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

September 22, 2010

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

Reported by:
Paul Gasparotti

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Panelists

Chairperson
Clifford Goodman, Ph.D.

Vice-Chair
Saty Satya-Murti, M.D., F.A.A.N.

Voting Members
Ray Baker, M.D.
Kevin J. Bozic, M.D., M.B.A.
Helen Darling, M.A.
Charles Davis, III, M.D., Ph.D.
Jeffrey G. Jarvik, M.D., M.P.H.
Susan Kendig, J.D., M.S.N.
Edward Kim, M.D., M.B.A.
Courtland G. Lewis, M.D.
Robert McDonough, M.D., J.D.
J. Sanford Schwartz, M.D.
Andrew Sloan, M.D., F.A.C.S.
Robert L. Steinbrook, M.D.

Industry Representative
Peter Juhn, M.D., M.P.H.

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Panelists (Continued)

Guest Panel Members
John S. Kirkpatrick, M.D., F.A.C.S.
Raj Rao, M.D.

Invited Guest Speaker
Julie Glowacki, Ph.D.

CMS Liaison
Tamara Syrek Jensen, J.D.

Executive Secretary
Maria A. Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:30 a.m., Wednesday, September 22, 2010.)

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 the evidence, hear presentations and public comment and make recommendations concerning the currently available evidence regarding the clinical benefits and harms of on-label and off-label use of bone morphogenetic protein, BMP.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statute prohibits 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 the introduction. We ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement in any company, including Internet or E-commerce organizations, that develops, manufactures, distributes and/or markets bone

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morphogenetic protein, or devices or services, hardware, implants, surgical instruments related to bone morphogenetic protein. This includes direct financial investments, consulting fees and significant institutional

support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

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 mike, and please state your name.

For the record, voting members present for today's meeting are Dr. Saty Satya-Murti, Dr. Ray Baker, Dr. Kevin Bozic, Helen Darling, Dr. Charles Davis, III, Dr. Jeffrey Jarvik, Sue Kendig, Dr. Edward Kim, Dr. Courtland Lewis, Dr. Robert McDonough, Dr. J. Sanford Schwartz, Dr. Andrew Sloan, and Dr. Robert Steinbrook. A quorum is present and no one has been recused because of

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conflicts of interest.

The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will be calculated, one for voting members and one for the entire panel.

I ask that all panel members please speak directly into the mikes, and you may have to move the mikes since we have to share.

There is a TV network broadcasting and recording today's MedCAC meeting. This is in addition to the CMS web NR and 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 personally identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information.

If you require a taxicab, there is a sign-up sheet at the desk outside of the auditorium. Please submit your request during the lunch break. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas

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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.

And now I would like to turn the meeting over to

Tamara Syrek Jensen.
MS. JENSEN: Good morning, and welcome. I'm Tamara Syrek Jensen, the deputy group director in the Coverage and Analysis Group.
In general we have two types of MedCAC meetings. Most of the times we have a MedCAC meeting because we have an open national coverage determination. In today's meeting we don't have an open decision, but clearly are very interested in the MedCAC panel's opinions about the evidence that they are reviewing, so we look forward to a very good discussion today, and again, thank you and welcome.
DR. GOODMAN: Thank you, Tamara. I'm Cliff Goodman, the chair of MedCAC. Today we've got a pretty ambitious agenda with a finite amount of time, so with that in mind, we do expect that all of our speakers, as well as our panelists, will be on point and concise today. Do speak into the microphone. If you've got something to say and you don't come to the microphone, you

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won't be heard by our court reporter and won't be in the record. So it just won't help us unless you have been recognized and are at the microphone. We've got I believe five scheduled public comments today, each of which has been allotted seven minutes. As you heard from Maria Ellis, it's really important to stay to those seven minutes, and I and my cochair, Dr. Satya-Murti, kindly but firmly suggest that each scheduled speaker think now about focusing your comments on information that pertains directly to today's voting questions, please do focus on that as much as possible in your limited amount of time. And if you plan to present material that you will soon find or later this morning find that might be repetitive of previous speakers or is merely background information about your organization or your association, you might consider dispensing with that material and focusing instead on what you want this committee to hear and know about for this particular issue today. So in any case, please do heed the traffic light system up there. Do know that we will proceed to the next speaker once you've used your allotted seven minutes because we do need to get to the core of this today.
Moving to disclosures, and I will start that off, I am Cliff Goodman, vice president of the Lewin Group. Lewin is one of multiple subsidiaries of a company

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called Ingenix, which is a healthcare information and analysis firm. Ingenix in turn is one of multiple subsidiaries of UnitedHealth Group. You may know that another subsidiary of UnitedHealth Group is UnitedHealthCare. I have a mutual fund with healthcare holdings that may involve one or more of the companies who have an interest in today's proceedings, but I have no financial interest pertaining to today's topic.

Dr. Satya-Murti.
DR. SATYA-MURTI: Saty Satya-Murti. I am a neurologist and independent consultant. I have no conflicts of interest.
DR. BAKER: I'm Ray Baker, I'm an anesthesiologist from Seattle, Washington. I have no conflicts of interest pertaining to anything being said today.
DR. GOODMAN: Dr. Bozic.
DR. BOZIC: I'm Kevin Bozic, from the University of California San Francisco. I have consulting relations with UnitedHealthCare as well as the Pacific Business Group on Health.
DR. GOODMAN: Thank you. Ms. Darling.
MS. DARLING: I'm Helen Darling from the National Business Group on Health, and I have no conflicts.

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DR. GOODMAN: Dr. Davis.
DR. DAVIS: I'm Charles Davis, with the Penn State College of Medicine, and I have no conflicts of interest.
DR. GOODMAN: Dr. Jarvik.
DR. JARVIK: I'm Jeffrey Jarvik from the University of Washington. I have no direct conflicts of interest, although I do consulting for the healthcare industry.
DR. GOODMAN: Ms. Kendig.
MS. KENDIG: I'm Susan Kendig, associate teaching professor at the University of Missouri St. Louis and coordinator of the Women's Health Nurse Practitioner Program, as well as an attorney in private practice. I have no financial disclosures.
DR. GOODMAN: Dr. Kim.
DR. KIM: I'm Edward Kim, I'm a psychiatrist and employee of Novartis Pharmaceuticals Corporation. I have no financial conflicts of interest.
DR. GOODMAN: Dr. Lewis.
DR. LEWIS: Courtland Lewis, I'm an orthopedic surgeon from Hartford, Connecticut. I have no conflicts of interest today.
DR. GOODMAN: Dr. McDonough.
DR. MCDONOUGH: I'm Bob McDonough, Clinical

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Policy and Research for Aetna. I work for a company that pays for bone morphogenetic proteins.
DR. GOODMAN: Dr. Schwartz.
DR. SCHWARTZ: I'm Sandy Schwartz, I'm a professor of medicine, health management and economics at the medical school and the Wharton School at the University of Pennsylvania. I also serve on the Blue Cross Blue Shield medical advisory panel and have served as a consultant in outcomes and effectiveness research for Abbott, Amgen, Bayer, Genentech, Johnson & Johnson, Merck,

but none of them that I am aware of are working in this area, but I have no idea what these people are working on most of the time.

DR. GOODMAN: Thank you, Dr. Schwartz. Dr. Sloan.

DR. SLOAN: I'm Andrew Sloan, I'm a neurosurgeon at University Hospital, Case Medical Center in Cleveland. I have no conflicts.

DR. GOODMAN: Dr. Steinbrook.

DR. STEINBROOK: Robert Steinbrook, Dartmouth Medical School. I'm an internist and I have no conflicts.

DR. GOODMAN: Dr. Juhn.

DR. JUHN: Peter Juhn, from Medco Health Solutions. I'm the industry rep. There are no financial conflicts, however.

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DR. GOODMAN: Dr. Kirkpatrick.

DR. KIRKPATRICK: John Kirkpatrick, professor and chair of the department of orthopedics at the University of Florida, Jacksonville. I have potential conflicts although not real, with stock ownership in Zimmer, Johnson & Johnson and Pfizer, and I also have departmental conflicts with educational support being received from Medtronic and Stryker.

DR. GOODMAN: Dr. Rao.

DR. RAO: Raj Rao, professor of orthopedics and neurosurgery at the Medical College of Wisconsin. No conflicts of interest.

DR. GOODMAN: Thank you all very much, thank you. We're now going to move to Dr. Julie Glowacki, is that correct? Pardon me. We're going to move to Deirdre O'Connor, who is going to provide the presentation of voting questions from CMS.

DR. O'CONNOR: Hi. I'm Deirdre O'Connor, I have no conflicts. I apologize for the contrast on the slides, that's my fault, so we will get on with this.

This is the MedCAC for on-label and off-label use of bone morphogenetic proteins. BMPs are growth factors that have the potential of inducing the formation of new bone. While BMPs were discovered in 1965, they did not become commercially available until 2001 in this

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country. Two recombinant BMPs have some form of FDA approval, rhBMP-2 and rhBMP-7. There are reports stating that up to 85 percent of BMP use is for off-label indications. There have also been a number of reports of adverse events associated with the use of BMP.

BMPs are available commercially in this country under FDA premarket approval, PMA, and humanitarian device exemption, HDE. For information on the PMA and HDE on-label uses of BMPs, the panel can look at the appendix that summarizes the FDA actions and public health notifications on BMPs.

There are three PMAs, INFUSE for lumbar spine,

INFUSE for open tibial fracture, and INFUSE for sinus. There are three HDEs, OP-1 for long bone nonunion, OP-1 for posterior lateral fusion in the lumbar spine, and INFUSE Mastergraph for posterior lateral fusion in the lumbar spine. This is just a one-page summary of the FDA actions for the BMPs that we're looking at today. The difference between PMA and HDE, this is a very simplistic definition of the difference, it's much more complicated. PMA is the most involved process under FDA. To reasonably assure that a device is safe and effective, PMA requires valid scientific evidence that the probable benefits to health from the intended use of the device outweigh the probable risks, and that the device

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will significantly help a large portion of the target population. PMA requires robust and independent evidence to support the safety and effectiveness of the device under review. HDE is a process used for a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. HDEs are exempt from requirements to demonstrate effectiveness. They must pose no unreasonable risk, or at least the probable benefit should outweigh the risk. The device must be used in a facility with an institutional review board. Off-label use is defined as any use for other than the specific indications and the specific manner in the FDA approval. We will move on to the voting questions. For all voting questions, the clinically meaningful outcomes of interest for CMS are pain, patient function and adverse events. A scale identifying level of confidence, with one being the lowest or no confidence and five representing a high level of confidence, will be used for the voting questions. The first voting question is: How confident are you that there is adequate evidence to determine whether

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or not the use of BMPs in each of the following indications improves at least one of the clinically meaningful health outcomes? A: On-label use in, one, the lumbar spine; two, open tibial fractures; and three, recalcitrant long nonunions. B: Off-label use in, one, cervical spine; two, lumbar spine; and all other. The second question: How confident are you that there is adequate evidence to determine that the use of BMPs in the lumbar spine for each of the indications identified below improves at least one of the clinically meaningful health outcomes? A, FDA PMA on-label use; B, FDA HDE on-label use; C, off-label use. Number three. How confident are you that the evidence is adequate to conclude that the use of BMPs for

FDA HDE on-label use in recalcitrant long bone nonunions improves at least one of the clinically meaningful health outcomes?
Number four. How confident are you that the evidence is adequate to conclude that the use of BMPs for FDA PMA approved on-label use for the treatment of acute open tibial fractures improves at least one of the clinically meaningful health outcomes?
Number five. How confident are you that the evidence is adequate to conclude that the off-label use of BMPs in the cervical spine improves at least one of the

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clinically meaningful health outcomes?
And number six. How confident are you that these conclusions are generalizable to the Medicare patient population, and B, the community-based settings?
We have one discussion question for the panel. In the absence of evidence-based guidelines, what types of research are needed to address evidence gaps so that physicians can appropriately counsel patients on the risks and benefits of the use of BMPs?
That's it.
DR. GOODMAN: Thank you very much, Ms. O'Connor. We will now be moving on to a presentation from Dr. Glowacki. As she is moving up to the podium, I just want to remind the panel and our guests of a few things with regard to the questions. First, do take note that these questions focus on the outcomes for patients, patient outcomes. You may hear a lot today about other kinds of things that these products may do or offer, but the questions that CMS has posed to us regard pain, patient function and adverse events. These are patient outcomes.
Second, for those of you that haven't been on this panel before, or those that have been before, the set of questions resembles those that we often see which distinguish between two sorts of evidence questions up

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front, what are the kinds of questions we ask first, and this is characteristic of question one, regards not what the evidence says just yet, but how good or adequate is the body of evidence to conclude something. So it's the adequacy of the evidence, number one, and then for those where there's adequate evidence as judged by the panel, then we look into what the evidence actually says. So there is a distinction between the kind of question one and those subsequent questions. That's important to keep in mind, and as we listen to the presentations this morning about the evidence and so forth from the scheduled presenters and others, it's always helpful, at least I know that Dr. Satya-Murti and I find, to be listening for things that address the questions in particular.
So at the close of the day we will ask about things pertaining to what we call generalizability or

external validity, that's question six typically when we say well, we've heard a lot of evidence today, but how applicable is it to the Medicare beneficiary population, and then we also ask about how applicable is it to community settings, sometimes we call it effectiveness in the real world.

And then question seven is not a voting question, it's a discussion question where we try to roll up our observations during the day regarding if there are

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any evidence gaps in particular, what sort of evidence might address or fill those evidence gaps.

So the flow of questions is generally the kinds of things we've seen before at MedCAC meetings, I just wanted to provide a little ramp-up to that.

And with that, we're going to have a presentation now from Dr. Julie Glowacki, who's a professor of orthopedic surgery at Harvard Medical School. She's also professor of oral and maxillofacial surgery at the Harvard School of Dental Medicine, and with orthopedic research at the Brigham and Women's.

Welcome, Dr. Glowacki. You've got about, they tell me here, about 20 or 25 minutes.

DR. GLOWACKI: I think I can do it faster than that.

DR. GOODMAN: Okay, but don't do it so fast we don't understand it.

DR. GLOWACKI: Okay. I have no financial conflicts, but I chose to disclose that in 2002 I applied for a gift from Wyeth of BMP-2 in the collagen sponge that was provided to clinicians in order to do research that they do not support, and I have been a past volunteer for many many years to the activities of the American Association For Tissue Banks.

