and by statute he can't

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serve anymore. He has done a wonderful job. He always keeps us on task, he always keeps us on time, and most importantly, he always asks very difficult questions that CMS may not be able to ask, and he's able to do it on our behalf. So again, thank you very much.

(Applause.)

I have also been asked to extend thanks from our boss, Dr. Patrick Conway, who is the chief medical officer and director of the Office of Clinical Standards and Quality where coverage resides. He couldn't be here today, but again, thank you from him as well.

So again, thank you very much, a very nice meeting.

Oh, I'm sorry, I wanted to announce our new chair, I just completely forgot. Dr. Rita Redberg is going to be our new chairman for the next MEDCAC, so if you'd stand up.

(Applause.)

Thank you.

DR. C. GOODMAN: Thank you all very much.

(Whereupon, the meeting adjourned at 4:27 p.m.)