I'm going to give a brief summary of the history

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of the BMP OP-1 story, but it's first important to get some terminology established. There are three important key words listed on this slide, representing the three mechanisms of bone formation that occur with bone grafts or implants. The first is osteogenesis, which is the direct formation of bone by osteoblast; osteoconduction, in which the material provides a passive scaffold for the growth of bone from the margins of the implantation site; and the third mechanism is osteoinduction, where the material stimulates non-skeletal cells to become skeletal cells wherever the material is positioned.

I'll also talk a bit about assays that are used to demonstrate something that is osteoinductive, I will spend a moment or two talking about the native BMPs and how we get recombinant BMPs, and then a number of research questions will be posed.

Regarding bone grafts, implants and substitutes, autograft really starts the history and is still currently

considered the gold standard. An autograft refers to the transfer of viable bone from one part of the body to another location. It relies upon osteogenesis, the transplanted osteoblasts must be alive, or they must be living pre-osteoblast, and then create new bone in the position where they have been placed.
An allograft or an alloimplant refers to bone

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tissue that's transplanted from one person to another person, usually through banking mechanisms. You have to be concerned, with respect to tissue transplantation, antigens and inflammatory materials that are the result of there being dead cells in there, and so the process is very important for addressing those issues. And once the material is cleaned, one still has to deal with the balance between resorption of the implant and the ingrowth of new bone by osteoconduction.
The third category refers to alloplastic or synthetic materials, which would include metals and recombinant methods.
The history goes back to Marshall Urist, who was the original champion of this, and he referred to his various things he was using back in the '60s as AAA bone, which is an abbreviation of autolyzed antigen-extracted allogeneic bone, and he was very concerned with coming up with a protocol that would reduce the antigenicity, would reduce inflammatory debris in order to enhance the incorporation of allogeneic bone, and what he determined was that in testing for inflammation and antigenicity, he implanted the test materials into a muscle pouch, and he discovered that the material when properly processed was osteoinduction, actually forming new bone in that muscle pouch where he implanted it.

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The key steps for AAA bone preparation is organic extraction with organic solvents to remove inflammatory and antigenic components, and the extraction in his case was primarily one or two millimeters of surface demineralization because he was using large allografts. Auto-digestion of the cellular material results if they're deprived of their blood supply. And then for storage, freeze-drying and vacuum packaging.
We were involved with demineralized bone, and the protocol was modified from what was done in rats by other investigators, the key investigator is Hari Reddi and Charlie Huggins. The key steps in what we were doing was to reduce the size of the bone to particulate it in order to get a faster reaction in vivo, organic extraction. After extraction we use the term demineralized bone, it's really just a jargon, because many other things are removed from bone, many acid soluble molecules are removed from bone by the acid treatment, but we just refer to it with shorthand as demineralized. And because of the acid extraction, it's very important to

remove all of the acids in order to neutralize the pH of the material and that has to be done with extensive water washes and the dehydration for storage. During the 1980s and 1990s, we had extensive clinical input on the material from plastic and

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reconstructive in pediatric and adult patients with craniomaxillofacial, periodontal and orthopedic surgery. The importance of acid extraction is shown on this slide. On the left is what happens histologically after the subcutaneous implantation in rats of demineralized bone products. On the ninth day one sees the appearance of those chondrocytes producing cartilage matrix in and around the particles of the demineralized bone, and by 14 days all the cartilage is gone, the tissue has been replaced by bone and hematopoietic matter, and then goes on in the sequence. If everything is done the same except for the acid extraction, a very very different tissue is formed, it's what I call gold particles, and here you see it with red staining, indicating the osteoblast-specific enzyme, and the appearance of osteoblasts should not be full of particles of bone, and they may be the resorption of bone particles, and by three or four weeks all this has been removed, a very very different fate. Here's a closer look at it. This scanning electron micrograph down in the bottom corner shows particles of demineralized bone two hours after they were incubated with human skin fibroblasts, which are important for osteoinduction, and within two hours all the cells attached to the particles and spread out. Histologically

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we can't follow it in humans, but here's a sequence scan in rats. An ingrowth of connective tissue cells is a very benign looking reaction, not inflammatory at all, the appearance of these beautiful chondrocytes, and once the tissue becomes vascularized it becomes mineralized, it undergoes chondrolysis, it's restored as shown on the slide here in a hematopoietic manner. Marshall Urist used a similar assay. That was with subcutaneous implantation, he used intramuscular implantation in order to purify and isolate the active component in the demineralized bone matrix. In 1979 he determined by biochemical means where he would subject the material to different very specific enzymes, and determined that the activity was chemically identified as a hydrophobic glycoprotein. Urist also identified another 18,500 molecular weight protein that he called BMP, solubilized with very very strong solutions of urea or guanidine hydrochloride, but he noted in this very important paper that in this soluble form the material was very very weakly active. So why didn't he call it BMP? Because that was the essential component in composites that he put together to show

activity.
Now this figure is very important; it describes
the x-ray showing all of the bone growth that was induced
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after he implanted the material, but notice that it's two
parts of the BMP protein, seven parts of other proteins,
one part of another one, and a total of three milligrams
showing up there. In other words, the material had to be
insolubilized before its activity could be tested in this
assay.
Meanwhile, Drs. Sampath and Reddi were also
pursuing a course of isolating the active components from
demineralized bone. Starting off with active bone, you
put it under the skin of the rat, and it induces new bone
formation when extracting from it this strong agent,
guanidine hydrochloride, and that left a residue that was
inactive on its own, and all of these solubilized
molecules were also inactive on their own. This was a
classic biochemical technique to separate and enrich for
these different proteins on the basis of their molecular
weight, on their charge, you could come up with different
fractions of it and then one by one add them back to this
inactive residue, and lo and behold, one of these when
added back rendered this reconstituted material active
when you put it into an in vivo assay, and so that
material then gets the definition of BMP. In their case
they refer to it as osteogenetic protein.
Once you have purified proteins with the
explosion of molecule technology and recombinant
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technology, it's possible to get a recombinant material,
and this is a quick summary of that partial amino-acid
sequence of these proteins, so you can then use the
genetic code to translate back to what the gene would be
that would produce that protein, and you design what's
called cognate oligonucleotide probes. That allows you to
then fish out into molecular cloning of genes that have
sequences that are like that.
Now you can't go the other way, you don't get a
single one, so you get an array of genes. Each of those
can then be placed into a phage and you can do expression
synthesis of this, you get bacteria to produce large
amounts of the protein that's encoded by that gene. Then
with all that material you can do safety and efficacy
studies in animal models, and move forward to clinical
applications.
In doing that, this is a brand new list of all
of the molecules that have been identified in this manner.
This organizational chart represents the similarity in the
protein structure when the two materials are identified as
being close on this. For example, BMP-2 as far as the
amino-acid sequence, BMP-2 is the material that is
marketed in the INFUSE products, and then you see quite a
distance from it, there is BMP-7, also know as OP-1, the

other marketed product or group.

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And then in the course of identifying all of these genes and their expression during osteogenesis, one comes up with a whole array of natural inhibitors that stop the activity of these proteins during their embryological development of the mouse usually, and then there are all of these BMP inhibitors then that are being investigated, again with this organizational chart. Here you'll see Noggin, one of the important natural inhibitors, and we'll refer to that in a couple of seconds.

This is one of the first preclinical models that showed real hope for using BMP recombinant proteins for clinical application, and there are two x-rays here showing the production of bone in this location and that location with the BMPs. This was done by a different surgical technique, a less invasive technique in this particular paper.

There will be a lumbar discussion about clinical efficacy that I'm going to show in a slide that showed the first clinical potential where a success was defined clinically with the Oswestry questionnaire scores, and in red I have highlighted the group that had the implantation of the recombinant BMP-2 versus the autograft that was a comparison of it, and one can see here in the number of patients that showed improvement, clinical improvement was

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evident three months postoperatively, and it continues to improve. Unfortunately it's not possible statistically to show whether this improvement shows superiority or inferiority with the other materials because the numbers are just a little too tight, but it showed the potential.

One of the big questions was why is so much of this recombinant protein needed, and in some of the literature that I reviewed it was between three and 32 milligrams of the protein per site. Well, think back to the Marshall Urist paper, think back to the way that it had to be purified, it can't be reprecipitated. One thing, as reported by Wozney, showed that one molecular gram of BMP could be isolated from one kilogram of bone, so how much would be necessary to substitute or to replace the bone? Concentrations of BMP a million times greater than that found in the human body, according to Dr. Hsu, an academic.

So the problem is posed in several ways. Is the carrier needed to deliver this soluble molecule to the site where you need it, is the carrier, does a special carrier need to be designed in order to contain it so it doesn't just diffuse away and just lower its concentration, or do you need the carrier to stabilize the protein, because once a protein is put into tissues, it is subject not only to diffusion but also to degradation by

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ubiquitous proteins? But it can also be asked whether the osteoinductive signal is not in a form that can be dissolved or fully reproduced with the recombinant protein. One can also ask whether multiple molecules are needed to reproduce the efficacy of AAA bone or demineralized bones.

We're now going to talk about some of the experimental basic science about these points. What we did is tried to compare the effects of demineralized bone versus the recombinant BMP-2 on a collagen sponge when targeted to the fibroblasts in vitro, and we were looking at early genes that are signaled in the target cells by these osteoinductive materials.

In this graph we can see that there's equivalence in our signal we're establishing. This was reassuring to us because it told us that we probably had a good concentration, a good equivalent in concentration, but many many other genes are not regulated in this early step equally by BMP and DBP, and so in this paper we concluded that although BMP was originally isolated as a putative inductive factor in demineralized bone, the recombinant BMP-2 and DBP do not affect all of the genes in all of the ways, and some of the ones that I put on this graph are targets of another protein called TGF beta, and I found with some literature on this side was BMP-2

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and on this side would be OP-1, which shows how you can enhance the activity.

I call your attention, let's just look at this Collagen II section here, TGF beta gives you this much induction, BMP-2 gives you this much induction, but when you add the two of them together, you get a much larger response just by itself.

Over on this side, this is a very interesting paper, it's induction in, intramuscular in baboons, old world baboons, conducted by Dr. Ripamonti in Africa. And what he showed here in blue hatched is the OP-1 alone, showing the increase in activity, in bone formation in vivo with increase in concentration. But in two of his 25, for example, starting with OP-1, when you add increasing amounts of TGF beta, you see more bone formation. The other startling thing is that in this baboon study, which has not been shown in any other animal model, is the osteoinductive effect of TGF beta alone, and that's represented by this bar. In the rats that we've studied, and the mice and other animals, TGF beta doesn't have independent activity.

We will skip that one.

One of the important factors in understanding the biochemistry of the actual BMP was the recognition that the native molecule is made up of two chains of BMP,

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but it's not two chains of BMP-2 into BMP-7, but it's made up of two chains, with one of each of those particular

amino-acid sequences, and the two chains are coherently bound together, linked together with what is called a bridge, making them a very stable parent.

So that raises the question of whether you need to have one BMP-2 and one BMP-7 in this heterodimer, meaning two, in order to get activity. And that's what's shown on this slide, is the BMP-7 story. Here's in the blue the four and four, in this is two chains of seven and seven, but if you have one chain of four and one chain of seven, much stronger activity, more like the native molecular activity considered in the studies.

Now looking at the BMP-2 studies, there's also literature out there on this, and this shows in the blue increasing amounts of the homodimer with two chains of BMP-2, and here's much more activity at lower concentration when you have one chain of two and one chain of seven.

There's an understanding, a partial understanding of why this is, so if you look at the inhibitors, and this is what one has to worry about with respect to the fate of these materials, what is the cascade of events that occurs? In this case we're looking at this Noggin, this is looking at muscle cells that are

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the target of the BMPs. In looking at how much Noggin or inhibitor is induced by each of them when you look at BMP-2 alone or BMP-7 alone, but the heterodimer of two and seven induces less of the inhibitor. Does that mean it's going to be more potent, does that mean it's going to be more enduring in its activity?

Another interesting thing is that knowing on its own, if you add BMP heterodimer, two and seven, and add Noggin to it, it's not as strong an inhibitor to that heterodimer. Yet, if you add Noggin to BMP-2 you will see this diminishing activity, and here's the BMP-7 showing the same thing.

Yes, you have a question?

DR. GOODMAN: No.

DR. GLOWACKI: Two minutes, okay. See, I told you I would be fast.

So some of the research questions that basic scientists around the world have been asking and are continuing to ask are listed on this. People are interested in what the appearance, what the temporal appearance, which BMPs occur in different stages of their development, as well as their inhibitors as the skeleton is produced in the embryo. What about its growth in adolescent growth of animals, which are the BMPs and which are the inhibitors that are more vulnerable. What happens

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to the fracture material, is it a complete recapitulation and then a regenesis, or is there something different going on in terms of the bone formation?

And a big area of research concerns osteosarcoma

and the role that BMP plays with sarcoma. An investigator at the University of Chicago, Dr. Ho is one of the people who is comparing the amount of BMP-2 within normal osteoblast or osteosarcoma cells, and I think right now that BMP-9 is the most disregulated of all the sarcoma cells.

Now in order to understand the mechanism of action of the BMPs, this whole field, we need to know about the receptors, signaling molecules, inhibitors, because this, the specificity, the tissue specificity of what cells the BMP is going to act on are required in this.

Now one of the things that we've learned with mice engineered with gene knockouts is when you knock out a BMP, there's many many activities beyond those, and in fact Dr. Reddi suggested that we shouldn't call them bone morphogenetic proteins, they should be body morphogenetic proteins because of other effects that these genes have on heart development, eye development, kidney development.

While clinical trials provide evidence that BMP contributes to bone formation alone or with an autograft,

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what further information is needed? What's the mechanism of action in humans, are these superphysiological activities, how can we safely improve on the efficacy and reduce the potential side effects, different complications, different locations, and what's the significance of an antibody formation that occurs in all of these patients? And I think these questions give an opportunity for academic scientists, company people and the government agencies to work together to answer these questions. Thank you.

DR. GOODMAN: Thank you very much, Dr. Glowacki. Well, there you have it, the molecular, cellular and tissue development up to preclinical, thank you very much, and also for the basic and technical vocabulary.

Next we're going to have a presentation on the technology assessment, and as Dr. Ratko approaches the podium, I just remind our panel that typically when CMS is anticipating a MedCAC meeting such as this, it will often ask AHRQ, the Agency for Health Research and Quality, also in the Department of Health and Human Services, to prepare a systematic review and an accompanying evidence report or a technology assessment. These evidence-based practice centers, among, there are 13 of them that are contracted under AHRQ, and there is a subset of them I believe that prepare these reports for MedCAC meetings such as ours.

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Also because of matters of timing, the evidence questions that are posed and addressed by the EPC don't always line up exactly with the evidence questions we actually see before us, so there's a lot of overlap here, but the set of questions don't go precisely hand in hand, so you want to allow for that.

In any case, our technology assessment presentation is going to be by Dr. Thomas Ratko, who is the associate director of the Blue Cross Blue Shield Association Technology Evaluation Center, i.e., one of our EPCs, and welcome very much, Dr. Ratko. I will remind our panel that we received this ahead of time, it's thicker, and this is the technology assessment in full. Welcome, Dr. Ratko.

DR. RATKO: Thank you, Cliff. As Dr. Glowacki and Dr. O'Connor led off, they took a lot of my slides away, I have no disclosures, so what I'm going to do is go right to the methods of the systematic review. They were originally taking questions that we were asked to review and I will talk about each one of them in order, except for number nine. So going to our methods, what we did was compile a systematic review. We developed a protocol a priori. We developed a search strategy and as far as our dates, we started with 1998 because we felt that would probably encompass what we

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needed, and then went through, the end of the search was July 28th, 2009, but we updated that on February 25th, 2010. We searched MEDLINE, EMBASE and Cochrane, and went from there.

The patient populations, obviously patients with some sort of bone-related condition for which intervention is undertaken. The interventions we've talked about, BMP-2, INFUSE, and BMP-7. Dr. O'Connor mentioned what the off-label determination was, and we were asked to look at that, but we only extracted that kind of material if the study was interrelated.

The comparators you see here, they're osteoconductive, osteogenic or osteoinductive agents, autologous bone, the gold standard, allogeneic bone, bone marrow, demineralized bone matrix, and also surgery and placebo.

When we do a systematic review, we first specify as much as we can what outcomes we're looking for. Dr. O'Connor mentioned the key, and Dr. Goodman mentioned the key outcomes that are important to the patient, pain, function, but we also looked at the radiography, conventional or computer tomography; that's almost a universal measure in these studies. We've seen pain scores, quality of life scales, combined scales, Oswestry Disability Index and the Neck Disability Index.

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Neurological status in the spinal studies. The dental, the maxillofacial applications have some very specific outcomes that we took a look at. And then because we were looking at off-label uses, we didn't know what exactly we were going to find when we got into the literature, so we couldn't really clarify that.

I just want to make a couple points as it relates to spinal fusion outcomes and the question with

regard to radiographic assessment. These are primarily standard anteroposterior and lateral flexion-extension radiography, but often CT is used when the radiographs are not conclusive. And typically in spine studies there was an independent evaluation by two radiologists who was unaware of the treatment, and there was an adjudication by a third as needed. The criteria are pretty standard, the presence of bilateral bridging bone between transverse processes, the absence of motion as defined there, and absence of radiolucent lines.

One of the key points I want to make is that as we've heard, the clinical outcomes reflect those that are important to the patient, but typically we would look at three or four of these together, and these are right here. Overall success in these spinal fusion studies had to meet these criteria, radiographic evidence of successful fusion, absence of severe device-related adverse events,

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the absence of the need for a second surgical procedure at the index level, and then maintenance or improvement in the neurological status, and this is typically reported as a proportion of patients achieving that.

I also want to make the point that the available evidence is inconclusive as to whether there is a necessary correlation between approved clinical outcomes and radiographic fusion success. That's an important point. When it comes to fractures, it's really been difficult to define fracture healing that's clinically and biologically accurate. For example with tibial fractures, non-union may be defined as ranging anywhere from two to 12 months.

Again, this is most often assessed using conventional radiography, which as everyone knows, is widely available, delivers a low dose of radiation, and it allows for qualitative assessment of callus formation, cortical bridging, loss of the fracture line, and trabecular crossing.

Again, the correlation between radiographic fusion and mechanical strength is not well established, and it's really still unclear whether the radiographic measures correspond to clinical outcomes that are important to the patient, those we're going to consider.

When you see the term clinical success, it's a combined

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outcome measure which involves conventional radiography and results of clinical questions on pain and weight-bearing, and these are typically reported as a proportion.

The importance of harms, we originally looked at the McMaster Quality Assessment Scale, a 15-question scale, and tried to distill it down in a way that would allow us to see just a view of how the harms were reported. And when you see the six questions there, is there an explanation of how they were identified, was a

standardized or validated instrument or scale used, was ascertainment similar in all study groups, was a measure of severity reported, were harms attributed to the study intervention likely causally associated, and were the number and type of harms reported separately for study groups.

Our study selection criteria are here. We prefer to see randomized clinical trials, and we also looked at nonrandomized comparative trials that would provide some sort of direct evidence that utilized BMP therapy in patients with a defect that required intervention. We also looked at other studies that reported harms that appeared to be related to the device itself, one of the two devices. We excluded non-English articles. We originally included them in our search but

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we came to the conclusion that their inclusion would not change the story any at that point. We assessed study quality using the United States Preventive Services Task Force criteria, the general approach, and then we did a data synthesis that involved the GRADE Working Group, which addresses the areas of bias, consistency, directness and precision. We did not do any sort of quantitative meta-analysis; this was purely raw data with a GRADE analysis.

Here's the results of the literature search. We found 1,608 citations in MEDLINE, about 500 in EMBASE, 54 in Cochrane, for a total of 1,992. We excluded 1,738 at initial title abstract review, we retrieved 254, and 114 were compiled in this report.

This sort of gives you a distribution of what we're looking at, and as we've heard earlier, these report about 85 percent of off-label use in the spine. Overall, we found in our systematic review about 73 percent, so very similar.

We also decided just to take a quick look at the, as one of our quality indicators, is what studies did any sort of power analysis, we culled through all of the statistical methods on every paper, and we found only 33 percent of the studies that were reported as on label had any sort of reporting on power and sample size a priori,

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and only seven percent of the studies reporting off-label indications had any sort of a priori reporting of this.

This is just a slide to show you what the universe of non-comparative studies of BMP-2 and BMP-7, and you can find the various ways, that these products are in use in many many applications, as I'll show you as we go on.

Coming back to the questions, key question one: What is the evidence supporting improved outcomes with on-label use of rhBMP-2 or INFUSE for fusion of the lumbar-sacral spine? We considered two randomized clinical trials plus a pooled analysis that we ultimately

didn't consider in the GRADE analysis. These trials reflect on-label use according to the PMA. Of note, our search did not identify any trial deemed on label for the product initially approved via the HDE, the INFUSE/Mastergraph.

You'll see that this study, the one by Burkus is a very substantial size study, and then a smaller one by Boden. We see typically a nice result with BMP-2, radiographic fusion success, ODI success, no difference in leg pain mean score, work status was improved a bit, patient satisfaction was the same, and this is versus autograft bone, and then a smaller study with similar results. Using the GRADE analysis we find that the

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strength of evidence is moderate to support clinical benefit from the use of rhBMP-2 in this setting, as patients can also avoid the additional procedure of autograft bone harvest. But we also have concluded that the size and duration of the randomized trials are insufficient to precisely determine the frequency and severity of device-related adverse events.

Key question two, what is the evidence supporting improved outcomes with on-label use of rhBMP-7, or OP-1, for fusion in the lumbar spine? We didn't identify any published comparative studies on this key question. However, we did take a look at the FDA submitted HDE study, which the panel can find at page 37 in Table 9, and you see the results here showing that generally versus autograft bone, the OP-1 had improved clinical success rates, radiographic success, and overall success. We don't have any significant differences reported on these, we just have these numbers.

The FDA when they did this, based their conclusion on the fact that there is preclinical evidence for the benefit, or the activity of rhBMP-7, the patients who it's intended for, which would be revision, revision surgery, have probably already undergone autograft bone and maybe are not good candidates for another harvest and another fusion. So they put all the data together based

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on this, these were patients in the primary setting, and made the conclusion that it would be approvable under HDE.

Key question three is, what is the evidence supporting improved outcomes with on-label use of rhBMP-7 in recalcitrant long bone nonunions? We identified two randomized trials and a cohort study, which I have shown here, but you can see them on page 40, Table 12. Again, what we have here is we have a nice comparison of fusion or clinical success showing a benefit of BMP-7 in the Calori study. We also show a very similar result in the Friedlander study, versus autograft bone.

We also find that due to the difference in the comparators and the quality of the study, in particular Calori, the strength of the evidence is low to support

improved outcomes with on-label use of BMP-7 for long bone nonunions.
Key question four is, what is the evidence supporting improved outcomes with on-label use of rhBMP-2 or INFUSE for the treatment of acute open-shaft tibial fractures? The main evidence here is the BESTT trial, a BMP-2 evaluation in surgery for tibial trauma compared to different doses of BMP-2, versus standard of care. There's also a subgroup analysis available for patients with Gustilo-Anderson Type III fractures in that, and there's a smaller study which to our knowledge had a total

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of 60 patients and used the identical inclusion criteria procedure that was put into this combined subgroup analysis.
You can see the key outcome here was the invasive secondary intervention rate, which showed a substantial benefit with BMP-2 versus standard of care in both the subgroup analysis and BESTT, as well as improved clinical success rates and a significantly shorter median time to actual healing in that study, and significantly lower infection rates. Putting it together, we find that the strength of evidence is moderate for on-label use of BMP-2 to enhance fusion in open shaft fractures.
Key question five is, what is the level of evidence and summary of evidence for the on-label use of rhBMP-2 or INFUSE for sinus augmentation? There are two randomized trials of staged bilateral or unilateral maxillary sinus augmentation and one RCT of extraction socket alveolar ridge augmentation procedures, which are found on pages 46 and 47, Tables 19 and 20.
What we see here is BMP-2 in the Boyne study compared to often a mix of autograft bone and allograft bone really did not seem to have any significant improvement or benefit, but they weren't worse, and this is universal in these studies, with the exception of the Fiorellini study where in the no treatment group there was

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a significant benefit of a higher dose.
These are three well done studies. We rated them good by USPSTF, and we find overall that the strength of the evidence is moderate that BMP-2 does not improve prosthesis implantation and functional loading compared to autograft plus allograft bone. We also find that the strength of the evidence is moderate that oral sensory loss associated with autograft bone harvest can be avoided by use of BMP-2.
I'm going to turn to key question six. For which indications are there clinical studies in which BMP is used off label? In such studies, what is the evidence of the effectiveness? We looked at three different settings, looking at the lumbar-sacral spine, we looked at the cervical spine, and then the rest of the indications that we came across.

What I'm looking at here is rhBMP-2 for lumbar-sacral spinal fusion. We have identified six randomized studies and also five nonrandomized comparative studies which I have not shown here, but they are available in the report.
The next slide shows the reasons why they're categorized off label. Boden et al., 2002, was the use of rhBMP-2 matrix in an unapproved posterolateral surgical approach. The Burkus study used INFUSE with cortical

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threaded allograft bone dowels rather than an approved interbody device. In Dawson the BMP-2 was used with an unapproved matrix; I want to note that this HDE was voluntarily withdrawn by Medtronic in early 2010. The Dimar study used BMP-2 in an unapproved matrix in a posterolateral approach. Glassman used BMP-2 in a posterolateral approach, and also did multilevel fusions with an additional discretionary use of autograft extenders. And finally, Haid used BMP-2 in a posterolateral interbody fusion, and this study was terminated early.
What we decided in our GRADE deliberations was we gave the greatest weight to the two largest RCTs, Burkus and Dimar. We both rated them fair, and their outcomes showed significant improvements in radiographic fusion success when compared to autograft bone. There were very similar ODI mean point scores, and significant improvements in leg pain, mean scores in SF-36 functional.
Our GRADE conclusion was that the strength of the evidence was moderate that rhBMP-2 improves radiographic fusion success based on the two largest RCTs.
We also find that no conclusions can be drawn regarding the potential impact of the off-label components of the radiographic fusion success, and that the strength of evidence is moderate to support clinical benefit from

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off-label use of BMP-2 as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events.
These are the off-label randomized trials of lumbar-sacral fusion spine fusion with BMP-7. We found four of them, as you see here. These are the reasons why we deemed these off label. Vaccaro et al. was OP-1 putty for primary fusion. Johnsson et al. was OP-1 implant, which is not indicated for spinal fusion. Kanavama et al. was OP-1 putty, which again was a primary fusion study, and Vaccaro again was OP-1 putty in a primary fusion study.
We decided that the best available evidence for the efficacy comes from Vaccaro, a nice sized trial with a nice length of 36-plus months, showing similar radiographic fusion success rates, a similar ODI success rate, a similar increase in ODI mean point score, and similar neurologic success rates. However, based on the

a priori designation that we needed at least two trials, comparative trials to do a GRADE analysis, we find that the strength of the evidence is insufficient to draw conclusions on the off-label use of BMP-7 in fusion of the lumbar-sacral spine.
Now turning to the cervical spine fusion, we've identified five trials that used BMP-2 in cervical spinal
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fusion. Three of them were primarily considered adverse events to the device. Two of the studies actually gave some results, Baskin et al., a 2008 study, and Vaidya et al., a 2007 nonrandomized study. Based on what we have here, we find that the strength of the evidence is insufficient to draw conclusions about radiographic fusion success or associated changes in neck disability measures in cervical spine fusion.
However, we did look at the incidence of swelling that has been reported, and we see three studies here that provide some data on that. Butterman et al. shows a significant amount of swelling compared to the use of autograft bone in the anterior cervical spine, as does Smucker et al., as well as some dysphagia. We find that the strength of evidence is moderate that off-label use of rhBMP-2 in anterior cervical spinal fusion increases cervical swelling and related complications.
Now I'm going to go to a few miscellaneous off-label uses. I'm not going to talk about them much. They're typically small trials, they're one off-spin, they really do not give us any sort of strength of evidence to draw conclusions about their outcomes in these settings. Here's a numbered list, just an exercise in compilation that I did, and as you see, the strength of the evidence is insufficient to draw conclusions about the outcomes.
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I want to turn to question seven. What is the evidence of adverse events with on-label use of BMP and off-label use of BMP, and at what dosage and administration do such adverse events occur? I'll dispense with dosage and administration because we really didn't find any studies that were intended to evaluate that in any sort of rigorous way.
The main conclusions that we have here are that overall, the summarized evidence on BMP-specific harms in comparative studies is insufficient to draw conclusions in most studies, and this is, again, found in the report at Table 36.
The strength of the evidence is moderate that off-label use of rhBMP-2 in anterior cervical spine fusion increases cervical swelling and related complications.
The body of evidence suggests that autograft bone harvest may be associated with pain at the harvest site, but it is not possible to systematically assess the frequency, duration and clinical significance of these harvests, and overall, autograft harvest-associated harms

were inconsistently reported. We find it's not possible to strictly associate the use of a BMP device with an adverse event in the non-comparative studies, and it's also not clear that the absence of reported harms in studies reflects a true

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absence, or whether the investigators didn't seek the information or report it. Now we're going to get to key question eight. What is the quality of reporting or adverse events in publications? Provide a summary to support the conclusion. This is where we bring in the McHarms or the distilled questions, and what you will see in this slide is that really the reporting of harms, as I alluded to, is very inconsistent. For example, was ascertainment similar in all groups; in 92 percent of the studies yes, eight percent no. But was the measure of severity reported; in 85 percent of the studies no, in 15 percent yes. This sort of gives us a picture of the overall quality of the body of evidence which allowed us to come to some of our GRADE conclusions. Here are the off-label comparative studies again. It's all over the world, there's inconsistencies in reporting, and what we find is that our main conclusion is that the reporting of harms amongst comparative studies was inconsistent, and again, whether or not the absence of harms reflects a true absence, or that the investigators did not seek such data or did not report it. I'm going to skip over key question nine and go right to key question ten. What is the age distribution

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of study patients compared to the Medicare population, age 65 and older? If you look at the entire body of evidence among all the studies, the mean reported age was typically in the mid to upper 50 years range. However, there is a range of 16 years to 87 years in the entire body of evidence, so we really aren't sure about the first question. And what are the considerations in generalizing evidence from trials to the age 65 and older Medicare populations, such as comorbid conditions and this population's susceptibility to adverse events? We identified one trial performed by Glassman and colleagues that's the study most relevant to age 65 years and older Medicare population. This study does not specifically lay out outcomes to age or comorbidities. And also, considerations relevant to generalizing from studies in the non-Medicare population include patient age, the presence of comorbidities such as osteoporosis or diabetes. However, in generalizing it from the available studies, we also believe the dose and surgical methods should be considered. And I think that's it.

DR. GOODMAN: Thank you very much, Dr. Ratko.

And Dr. Ratko, if you wouldn't mind staying at the podium, we're going to take a few minutes now for discussion if you don't mind. And if did Dr. Ratko's slides could come
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back up, because we want to make reference to some numbered ones.
Well, panel, Dr. Ratko covered a lot of territory very quickly there, and I know we all did have a chance to look at our full text technology assessment, and I wanted to thank MedCAC staff for handing out his slides if you hadn't printed them before. I wanted to take some time now just to kind of cover some items that you might have gone through pretty quickly there, and it was a very effective presentation, I might add. A few things here. Can you go to slide 26, and I will just start this off, and if you have some other questions, we will do this. Thank you.
Panel, just to kind of get our bearings once again here, this is sort of a 50,000-foot view of the number of comparative studies, so this is kind of a high level lay of the land here. And I know that some of our questions deal with on-label, off-label, so forth, and you'll see some of the various kinds of BMPs at the top, the twos and the sevens and so forth, but do just take a look at how big this body of evidence is. You will see that the on-label studies covered there, you see the number there, 12, or 27 percent of the total; off-label studies there's 29, which comprises 73 percent of the total, so there are, basically the body of literature that
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we're looking at, I think comprises the 41 studies, correct?
DR. RATKO: That was the body of literature that met our selection criteria.
DR. GOODMAN: And the selection criteria are outlined. Yes, Dr. Jarvik.
DR. JARVIK: Relating to the number of studies in the search strategy, was there an attempt to identify trials that were registered but not published?
DR. RATKO: No, we didn't.
DR. GOODMAN: So as is typically the case when we look at stuff that's been peer reviewed that's out there, sometimes the presenters will say things about other things in the pipeline and so forth, and you may use your judgment on whether or not those are relevant for our proceedings today.
DR. JARVIK: And I think we have to keep in mind the issue of publication bias, and I understand we always deal with that.
DR. GOODMAN: We do like peer review, not a bad thing, but yes, it's important to maintain that distinction, and there are things in the pipeline. Yes, Dr. Schwartz.
DR. SCHWARTZ: Are you done with this, Cliff?

DR. GOODMAN: I've got a few more to go over.
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DR. SCHWARTZ: I've got a quick question that's not directly related, so I will wait until you get done.
DR. GOODMAN: Okay. Slide 27 please.
DR. JUHN: Can I ask a question?
DR. GOODMAN: Sure, I'm sorry. Slide 26 for Dr. Juhn.
DR. JUHN: I have a question about your bottom bullet points here about the reporting of power or sample size.
DR. RATKO: Yes.
DR. JUHN: When you say that there was some level of reporting, can you give us some sense of what you mean by some level of reporting, does it mean that they actually did a power calculation or did they provide the numbers so a power calculation could be done, could you just clarify that?
DR. RATKO: Yes, that is exactly it, whether that was even mentioned or presented.
DR. GOODMAN: So again, before we leave this slide, comparative studies, A versus B, what have you, 41, that's the body of evidence of the published studies. Next slide, please, slide 27. Thank you. These are the number, this is the number of non-comparative studies by surgical study down the left-hand column, and by BMP type, the sevens and the
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twos. So this is another way to kind of get a lay of the land here in terms of distribution of the evidence, not saying anything about the quality of the evidence at this point, but the distribution of the evidence for those studies. There's certainly more non-comparative studies than comparative studies, and we see that a lot of the action here is with the BMP-2 for cervical and lumbar, those are two of the biggest chunks of evidence there, so do take note of the size of that body of literature. Next slide, please. This is an example of one of the key questions, and you will notice here a couple of things. First of all, this has to deal with improved outcomes, we care about outcomes. This is on-label use for BMP-2 for lumbosacral. I just want to point out to the panel that we're looking basically here at two studies, so this is looking at two particular studies that fall into this particular niche. Notice on the right-hand side the column that deals with USPSTF study quality. I want to make a distinction here because we'll be using it for the rest of the day. The U.S. Preventive Services Task Force has a well recognized evidence appraisal scheme, and their scheme at this level is on a study-by-study basis, okay? And this is described in more detail in our technology assessment at pages 27 and 28, but what's important to
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keep in mind here is that on a study-by-study basis they're graded good, fair and poor. In this particular case these are two fair studies, all right? And that's different from what the GRADE approach does, which we will see later. In the GRADE approach, rather than looking at the single study level, the body of single studies, we'll look at the body of evidence, the set of studies comprising the evidence for any particular evidence question. So the USPSTF is for individual studies, GRADE is for the body of studies, are they kind of constant or aligned, or are they in opposition and so forth. So that will be a very useful distinction, I think, for the rest of today.

In this case you will see at the bottom of the slide under GRADE conclusions, there is a reference to the strength of evidence being moderate, and then the size and duration of the RCTs are not sufficient to precisely determine in this case frequency and severity of device-associated adverse events. So you're going to see comments about how good is the evidence, is the quality of the evidence, and then other statements about what the evidence might say, and that's relevant to our questions as well.

Okay. Those are just by way of some kind of navigation points. Dr. Satya-Murti. Oh, was it

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Dr. Schwartz?

DR. SCHWARTZ: The question I had is, you noted earlier, I don't have the slide in front of me, but you noted earlier that there was insufficient evidence basically across the board for potential harms, particularly outside the site of the implantation. Are there any sort of meta-analysis or has anybody gone back to do any evidence, people trying to aggregate these relatively small studies to see if there was anything that showed up in that area?

DR. RATKO: I'm not aware of any meta-analysis. There was a study by Cahill in JAMA last year that used, it was a database study that tried to look at some harms, but it didn't distinguish between the devices, and I believe it was mostly in the spine. Other than that, I'm not aware of any distillation of that, except there is one -- actually, I take that back. There is one from HTA that came out, I believe two years ago, and that's the only other one.

DR. SCHWARTZ: And what did that show, what did they conclude?

DR. RATKO: Well, their conclusions are very similar.

DR. SCHWARTZ: So even having done that, the information base is inadequate.

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DR. RATKO: Correct.

DR. GOODMAN: Thank you, Dr. Schwartz.

Dr. Sloan I think is next.
DR. SLOAN: With regard to the USPSTF study quality, what are the ratings, fair?
DR. GOODMAN: They're good, fair and poor.
DR. SLOAN: Good, fair and poor.
DR. RATKO: Yes, sir.
DR. SLOAN: And can you give us sort of a breakdown of clinical studies in general, is there an even breakdown, or what percentage are good, what percentage are fair, what percentage are poor?
DR. GOODMAN: I'll take a shot at that because we only asked Dr. Ratko to look at this body of evidence. It's quite different. I mean, in some clinical indications and some evidence questions it all kind of bunches up at the good end and for some it bunches down at the poor end, so there's no typical distribution across all the different types of evidence questions in clinical areas.
The criteria, by the way, used for USPSTF is shown on page 27 of our complete evidence report.
I believe, is it Dr. Lewis who was next? Yes.
DR. LEWIS: Dr. Ratko, just a quick question for you. I understand that your key questions were developed

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somewhat independently of the ones we're asked to look at today. You have addressed the issue of adverse events in one of the later questions, but using key question number one as an example, we're asked to look at meaningful health outcomes including pain and patient function, and the primary endpoints for these two studies, for example, are primarily radiographic endpoints. My question is, do you have any sense of whether the GRADE conclusions would be changed based on the use of a secondary outcome in these particular studies as opposed to radiographic outcomes? In other words, can we extrapolate from your GRADE conclusions in general, not for specific studies, but in general to our questions that are put before us?
DR. RATKO: Well, I think we can see, in particular the Burkus study, that the ODI success as a composite measure showed a little benefit, not of statistical significance. Again, we see a similar increase in mean score improvement in work status. So I think if you took away the radiographic success, I think it wouldn't really change things.
DR. GOODMAN: Thank you. Dr. Bozic is next.
DR. BOZIC: My question is actually clarification for you and for CMS, that we are in fact not to consider radiographic outcomes, radiographic fusion, and/or, or radiographic fusion as a clinical outcome for

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purposes of our voting and our consideration in these questions?
DR. GOODMAN: We are specifically to look at those three types of patient outcomes, none of which

include radiographic. I would allow, or mention that in some clinical areas, and I'm not saying whether that's true here or elsewhere, but in some clinical areas sometimes there is very strong evidence of association between a biomarker or intermediate outcome and a clinical outcome of interest, and I'll leave it to your judgment to make that connection if indeed it's here, and I don't know that it is. But for purposes of our questions we are interested in those three types of outcomes, and correctly as pointed out, various columns on this slide, yes, radiographic fusion is shown, but then there are one, two, three, it looks like four columns to me that show more patient-oriented outcomes, okay? Was Dr. McDonough next? I believe so.

DR. MCDONOUGH: Following up on that point, though, can we infer from radiographic evidence of fusion that one can avoid pain from harvest of an autograft? In other words, that the benefit may not be directly from the fusion but the idea that you may be able to avoid an autograft?

DR. GOODMAN: I don't know that that was the

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line of questioning or inquiry from CMS. I will leave that up to you. I know we have to get to our three outcomes when all is said and done. If you think that there is --

DR. MCDONOUGH: I don't know if I phrased that correctly, but you understand what I'm asking? Sort of an indirect evidence of reduction in pain by avoidance of a second procedure.

DR. GOODMAN: Yeah. I'll ask CMS if they have an opinion or a view or some guidance on that. We're not talking about the patient himself or herself just getting the procedure, but at that time something apart from it, the avoidance of pain, correct? Any comment from CMS about wanting to go that way?

SPEAKER: We have our opinion, but it's up to the panel.

MS. JENSEN: CMS does have an opinion but we really would prefer before we tell you our opinion to hear what you have to say, instead of advising you what ours is.

DR. MCDONOUGH: In my opinion I would believe avoidance of pain from harvest of an autograft to the extent that there is evidence that it can reduce pain is a clinically relevant outcome.

DR. GOODMAN: Thank you, Dr. McDonough, well

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heard. Ms. Darling.

MS. DARLING: Noting that I'm not the clinician on the panel, I think on that last point I would add it's an additional procedure, but it's always additional patient safety risk, and given what we know about the probability of there being an adverse event, we have to

add that in, it seems to me.
DR. GOODMAN: Thank you, Ms. Darling, so the CMS staff is hearing the opinions of this panel.
Dr. Steinbrook.
DR. STEINBROOK: I wanted to go back to questions one or two earlier, with the issue of radiographic success and how that correlates, but I think it's slide 35 where you're talking about, let's see, so this is off-label use in the lumbar-sacral setting; is that correct?
DR. RATKO: Correct.
DR. STEINBROOK: So there is a GRADE conclusion about radiographic fusion success, and the word used is moderate there. So to follow up on what I think the people with earlier questions were getting at, if we were to eliminate the notion that radiographic fusion could be considered as somewhat synonymous with a meaningful clinical outcome, how might that be viewed in terms of the grade of the evidence? Did I say that clearly? If we had

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to wipe away radiographic fusion because we were told earlier that we couldn't necessarily draw a correlation there with some of the earlier slides, where would that leave us in terms of the evidence?
DR. GOODMAN: If I may interject, if that column weren't on the slide, Dr. Ratko, where might USPSTF find us in terms of the evidence?
DR. STEINBROOK: Or GRADE.
DR. GOODMAN: Or GRADE as a group.
DR. RATKO: I believe we would still be in the same place.
DR. GOODMAN: Okay. Dr. Kirkpatrick, I believe, and then -- oh, excuse me, Dr. Rao, yes, sir.
DR. RAO: Just a couple of quick responses that I noted as you were going through earlier in this discussion.
DR. GOODMAN: Yes, sir.
DR. RAO: Lack of radiographic fusion, whether it's in the tibia or in the spine, may be considered an adverse event if you have a nonunion, for example, that may be considered an adverse event, the lack of radiographic fusion of the tibia leading to nonunion may be considered an adverse event.
Another quick response to a point raised earlier in this discussion on whether there are any overarching

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meta-analyses looking at harm, there are two studies, there's a Medicare database and a Wyeth database both looking at the risk of cancers in populations that have been exposed to BMPs and populations that have not been exposed.
The question I have for you, Dr. Ratko, specifically is why does your methodology not allow for the use of FDA PMA submissions, which are possibly the

best and most peer reviewed submissions that we have in the public domain?
DR. RATKO: We did use an HDE submission for key question two, we just didn't consider the PMA submissions. We felt we had adequate evidence in the peer reviewed literature.
DR. GOODMAN: Yes, Dr. Rao, and as you know, not all data submitted to the FDA for regulatory review finds its way into the peer reviewed literature, some of it does, some of it does not, and so they needed to stick to some straightforward criteria. Dr. Rao?
DR. RAO: I would say perhaps, Mr. Chairman, that the FDA submissions are possibly better than any of the peer reviewed journal publications that we have, and it would seem to me that the inclusion of the FDA data in your analysis might be helpful.
DR. GOODMAN: Thank you for your point. I will

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just add that we like peer review, and not everything that's submitted to the FDA is submitted for peer review, it's somewhat selective, but your point is well taken. And your point earlier was very well taken with regard to lack of radiographic fusion regarding adverse events.
Dr. Kirkpatrick.
DR. KIRKPATRICK: A follow-up comment to Dr. Rao, and we're friends, but we disagree on the point that the FDA submission is high quality and peer reviewed. They are absolutely high quality but they are sponsor presentations solely by the sponsor, and so that's part of the rules.
The other thing is, I heard CMS ask the question to help them understand what we think about pain from graft harvest and that sort of thing, and then a comment was made about graft harvest. Pain from the graft harvest is going to be reflected in your overall clinical score, it's going to be in the ODI, it's going to be in your DAS, it's there. Yes, if you ask specific questions about do you hurt at the graft site, patients will give you an answer that is rarely incorporated into the data, and I think our colleagues that reviewed the literature showed that.
As far as safety from a graft harvest, it also depends on whether it can be done through the same

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incision, how much added risk there is to a patient, versus a different region. For a cervical spine we usually get iliac crest harvest to put in the cervical spine. That is something that is two separate incisions. For a posterior lumbosacral spine approach we generally can get it through the same incision, that minimizes that extra risk, but it does penetrate into another area and takes the bone from another area.
The safety issues always are balanced in clinical medicine as opposed to what's safer and what do

we know. Right now we don't know what the BMP antibodies are going to do in the long run. We just heard about the database looking at cancers with BMPs, and we don't know these things. We do know that we have over 50 years of autograft bone use and we know what the safety risks are, versus the unknown risks of the BMPs.

DR. GOODMAN: Thank you very much, Dr. Kirkpatrick, points well made. I believe Dr. Satya-Murti was next.

DR. SATYA-MURTI: The submission for the FDA for approval, one of the criteria, unlike what we're doing now, was in fact a radiologic fusion or not. So what we're asked to answer here, part of it is based on what FDA indications have been, both on label and off label, although FDA can dictate largely radiographic instability

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and fusion and so on. So that's yet another point for us to remember in answering whether we stay within the indication. And when we say indication, our assessment is slightly different from what FDA indications were.

DR. GOODMAN: Thank you. At this time, it's about ten o'clock, we had a scheduled break a few minutes ago. Do we want to still take a ten or 12-minute break, panel? Yes. Let's have one question from Dr. Schwartz and then we'll take a ten or 12-minute break.

DR. SCHWARTZ: One of the things I learned from a colleague of mine in neurosurgery at Penn in working with him in the last years is that the surgical approach, anterior or posterior, can make a big difference in what you see, both in terms of results as well as complications. Did any of these studies differentiate between anterior and posterior surgical approach and report the results? I don't know what neurosurgeons might think about this, so I'm just raising the question, and I guess we can hear from our neurosurgery and orthopedic surgery people a bit later about that, but I wondered in terms of the literature review, was there any separation or separate analysis between the type of surgical approach that was done and the results?

DR. RATKO: Within the studies, the on-label use of BMP-2 for lumbar-sacral spine fusion requires an

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anterior approach, so they are broken out that way.

DR. GOODMAN: Dr. Jarvik, if it's a quick question, we'll take it.

DR. JARVIK: Well, I'm going to switch my question and follow up on what Sandy just mentioned, which gets to the issue of was the comparator state of the art, you know, and back when these were published in 2005, with just the anterior approach, would that be considered state of the art today as a comparator?

DR. GOODMAN: Am I correct, I know that your literature search ran to a certain point, and then it was updated early this year?

DR. RATKO: Correct. I can't address that question.
DR. JARVIK: Right. This is again maybe more for the panel.
DR. GOODMAN: Thank you, Dr. Ratko. I trust you won't disappear, we have time later on today to ask you further questions, but we very much appreciate the report from the EPC and appreciate how direct and clear it was. Thank you, sir.
We're going to take a 12-minute break, so take a look at your watches, add 12, and we will see you then. Thank you.
(Recess.)

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DR. GOODMAN: We're going to get started now, so if the panel could take their seats.
We're scheduled next for the so-called scheduled public comments, of which there will be five, seven minutes apiece. But before we do so, I thought it might be a good idea to, in a concise fashion, have a little recap or short discussion about a couple of issues that arose prior to the break, and one issue has to do with how this panel will regard adverse events, there was mention made of that. And there was also mention made of the approach for the procedure and whether or not basically the front approach or the posterior approach are indeed different kinds of procedures for different sorts of indications, and I want to have a brief discussion about that because it will help to have that discussion now as opposed to later.
So with regard to the adverse events, I want to ask Dr. Davis and then Dr. Baker, if they would, to briefly tell us what they think about inclusion of certain kinds of adverse events. Dr. Davis.
DR. DAVIS: I think a key question, as was brought up, the adverse events related to the iliac crest bone grafting, it's unclear to me from the initial questions that we have which say adverse events related to the use of BMPs, whether adverse events related to iliac

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crest bone grafting that's avoided with the use of BMPs, whether that's to be considered or not, and indeed, what those adverse consequences are. Not much mention is made in the technology review because it sounds like there isn't, the data is not very high quality on that, but I think that's an issue that we need to resolve, whether we're going to consider those as adverse events in our analysis of the question.
DR. GOODMAN: Thank you, well stated. I'll just remind us all that CMS has made clear that they want to hear our opinion on that, so there's no right answer as far as CMS is concerned here, but they are very interested in your views. Dr. Baker.
DR. BAKER: I would reiterate that it's

important for this panel to come to a consensus on this. I think that a lot of the data is going to rest on that iliac crest bone graft donor site pain. And if you look at other issues, for instance open tibial fractures, you have a reduction in infection rates, and that's certainly a reduction in adverse outcomes. But when you're talking about reduction in pain, we've heard two different speakers. We heard Dr. Kirkpatrick say it could actually be reflected in the ODI, but we had our health technology assessment that said there was an improvement in outcomes by reduction in donor

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site pain. So what we're really seeing is two different answers to that same question, and I think that we really need as a panel to come to some sort of consensus.

DR. GOODMAN: Dr. Kirkpatrick, let me pick on you for a moment. You were quite eloquent in your statement before the break. Can you give us your guidance or opinion with regard to including this aspect of iliac crest graft and so forth and how it might bear on our consideration of what comprises an adverse event?

DR. KIRKPATRICK: Fundamentally it depends on what specific indication you're looking at. For a posterolateral lumbar fusion the risks of adverse event from the iliac crest harvest are very different than they are when you're doing, as I mentioned earlier, an anterior cervical fusion. The anterior cervical and the anterior lumbar where you harvest iliac crest lead you to the risk of fracture of the iliac crest if you, you know, don't have perfect technique, and even if you do, some people are osteoporotic and they'll fracture, that's an adverse event. A separate incision to get your graft leads to a separate opportunity for an infection, that's another adverse event, so it really has to be specific to the one indication you're looking at, in my opinion.

DR. GOODMAN: The specificity with regard to indication is well taken. Let me posit that CMS does care

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about the health and wellbeing of its Medicare beneficiaries and if we think that an adverse event of any type can be avoided or diminished through the interventions we have been discussing, I would think that should be on the table. Now that may be measured in different ways, but we do care about the adverse events that may affect the Medicare beneficiaries whether they get them one way or another with regard to managing this indication.

DR. KIRKPATRICK: Let me follow up with that. CMS also asks frequently black-and-white questions in a world that's very gray. For example when we're asked to, and later I was going to comment, that I think it's great that we asked to look at some quality adjusted life year analysis and things like that, because we weren't able to even bring up dollars in this forum before, so that's a

great enhancement because, just as we look at adverse events between BMPs and iliac crest harvest, we don't know what some of those long-term effects of BMP, if we have to go higher doses in elderly, is that going to lead to more problems, we still don't know the antibody questions. So don't talk about it as avoiding something, it's trading one set of circumstances and adverse events for another at an added cost, and I'm sorry I use that, but we were able to open that door when we saw the quality of life year

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analysis that was presented. So again, it's not black and white.

DR. GOODMAN: Fair enough, and the reason they asked this panel to meet is to get beyond the black and white to some more subtle aspects from time to time. With regard to this matter of the iliac crest harvest, is there any member of the panel that would be opposed to including that with regard to how it may affect adverse events or our definition, does anybody want to keep that outside the tent or beyond the boundary of what we care about with regard to adverse events? All right, that helps.

Any other comments about what is in or out for adverse events? Dr. Davis.

DR. DAVIS: My question is not directly related to that, but I wonder, and perhaps I missed this, but maybe Dr. Ratko could comment on the technology assessment, the data regarding adverse events from iliac crest bone grafting. I don't know that that came through clearly to me in the presentation.

DR. GOODMAN: That's a fair enough point. Dr. Ratko, would you approach the mike, please? Sorry, we always have to speak into microphones; otherwise, no one heard the tree fall in the forest. Dr. Ratko, in your technology assessment, were you able to address or

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distinguish this particular aspect when you looked at adverse events?

DR. RATKO: Well, we took a look at it separately after we got into the literature, and we did distinguish it, and we felt it was inconsistently reported and we didn't feel that the randomized trials provided sufficient evidence to adequately assess the autograft harvest site.

DR. GOODMAN: So you're saying you looked for it but found little evidence about it?

DR. RATKO: Yes.

DR. GOODMAN: Okay. Well, the fact that you looked for it and found little evidence is relevant, because we have to talk about adequacy of evidence and we're going to talk about that. Dr. Jarvik.

DR. JARVIK: I just have a follow-up for that, and it's this sort of seeming disconnect between the general health-related quality of measures, the ODI and

patient satisfaction measures that you put up there in the evidence tables, and this issue of donor site pain, and why do you think there is this disconnect? Because, one, it's not reported consistently and hard to assess, but in those cases where it was perhaps reported better but not reflected in these other measures, how should we weight the relative importance on patient outcomes?

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DR. RATKO: I'm not really sure how we go about weighting this. We just felt that it was inconsistent and we were unable to connect it to the outcomes. We looked at it separately.

DR. GOODMAN: I'll remind the panel that the way the questions are typically worded, if there's not adequate evidence to make a judgment one way or another, we typically stop there with regard to coming in with an answer about whether something is truly beneficial or harmful, so if there's little evidence, we just don't have much to go on. Dr. Bozic is next.

DR. BOZIC: The points are well taken about incorporating the iliac crest donor site morbidity into adverse events, but I'm not sure which key question will allow us to address that, because the question that specifically deals with harms or adverse events is question seven, and it talks about the evidence of adverse events with on-label and off-label use of BMP, and it doesn't talk about the alternatives. There's another question --

DR. GOODMAN: Dr. Bozic, let me just interrupt you, I'm sorry, before you go on. The three types of health outcomes about which we care are pain, patient function and adverse events, and so in a question that asked about impact on an outcome, adverse events would

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fall under that, so I believe it's still within our boundary on the table.

DR. BOZIC: Okay. Because the questions say what's the evidence supporting improved outcomes, so you're saying that we would incorporate an adverse event into the improved outcome question.

DR. GOODMAN: Well, when you're referring to CMS's questions that we have before us today, they say for all voting questions, the clinically meaningful health outcomes of interest for CMS are pain, patient function and adverse events.

DR. BOZIC: Okay. Each of the key questions has a different parameter, some of them say what's the evidence for improved outcomes, others say what's the evidence for improved effectiveness, others are nonspecific, and others say what is the evidence for adverse events. So I was assuming those were general framers, and each question asks for a different outcome issue.

DR. GOODMAN: Where the question is specific

about an outcome we can address that specific outcome, but one way or another, let's make sure what is on our table, and before our day is done, that CMS has heard what you have to say about impact of adverse events. Dr. Baker.
DR. BAKER: You know, I guess I would challenge
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Dr. Ratko on the idea that there's insufficient evidence. You'd clearly say that there is insufficient evidence when you're looking at BMP alone, but then when you're looking at clinical outcomes you're saying that there's an improvement in clinical outcomes by reduction in donor site pain. So you seem to be saying two different things, I guess. You're saying that when you were looking at the body of evidence, the fusion rates, the ODI and other things didn't change, but yet, by reducing donor site pain you felt it was clinically improved.
DR. RATKO: Well, it's a balance and we kind of looked at it that way, benefits and harms.
DR. GOODMAN: Okay. We're still on the matter of adverse events and want to wrap it up pretty soon. Dr. Schwartz.
DR. SCHWARTZ: I just want to clarify something that was raised later, and I just underscore that in this particular case that when we're talking about pain, we're talking about pain in the donor as well as the recipient, and that's true for adverse events too. So the question is what we need to consider if there would be a reduction in adverse events in somebody who donates marrow as the alternative.
DR. GOODMAN: Well, let me look at our CMS colleagues. We're looking at the impact of the BMPs on
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these outcomes. Any guidance with regard to donors for comparator? Dr. Baker.
DR. BAKER: I think he meant donor site.
DR. SCHWARTZ: Right.
DR. BAKER: And the allograft, if you're talking about that, are catameric or from another source, so I don't think you're literally taking allografts into consideration, and autografts are the same patient.
DR. GOODMAN: Understood, but that site of pain is still relevant to our Medicare beneficiaries, correct? Okay. Dr. Davis.
DR. DAVIS: Again, Dr. Ratko, I'm still not clear on this question of the iliac crest bone graft and the adverse events because you say there's not sufficient evidence. But for question one the conclusion, again, says that the evidence is moderate to support the clinical benefit from the use of recombinant BMP-2 where patients can avoid the additional procedure of autograft bone harvest and its associated adverse events. So it's unclear to me how the conclusion can give support to the use of BMPs because of fewer adverse events but there's no data, so I guess I still remain unclear on the answer to

that question.
DR. RATKO: Well, the outcomes, the clinical benefits clearly suggest that the BMP-2 is effective. We
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did look at the iliac crest events where they were reported and took them in the balance, so if you could avoid that second procedure in the face of what looks like similar or improved outcomes, we felt that that should be taken into account in that situation.
DR. GOODMAN: Okay. Any further comments on this issue? Dr. Kim.
DR. KIM: It seems that we're looking at sort of two different paradigms within the pain domain, one is using the ODI, leg pain is more a therapeutic intent for the spinal surgery. The second would be within that domain then, there is adequate evidence for comparison of BMPs versus the EMG. The second piece with the iliac crest pain is, we're considering that in AE, but at a patient level they're experiencing pain from either therapeutic failure or an adverse event, and I think that may be where we're maybe having a disconnect, trying to get them all under one tent. Obviously patients who are not getting the iliac bone crest are not at risk for that event, so I think that's where we're struggling.
DR. GOODMAN: Well, that's all right, and clinical care is complicated. I haven't heard anything yet that would suggest that any of the types of adverse events we've discussed are outside our realm of consideration. Dr. Juhn, a final comment on this?
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DR. JUHN: It's really a question perhaps from the technology assessor, but also from the researchers that we have on the panel, which is, the ODI, would the ODI also capture enough functional deficit because of adverse events at the donor site, would that actually be captured within the ODI score?
DR. GOODMAN: Dr. Kirkpatrick, didn't you address that earlier, your view on that? I thought you did.
DR. KIRKPATRICK: I think in general it would get back to the specific indications. The ODI clearly would capture somebody that has iliac crest pain from a posterior harvest or a posterolateral fusion. It would also typically give a patient that had an anterior iliac crest harvest or an anterior lumbar fusion, but when you're looking at a cervical fusion and you have an iliac crest bone graft, an ODI would not detect that, and neither would the NDI. That would be a separately evaluated process which hasn't occurred and is not relevant according to the literature.
DR. GOODMAN: Point well made. Dr. Baker.
DR. BAKER: When you're looking at the clinically meaningful outcomes, you're looking at pain function, and so in this case pain from a research

standpoint is probably going to be taking into
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consideration the pain from the procedure and not pain from the bone graft, and in most cases I think we're probably going to be looking at a more specific view of the VAS.
DR. GOODMAN: Okay. Dr. Satya-Murti, and then we'll move on.
DR. SATYA-MURTI: I have a question less for the presenters and more for the orthopods on our panel. The indications for these fusions are also diverse. We haven't heard about that. Some of our presenters will probably talk about scoliosis and instability, but that is also a heterogeneous indication. Some are failed surgeries, some are previous surgeries, and some are clearly congenital, and some are scoliosis. So I just wonder how much dilution there is in assessing pain when the indication for the fusion itself tends to be multiple and it's not a single monolithic indication, so that has always concerned me.
And the other minor concern is from, in my day iliac crest graft was a common source and we didn't hear so much about our patients coming back with pain, maybe because there were fewer alternatives to complain about. And then came the hardware and then now the BMP, so I just wonder if iliac pain is becoming amplified now as a reflection of the times.
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DR. GOODMAN: Any direct -- Ms. Kendig, on that?
MS. KENDIG: Regarding the pain question, I think that the point was well made regarding what we're looking at from a research perspective. I wonder from a patient perspective, when we look at outcomes in terms of pain and functionality, I do think that those are important, and I agree with what you just said, perhaps we'll hear more about it, but I think we can't discount that patient perspective within the outcomes.
DR. GOODMAN: Okay. Acknowledging that -- Dr. Kirkpatrick, on this very point, sir?
DR. KIRKPATRICK: I just was going to ask your permission as to whether you wanted to hear about future directions, because that would answer the indication question that we just heard.
DR. GOODMAN: I think we'll pick that up in the discussion section later on, so we'll just stick with this.
So just, you will forgive me to put this back at a higher level. No one has said on this panel anything that would make me think that the types of pain or sources of pain or adverse events that have been discussed are off the table. We care about the health and wellbeing of the Medicare beneficiary, and whether the pain comes from the iliac crest harvest or something else, we care about it,
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so let's use that guidance when we look at our questions. I wanted to address the manner of approach, and I'm going to pick on Dr. Lewis for this. Dr. Lewis, before the break -- and Dr. Ratko, you can have a seat. Dr. Lewis, we did not hear much evidence from the technology assessment this morning that would differentiate between those two means of entry and the related indications, and perhaps we need to get a little more guidance for our panel about how to think about that when we appraise the body of evidence. Dr. Lewis.

DR. LEWIS: Thank you. I just want to make the point, and based on a couple of comments or questions right before the break, that we may or may not be completely on the same page. I am not a spine surgeon, I'm an orthopedic surgeon, but I'm not a spine surgeon, and so I do not perform these operations on a daily basis. But I would say that it's important for us to recognize, and I think we'll learn probably in the preparations more about this, but it's important to recognize that the different approaches, anterior versus posterior, are not interchangeable, different cohorts of patients, different indications for the surgeries that are being done, and therefore we have to be careful when we look at the information available to us not to mix and match in terms of our discussion and our deliberations.

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DR. GOODMAN: Thank you. Other comments about this point, these differences? Dr. Lewis, concerning the CMS questions that were posed to MedCAC, do we necessarily need to a priori make that decision when we answer these questions, or can we talk about them insofar as whether it's one approach or another, is there adequate evidence, whether it's one approach or another, is there effectiveness, can we approach it that way with some discussion comments to accompany our votes, or do you propose another approach?

DR. LEWIS: No, I don't necessarily propose another approach. I think the on-label studies are fairly clear. Where it talks about off-label trials, they're not always necessarily comparable in terms of the indications for the surgery, so we want to be careful not to lump those findings prematurely, I would say, from the tech assessment. That's all.

DR. GOODMAN: Okay. Ms. Darling.

MS. DARLING: This is on a slightly different subject but this last conversation has triggered my thinking. As I recall, there's relatively little data on the over 65 population, but we know more about the population that would be among the disabled in Medicare, and so I realize it would be very hard to do this, but would it be useful to think in terms of those two

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different populations for purposes of our thinking and advice, because they will be very different.

DR. GOODMAN: Right. The questions, except for question 6.A, the previous questions don't address the matter of age yet, so I don't think we need to make that distinction in the first five questions when we vote, but if you have a particular comment or observation about the relevance of evidence that may be applied to them, if you don't do it for questions one through five, certainly we need to bring it up explicitly for question 6.A. Okay. May we proceed, then, panel, with our scheduled speakers? Okay, thank you. And we have five scheduled speakers, each of whom has been allotted by CMS seven minutes. And our first is Dr. Brian Kwon, he's an associate professor in the department of orthopedics at the University of British Columbia, BC. Dr. Kwon, welcome, sir.

DR. KWON: Good morning, thank you. My name is Brian Kwon, I am a spine surgeon from the University of British Columbia in Canada, and I hope to add to this discussion by providing a clinician's perspective on the use of BMPs in spine surgery.

I should disclose that I have a consulting relationship with Medtronic, that my spouse is an employee of Medtronic, and that my travel to Baltimore was provided

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to me by Medtronic. I, however, am not receiving any consulting fees for my appearance here today.

So when Marshall Urist first identified bone morphogenetic protein in 1979 as the explanation for this very robust formation that he had reported on almost 15 years earlier, it was pretty clear to people even back then that this was a major scientific advancement, because Urist and others understood that there are millions of patients that have conditions that ultimately require bone healing, and that getting bone to heal in some of these very complex situations is oftentimes very challenging.

Now, spine surgeons were very interested in this because they had been trying to heal the spine and obtain spine fusion ever since Fred Albee first described this in September of 1911, and really in the 100 years that have followed, spine surgeons have been trying to find better ways and techniques and technologies to improve their rate of fusion of the spine. So we eventually started taking iliac crest bone grafts and laying that along the back of the spine, and then a whole new technology evolved around putting screws and rods into the spine to stabilize it and giving the bone grafts collaterally a better chance of healing, and what we're trying to achieve is this kind of radiographic fusion as seen in the model here.

Now, with all this effort being put into try to

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heal the spine to fuse, it's certainly not a surprise to anybody that spine surgeons would be very interested in a technology that could potentially facilitate this bone healing, and that of course leads us back into

utilization, and thus the technology assessment. Now you want to see very complex statistics and sophisticated health economic analyses and whatnot, but for a practicing physician the question becomes much more human, and that question literally is this. Is this 73-year-old gentleman who comes into my office going to need an operation? The question for me is what can I do to give him the best possible outcome? And if that is going to actually require a spine fusion, then I'm going to do everything in my power to achieve that spine fusion. So here's an example. This is a 69-year-old woman with an L3-4 degenerative spondylolisthesis where the L3 vertebral body has slipped forward on L4. You can contrast that with the normal spine where all the vertebral bodies line up nicely. The spinal nerve roots are in the spinal canal behind the vertebral bodies, and in a spondylolisthesis condition the nerve roots get squeezed and pinched off in the level of the spondylolisthesis, and that causes the severe leg pain. Now this, there may be some kind of ambiguity around this association between fusion and clinical

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outcome, but I can assure you that failing to achieve fusion can certainly lead to a bad outcome. This 69-year-old woman underwent three operations and at each time point the spine surgeon failed to achieve a solid fusion between L3 and 4, and you can see this progressive almost dislocation of L3 on top of L4. And when she presented to my office she was on so much morphine she could hardly stay awake, and she recalled how at nighttime if she needed to go to the bathroom, she would literally roll out of bed and crawl on her hands and knees to get to the bathroom because it was too painful to stand. And I'm very confident of the fact that the achievement of fusion in the end for this patient led to her good clinical outcome.

And this was reflected in this long-term follow-up of patients that again, like my patient, had degenerative spondylolisthesis, where they compared the patients that achieved a solid fusion, in blue, and those patients that did not achieve a solid fusion, in orange. And you can see that the patients that achieved the fusion had a higher clinical outcome, higher levels of overall satisfaction, lower levels of back pain, and lower levels of leg pain.

Tomorrow I'm going to do a decompression fusion on a patient with degenerative spondylolisthesis, and I

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don't know, I don't have my crystal ball, to know what she's going to be like two years from now, but I'm going to do my best to put her in the blue category. And I think if she saw this slide, she would also prefer to be in that blue category as well.

I think this ability to obtain fusion is

particularly important in healthy patients like mine, and that's for two particular reasons. One is that there are biological limitations of autogenous bone graft, and that there are the risks of complications associated with that graft harvest. Let's talk about the biology first. We understand that as you age, the number of bone cells that are present in an iliac crest bone graft decreases with time, as shown here on the left. Furthermore, we know the cells that are actually within that bone graft are less able to form bone as you age. This is a study demonstrating the osteogenetic potential of bone cells from ten young patients as compared to nine elderly patients. Those have a lower fusion rate when they had an iliac crest bone graft, and that was demonstrated and illustrated in Steve Glassman's randomized controlled trial of patients over the age of 60, with a mean age of 69. It showed that the patients receiving BMP-2 had a higher fusion rate, and importantly, the number of patients that needed a second operation,

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only one in the BMP group and five in the patients with iliac crest bone.

We do recognize that harvesting bone is indeed a surgical operation that is done under different indications, but in seeing that graft and as an alternative we have a technology that we can take off the shelf, pick off the back table, implant something like this in the spine, and avoid the morbidity associated with graft harvest, which includes potential pain, nerve injury, fracture, blood loss or vascular intrusion. This was really demonstrated to me in a patient I operated on in 2006, who had also a degenerative spondylolisthesis, and I took her own bone, I took her iliac crest, and she healed beautifully, and I showed you her x-rays earlier. The wound that I took the bone graft through got infected, and she needed two subsequent washouts, two returns to the operating room to get that washed out, and because of her social situation needed three months of hospitalization receiving intravenous antibiotics to eradicate that infection, so that's a real complication. And while her SF-36 scores and Oswestry scores may not actually be that different from the mean, it's clear to me that she did not have the best possible outcome in my hands.

DR. GOODMAN: Less than a minute.

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DR. KWON: So this brings us really back to the question, and the question for people like myself, how can I use the technology to maximize the chance of giving my patient the best outcome? The technology can facilitate other techniques, so we have now surgery that we're trying where we typically have made large incisions, and now we have technology to do them minimally invasively, and bone morphogenetic proteins facilitate this technology by

obviating the need to take a bone graph, and reducing the length of the incision almost as long as those incisions combined.

So in summary, I think that the potential to heal bone has many applications across the scientific field, that the spine surgeons are going to continue to try to facilitate bony fusion, and I think there are many occasions where we take that achievement as a challenge. I certainly don't think we have all the answers yet for BMP, but I think that sound scientific evaluation will allow implementation of this technological innovation that will benefit our patients.

DR. GOODMAN: Thank you very much, Dr. Kwon, we appreciate your input. Thank you for coming down from B.C., it's a beautiful place.

Next is Dr. Patrick Jacob, who's the Dunspaugh-Dalton Chair, Cranial and Spine Surgery,

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Department of Surgery at the University of Florida, and from what I'm reading here, he's representing the American Association of Neurological Surgeons and Congress of Neurological Surgeons. Welcome, Dr. Jacob.

DR. JACOB: Thank you very much for the opportunity to present this morning. By way of disclosures, I have no conflict with BMP. I am a consultant to a manufacturer of spinal implants and representing AANS and CNS. It's a slightly different slide approach, but basically we congratulate the authors of the technology assessment. We feel it was a fair and balanced approach to the presentation of the data and review of the information at hand.

We feel that as indicated, that the use of BMP in the anterior lumbar spine is appropriate, reasonable, and supported by the literature. We feel that the routine use of BMP in the anterior cervical spine is probably not reasonable and there is probably not support in the literature for that technique.

Some of the things that were not brought out in the technology assessment perhaps identify areas that we would like to focus on, and those are the high risk patients, patients who are end stage renal disease, are on disease-modifying drugs for their rheumatoid problems, and things of that sort, smokers, osteoporotic patients.

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Although the literature does not specifically address this, we feel that these are areas of great interest and need from a clinical standpoint, and what we can do as clinicians, as the prior presenter just mentioned, that what we can do to get our best possible outcome is, these areas are something that as neurosurgeons and spine surgeons, we are keenly interested in. These admittedly have not been well studied in the IMEs and we cannot present compelling evidence. However, clinically and empirically we believe that there is opportunity here for

improved outcome.
There has been some discussion about how spine fusions are done, and I thought briefly for some panel members or members of the audience to just look at the anatomy for a moment or two. This would represent an anterior lumbar interbody fusion; it's done through an abdominal incision where a bone graft is placed into the disc space, and here you can see it pre and post-op. This would be the titanium fusion cage which is mentioned in the assessment, and you can see the postoperative view where the cage is in place in the interbody space. Other techniques can be used for that same approach, but that gives you a reasonable idea of the anterior lumbar approach.
The posterior lumbar approach for lumbosacral

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fusions are primarily either a facet fusion where the facet joint would be included into the fusion, or an intertransverse fusion where the red indicates the fusion substrate, be it bone or BMP, being added to the spine in order to help immobilize that segment.
The posterior lumbar interbody fusion is exactly as it says. Bone graft would be placed into the intervertebral space through a posterior or posterolateral approach, fusing anteriorly from the posterior, if you will.
So in sort of the current uses of BMP, we agree with the data that suggests that the anterior lumbar interbody fusion cage has good evidence in the literature, the fusion rates are at least equivalent if not better, and we decrease bone harvest morbidity. The posterolateral fusion techniques as seen, these are by far the most frequently performed uses of BMP. There are randomized and nonrandomized studies supporting the use, demonstrating superior or at least equivalent radiographic outcomes, and some data supporting the reportable outcomes in terms of reduced pain or perhaps avoidance of pain as outcome measures.
In terms of whether or not this should be used as a primary alternative to bone graft, obviously we don't have the compelling literature at this time in terms of

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quality adjusted years and cost effectiveness, and we think this is an opportunity for further investigation.
But when we look at the growing off-label uses, we see patients who perhaps have had prior bone graft harvest and there is physically inadequate volume of bone. We feel those represent a great patient population for this technology, or patients who are osteoporotic, renal failure, or some other problem that would inhibit bone formation.
The routine use of BMP in anterior cervical spine is not, in our opinion, an appropriate use of this technology. We believe that in very low frequency

operations, the three or four-level anterior fusion, because they have a very high nonunion rate, and if we believe that a nonunion or a failed procedure is an adverse outcome, then in these extremely uncommon procedures it may be a reasonable alternative to consider between the doctor and patient to use these, even though there are increased risks of complications such as soft tissue swelling and that sort of thing. If we know we have a higher nonunion rate and this can eliminate that, it may be a consideration in those highly selected cases. Again, the comorbidities of osteoporosis, smoking, which you know, is a major problem we deal with every day, that sort of thing.

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Additional studies, we're dealing with the cost effectiveness of this technology, It's extraordinarily expensive, and how we justify this to the hospital and to the patient and to the nation is I think a major issue. I want to go through very briefly some of the -- no, I think we've covered that. One major point that I would like to make is the cervical spine is not all the same thing. The posterior cervical spine, if you were to use these in posterior cervical applications, is probably more anatomically and physiologically akin to the thoracolumbar spine. The issues of soft tissue swelling and airway compromise are not going to be present in that region of the spine because they're not anatomically proximate to the BMP. So in your considerations for this, I would ask you to separate anterior versus posterior cervical spine. In terms of the use for revisions, I would also remember that the alternative options, if a patient has had a failed lumbar fusion using iliac crest bone graft, to repeat that same failed experiment probably is not the right thing to do for that patient, and the use of BMP technology where we do have improved fusion rates I think offers an advantage in terms of outcomes to that patient.

DR. GOODMAN: One minute, Dr. Jacob.

DR. JACOB: Thank you. The cervical spine

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application, as I said, anterior and posterior are very different. In terms of can we generalize this to the Medicare population, I think the Medicare population was represented in these studies, and although specific age was not a specific variable, I think certainly the representation of that age group within the studies makes a statement about application. In terms of the community-based setting, I think this is something that is applicable to virtually every hospital in America where these procedures are performed. And in terms of future investigations, we're very interested in the primary use of this versus autograft for cost effectiveness, we're interested in

determining the dose response, how much BMP is necessary per level per patient, does it vary with age, does it vary with bone density, those types of things. And exactly which of these disease processes put the patient at highest risk for nonunion or adverse event where BMP is justified, I think is a very legitimate area for further investigation.

I thank you for your time and attention.

DR. GOODMAN: Thank you very much, Dr. Jacob, and thank you in particular for providing information that's directly relevant to our questions. We appreciate

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that.

Next is Dr. Richard Kuntz, who is the senior vice president of strategy and scientific operations for Medtronic. Welcome, Dr. Kuntz.

DR. KUNTZ: Thank you, and good morning. My name's Rick Kuntz, I'm the chief scientific clinical officer at Medtronic, and I appreciate the opportunity to present the ongoing evidence demonstrating the clinical effectiveness of BMP-2.

I want to make three points in this presentation. First, BMP-2 is a unique clinical innovation that eliminates the need for autograft associated with the harvest procedure that we were just discussing. Second, Medtronic has supported and will continue to support significant research efforts to strengthen the evidence of BMP and its use. And third, there's a growing and well established basis for current and working evidence to support positive conclusions, we think, on the voting questions that you have going forward.

BMP-2 has received premarket approvals for anterior lumbar interbody fashion both in tibial fractures and certain oral maxillofacial applications. With the common goal of achieving solid bone growth, BMP-2 is used in association with distinct clinical benefits, including

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reduced blood loss, shorter operative time, improved bone healing.

Here is another paper that combined outputs of four independent studies that focused on this issue we talked about with harvest pain. Essentially what I want to show is that there is a correlation, at least in these studies, with sustained pain over time with the amount that's removed from the iliac crest, so the highest graphs are those associated with continued pain where there's a lot of volume taken out for posterolateral procedures, a moderate amount in the anterior procedures, and a lower amount in the cervical has been correlated in this overlay with pain that can sustain out to a couple years.

Medtronic continues to make significant investments to grow the body of evidence, to benefit further indications, and to enhance our understanding of

BMP-2's long-term outcomes. Each of the three currently approved indications are supported by robust evidence, and we have moved forward with a significant investment in our clinical trial program to support FDA approval of BMP-2 in multiple indications, specifically posterolateral lumbar fusion and anterior cervical fusion.

This is just a slide to demonstrate something we learned earlier. There is peer reviewed literature out there, and we saw the 41 that were qualified by the AHRQ.

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As a company we're committed to insuring the safety of BMP-2 across all the indications. We recognize that one area of concern is to the anterior cervical spine surgery where there's a small percentage of use, approximately nine percent currently, of all Medicare cervical fusions in 2008. Medtronic began proactively addressing these concerns in 2004 when we took early and voluntary action working with the FDA to provide a dear doctor letter demonstrating the concerns about evidence that was raised in the literature.

We recently completed enrollment in a pivotal IDE study which will address this more fully and formally in a randomized control study, and the one or two-year follow-up is starting at this point and we will have that data soon, in one or two years.

Here's a graph of the outcomes of the Medtronic regulatory studies where we compared the healing rates that we talked about earlier, with radiographic fusion. And this is an issue that I think we can see in your discussions, that show using that definition, equivalent or better fusion rates compared to iliac crest.

As Dr. Kwon pointed out earlier, Dr. Kornblum's study demonstrated that patients with autograft who achieved solid fusion did have reduced back and leg pain compared to those with failed fusion, so there are a few

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studies that have more specifically, when defined by radiographic fusion, are they associated with clinical outcomes that are different, and this study is one of them. So therefore, achieving the solid fusion is an important clinical outcome from our perspective.

In the following slide we provide information of clinical interest related to each of the indications of MedCAC interest. The AHRQ TA discussion earlier this morning included a two-year randomized trial by Dr. Burkus, evaluating BMP-2 against bone graft in lumbar fusion. That study demonstrated that patients receiving BMP-2 reported statistically significant improvements in patient functioning and pain from post and preoperative status. This initial cohort has now been reported and followed out to six years with a sustained benefit.

BMP-2 also improved outcomes in treatment of open tibial fractures, which is a challenging patient to treat. We talked about the BESTT study earlier, which

demonstrated improvements, and we -- I've got these out of order.
Anyway, essentially we showed that most importantly, there was reduction in second surgeries and in those patients who had the worst fractures, there was some reduction in the infection rate overall, demonstrating at least some value of this device used for
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fusion.
Although we're not going to talk about this because of time, we did provide you some evidence for maxillofacial as well.
DR. GOODMAN: Dr. Kuntz, you've got less than two minutes. You may want to go to your most important points.
DR. KUNTZ: Okay. We previously discussed our clinical development program for evidence on spine. AMPLIFY is a new formulation, a new carrier for BMP-2, and we published these results. It was the subject of a panel review recently by the FDA where they voted in favor of approval pending the FDA's decision, and this shows a superior fusion rate compared to iliac crest, including a 50 percent reduction in second surgeries.
Dr. Glassman's randomized study of patients over the age of 60 with a median of 69, were a study of patients in the real world with multilevel disc degeneration, including multiple comorbidities. It demonstrated that these rates were higher than those in BMP-2, it was a very important study, and he found fewer secondary procedures and complications overall.
So, to review, the PLF data has been published and reviewed by the FDA. The ACDF study, we have completed an enrollment. Several clinically initiated
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studies continue. Our forum to develop evidence to support ten more potential PMA applications is underway, and three IDEs have already been approved by the Food and Drug Administration, while five are in the current design phase going forward, so we have a very serious and comprehensive effort to continue to study all the applications that have been talked about today.
This is my last slide. In summary, the evidence supports positive and durable health outcomes for BMP-2 across multiple clinical applications. BMP-2 patients report improved patient function, a decrease in pain with global adverse events in many studies. The evidence also supports that these benefits apply to the Medicare population, especially with respect to Dr. Glassman's study.
I won't read this slide for time, but thank you very much. My colleagues and I would be happy to answer any questions you may have.
DR. GOODMAN: Great, thank you very much, Dr. Kuntz, and we do appreciate especially your summary

slide, which consolidated your earlier observations. Thank you very much, sir. Next is Dr. William De Long, Jr., who is the chief of orthopedic surgery for St. Luke's Hospital & Health Network in Bethlehem, Pennsylvania. It is noted

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here that he represents the American Academy of Orthopedic Surgeons. Welcome, Dr. De Long.

DR. DE LONG: Thank you very much, Mr. Chairman. Today I'm here representing the American Academy of Orthopedic Surgery. I am an orthopedic traumatologist, not a spine surgeon; however, I do treat spine fractures. I'm going to skip over the material that was covered already this morning and just go to extremities. In order to get the fractures to heal we need several elements, the responding cells that form bone matrix, and bioactive factors, this is clear. Something here in this element actually makes autogenous bone graft work, but we really don't know why it works, no one has really figured that out. It's the gold standard, except it's unstudied. TGF beta, a super family of growth-enhancing molecules, really helps promote bone healing by changing the milieu for the cells. There are two available applications at the present time, as we've discussed this morning. Marshall Urist was a candidate for a Nobel Prize when he discovered BMP back in the '60s. He eventually isolated BMP and started treating humans with nonunions and delayed healing of the long bones. BMPs are, for BMP-2 we're talking about use in open fractures. BMP-7, the application is for nonunions.

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There are other BMPs being studied, there are 20 in all today, tomorrow there may be 24, who knows? The way this works is the mesenchymal stem cell is stimulated to differentiate, and also, a chemotaxis brings the stem cell to the area of need in the region of the surgery. You know, how does autograft work? Is it the stem cells that are transferred with it? Is it growth factors that are located in the bone that's transferred? Is it the conductive property that applies? Or is it another substance that we don't know about? I don't really know the answer to that question and I don't think anybody really does, and we don't have any safety data on autograft bone either. I just know that it's been valuable over the years. BMPs exert their influence on the cell surface and they actually trigger downstream molecular events that up or down regulate cell function. We can see here in this table from left to right increasing potency. The BMPs are far and away above everything else that we use in potency, except for stem cells. The Govender study has been talked about this morning. This is a large study that was controlled,

looking at open fractures. The outcomes showed that there was a decreased infection rate in the severe group. III-A and III-B fractures, which generally have a very high

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infection rate, close to 50 percent. It also provides faster fracture healing and fewer hardware failures, which just means that the fractures healed before the metal fatigued and reached the ultimate yield. Faster wound healing was also established in the patients with BMP. In terms of what the Journal of Bone and Joint Surgery considers level of evidence, this is Level I evidence, this is a controlled prospective study with strong statistical support.

Another group studied the use of BMP-2 in bone defects, which, this is really a very difficult problem in bone surgery. When we get cortical bone defects a centimeter or greater, we have a very difficult time getting them to heal. They found that they had improved healing in the BMP group versus the auto group, and there was less blood loss, and there was an improvement in SFMA scores compared to the autologous bone. The conclusion from this study was that the recombinant BMP-2 allograft was safe and effective as a treatment for significant bone defects, and this was considered Level II evidence by the measures in the Journal of Bone and Joint Surgery.

BMP-7 was studied for its effectiveness in nonunions. The Friedlander study showed that the allograft and the autograft were very close but the, or the BMP was just slightly below effectiveness, about 81

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percent compared to 85 percent, and part of this was actually the addition of orthogonal views, healing in three views was required, and clinically a lot of those patients in the BMP group were healed because they could walk painlessly.

DR. GOODMAN: Doctor, about a minute left, so you may want to go to your summary slides.

DR. DE LONG: There are several studies that show that currently off-label use is providing some positive effects in treatment of nonunions and open fractures in other areas, and I will just go to the summary.

In actuality, any use of BMP for things other than open fractures of the tibia and BMP-7 for nonunions are considered off label, that's really clearcut, but there are many studies that support BMPs in the upper and lower extremities, and show relative effectiveness compared to autograft.

Only one study provides Level I evidence, and the Level II evidence in the bone defects is very compelling and very important.

We have a whole host of problems in the Medicare population facing us, we currently have an epidemic in peri-prosthetic fractures. A large portion of these are

open fractures, not high energy fractures, but nonetheless
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they're going to need treatment. You've already heard today, you've heard testimony that as we get older, the stem cells and iliac crest actually become less effective, and I think the BMPs are going to provide an effective way of treating Medicare recipients that fall into this category.
Thank you very much.
DR. GOODMAN: Thank you very much, Dr. De Long, and we appreciate your condensing what I believe were 37 slides into seven minutes, and thank you for that selectivity, I think some would call it. Thank you, sir.
Next is Dr. Christopher Bono. He's the chair of the professional, economic and regulatory committee of NASS, which is the North American Spine Society, associate professor of orthopedic surgery at Harvard, Orthopedic Spine Services at Brigham and Women's. Thank you, sir.
DR. BONO: Thank you very much, and as far as disclosures besides the association with NASS, in the distant past I was involved in a Medtronic-supported study group and I did disclose that on the form.
We're going to skip these slides. We tried to organize it as far as what the societies presented to try to find some common ground, so you'll see a lot of these different slides about orientation, orientation of the way we do fusions, so leading up to this meeting we did try to
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find some common ground between the AANS, AAOS and NASS. You've seen these slides about areas of agreement, about high risk patients being an exception, and these other areas of agreement about the quality of the AHRQ assessment, and other various things about the quality of BMP-2 literature versus BMP-7.
My job here in representing the North American Spine Society is to demonstrate why NASS supports these statements. Basically it's rooted in evidence and supported by the literature that's available. The goal of this presentation is to make this position clear.
The evidence is from multiple RCTs and some of them are high quality, some of them are not such high quality. You've seen this exhaustively before so I'm not going to belabor the details of the studies. We know what the anterior lumbar literature is, we know that there are two RCTs, one's a larger series, this is the smaller series by Boden and this is the one by Burkus that does demonstrate higher fusion rates, and we've belabored this over and over already so far.
As far as the data about anterior cervical surgery, we do see some efficacy as far as fusion rates, but the problem is the equivalency of the clinical outcomes and also of the complications, specifically of dysphagia.
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This is probably the biggest target of this panel advisory committee because it constitutes most of the use, or most of the use of BMP in the spine, and this is off-label use with posterolateral lumbar, and we've seen this data as well, this one by John Dimar, in which there was a prospective randomized control trial. But importantly, to answer the questions proposed by the panel, the clinical outcomes were similar despite different fusion rates with slightly higher fusion rates in the BMP group.

Looking at this additional study by Kanayama, which again was a PRCT, not a lot of patients, just nine in one group and ten in the other, with about comparable fusion rates radiographically, and more different with surgical exploration.

And finally the study by Vaccaro, which was BMP-7 OP-1 in which clinical success was defined very specifically, and fusion rates were found to be higher in the OP-1 group, but clinical outcomes were not that different.

Then finally another study by Boden demonstrating pretty much the same thing, but fusion rates being higher in the BMP group, but with only one-level fusions.

Specifically looking at a different indication,

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which is isthmic spondylolisthesis, so we thought we heard about the indication making a difference. This was a very small study comparing ten patients with OP-1 to ten patients with iliac crest, and the fusion rates were no different.

And then this study by Glassman specifically addressing the over 60 years of age population in which clinical outcomes are improved in both groups, but the additional surgery appeared to be more frequent in the iliac crest group.

This is an indication I just want to shed some attention to, which is PLIF and TLIF, so this is interbody fusion performed through a posterior approach which currently is perhaps more controversial than posterolateral because there are no RCTs. It's commonly used with minimally invasive techniques but there have been a number of complications reported, such as radiculopathy, increased radiculopathy rates with BMP use, as well as bone formation, heterotopic bone formation in the spinal canal around the nerves.

For posterior cervical there is not a lot of data there. Perhaps we can extrapolate the data from posterior lumbar, but with this paucity of data we really don't have anything definitive to say.

This is perhaps the most judicious use of BMP,

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it's a higher risk patient, a patient who is a redo, redo, redo, as my mentor Steve Berken would say, in which we're

trying to get something to heal which didn't heal the first, second or third time around. But this is difficult to study and we're never going to have a big RCT or even a high number of case series with this particular indication.
In summary, based on the data, we stand by the position that anterior lumbar interbody fusion has reasonable evidence for its use and that BMP-2 appears to be equivalent to autograft. In the posterolateral lumbar spine it might work as well, it seems to work as well, maybe slightly different, clinical outcomes appear to be equivalent, and the evidence is with BMP-2.
As far as anterior cervical, there is already a very high fusion rate with autograft or even allograft for a one or two-level procedure, so the question of what the use would be clinically for BMP-2 outside of the efficacy or the complication rate, that is still in issue.
As far as posterior cervical, we really have limited or no data.
And for TLIF and PLIF, which is this halfway in between an anterior and posterior procedure, we have no data, we need data if this is going to be a frequent use of the device, and complications have been reported thus

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far.
Thank you very much.
DR. GOODMAN: Thank you very much, Dr. Bono, and we do take note and appreciate that I think you're one of the few presenters who mentioned it, but there was a half dozen professional medical societies who have put their heads together with regard to these issues and looked at the evidence, and thank you very much for taking part in that.
In addition to our five scheduled speakers, CMS provides for nonscheduled speakers to sign in at the beginning of the day, and I do see that one person has signed up and there will be time for him to approach, I believe the floor mike here, and I believe we only allow one minute typically for these, or is there two this time? They're very generous this time, sir, and you have two minutes, 120 seconds, so how about that?
This is Jeffrey Ziegler, who's a consultant with MCRA, and will you please let everyone know about MCRA, what that is?
MR. ZIEGLER: Thank you. As the chairman mentioned, my name is Jeffrey Ziegler. I serve as reimbursement manager for Musculoskeletal Clinical Regulatory Advisers. MCRA is a Washington, D.C.-based consultancy providing counsel generally to the medical

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technology and investor communities.
Following the Agency's announcement of this meeting, MCRA undertook a small literature review of the published evidence on the on-label and the off-label use

of rhBMP-7 or OP-1 specifically. We do not represent the manufacturer, Stryker Biotech, but we did this review as an interested third party in the subject matter.
Qualities of BMP-2 have been well covered during this meeting. We would urge the panel to consider the following regarding BMP-7.
First, BMP-7 has a very strong safety profile as reported by the animal as well as human clinical data. As we heard earlier, for long bone nonunion indications and in a putty or the revision spine PLF indications, they are each supported by a number of scientific articles offering good support for its continued use and coverage by the Medicare program. MCRA identified 35 published sources in peer reviewed journals from case series randomized control clinical trials to meta-analyses on this topic. We heard earlier that there were a total of 42 for BMP-7, and we believe that the full body of evidence includes these 30 or 35 more complete sources specifically for long bone nonunion indications. As we heard before, studies found that OP-1 increased or improved upon healing rate of those long bone fractures in recalcitrant patient populations on

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label.
Autograft was mentioned a lot today and it is my pleasure to provide the panel a little bit more incident rates of autograft complications. A study by White, excuse me, by Oakley in 2007 found minor complications, including the pain that we have been discussing, as well as other neuropalsy issues has an incidence of 10 to 39 percent, and the more severe complications, including severe nerve damage, occurs up to ten percent of the time when iliac crest is harvested.
Friedlander in 2001 found OP-1 to be equivalent to autograft in clinical success criteria, with none of the autograft-related adverse events associated with those autograft patients. And I think also in 2007, White and colleagues noted that the OP-1 group in the Friedlander study was actually composed mostly of smokers, and were highly at risk for some arthrosis, which as you can tell, they did very well compared to the autograft group.
For spine fusion indications, we found those articles were off label, in fact all were off label.
However, these are typical RCTs to enroll patients into, and therefore, the best approach were the studies that attempt to find those patients who are also high at risk patients for pseudarthrosis. Fairlane in 2007 found those two groups of patients with connective tissue disorders

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and other issues that would affect healing. Despite the setbacks, these patients still saw an 80 percent success rate.
DR. GOODMAN: You might want to wrap up, Mr. Ziegler.
MR. ZIEGLER: Absolutely. So thanks very much

for your time. I would encourage MedCAC and CMS to support the future use of this technology through its coverage pathway now, and in the event that it finds inadequate evidence for OP-1, we would encourage them to utilize the coverage through evidence development mechanisms. Thank you very much.

DR. GOODMAN: Thank you, Mr. Ziegler.

All right then. Panel, we've heard from, in addition to our presenters earlier this morning before the break, including the TA, we've heard from five scheduled speakers and one nonscheduled speaker this morning. And what we're supposed to do at this point is to have our discussion, our initial discussion as a panel, and we typically do that by starting with any questions that you may have for the presenters. And so the presenters would include, starting with Dr. Glowacki this morning, and the TA from Dr. Ratko, the five presenters and the one unscheduled. If we have specific questions for them, I hope that all of those speakers will, A, stay in the

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vicinity, and B, not speak until you come to the microphone. Otherwise, your various information will be lost.

When we do this, panel, I'd also suggest that when we ask these questions, let's try to keep in mind that we're after, most of all, information that will help us answer our questions. So, there are so many issues that have come up today that we could address that would be of great interest to many, but we've got to come down and answer those seven questions by the end of the day, and let's use our time as best as possible.

Dr. Satya-Murti, did you want to start, or have a comment?

DR. SATYA-MURTI: Yes. This is for Dr. Glowacki and any of the others.

We've heard of this compromised patient, let's say from smoking --

DR. GOODMAN: When you hear your name, please come up to the front of the room and I think that -- sorry for interrupting, Dr. Satya-Murti, I apologize. I think it would help if the people who have spoken today came up to these seats in the front of the room, so it might be a lot better. So Dr. Ratko, and the five scheduled speakers, that way we can find you faster, and I thank our court reporter for reminding us of the reason why those seats were reserved. I apologize, Dr. Satya-Murti, back

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to you.

DR. SATYA-MURTI: No problem. Getting back into the question, so smoking and osteoporosis are deterrents for good healing with an autograft, so do we know if BMPs specifically are superior, how do they combat the deterrents to healing, and has it been shown or are they assuming?

DR. GLOWACKI: That's one of my pet peeves, is

that all of the animal experimentation is done in young healthy growing animals, so there are no research preclinical studies that directly relate to your question.

DR. SATYA-MURTI: So these BMP cases, although they show union at first, may run into the same problems that are brought on by aging and smoking sooner or later?

DR. GLOWACKI: Well, many of those complications are shown very very early in the clinical course of fracture healing or graft incorporation, so I would say that if you have early good success in a particular patient, that may be encouraging, that's not an automatic failure.

DR. SATYA-MURTI: Okay.

DR. GOODMAN: Yes, Dr. Kwon, sir.

DR. KWON: I would point out there is actually a rabbit nicotine study that showed improved fusion rates with the BMP-7 done by (inaudible), so that was a model

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where they created pseudarthrosis, they actually administered nicotine to the rabbits, and then once the pseudarthrosis was established, treated them with autograft or BMP-7, and showed that the fusion rate was in fact higher in the BMP treated group, so there is some preclinical evidence.

DR. GLOWACKI: But they didn't continue the nicotine during the healing.

DR. KWON: That is correct.

DR. GOODMAN: Thank you, Dr. Kwon, and I don't think health care reform has expanded Medicare benefits yet to rabbits, we will look for that in the next Congress, but sometimes we do look at preclinical efforts. Thank you very much.

Dr. Bozic is next, followed by Dr. Baker.

DR. BOZIC: For either Dr. Ratko or any of the clinicians who spoke this morning, so, we have a specific question we need to address about the generalizability or external validity to the population of interest here, and we've heard about there are Medicare patients who are under and over age 65. I would argue that age is probably not the most important covariate in determining clinical outcomes here, but I think what I'd like to hear from you is the populations that have been studied in these 41 articles that we looked at, how relevant is that to the

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population that we're considering and the factors that we know are important in the medical comorbidities that influence fusion success, but also the other covariates that influence pain and clinical outcomes, which include things like depression, socioeconomic status, et cetera, how do the populations under study here compare to the Medicare population specifically with respect to those factors?

DR. GOODMAN: Do we start with you, Dr. Ratko? Dr. Ratko, why don't you take that first, if you don't

mind.
DR. RATKO: We looked at Dr. Glassman's study, and we did not systematically look at any of these factors you're talking about.
DR. BOZIC: Because I would argue that age is not the magic covariate here in terms of generalizing it to the Medicare population. There are many many other comorbidities and covariates that influence outcomes that have nothing to do with age and they may be self-reported.
DR. RATKO: And we didn't systematically look at that.
DR. GOODMAN: That's very useful. Thank you for asking that question, Dr. Bozic, that will apply to question 6.A for us. Did any of the other speakers have a comment specifically on the applicability to Medicare

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patient population and taking note that Dr. Bozic's mention about whether age might be or might not be so relevant as opposed to comorbidities. Dr. De Long, sir.
DR. DE LONG: I would like to say that the data from Govender was an experiment on mostly young males, because that's the patient that suffers from the trauma disease the most, as you know, and in that setting the autograft worked as good as BMP. So if you translate that to the Medicare population, we know that you could think about things other than age, but the age specifically affects the number of stem cells that they have available in their autograft if in fact that's the element that heals when you use autograft in fusion.
Well, if the BMP works as well as autograft in the young population, that autograft is much better than autograft in the older population just because of the nature of the stem cells and the other growth factors that are available there. So we'd say that it would certainly provide an improved potential for healing in an elderly population whose natural substance wouldn't be as effective.
DR. GOODMAN: Thank you, Dr. De Long. Just to remind us, the Medicare beneficiary population does include some people that aren't 65 or over.
Dr. Baker is next.

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DR. BAKER: I have a question for Dr. Kwon, and that is that both you and Dr. Kuntz mentioned the Kornblum study as showing a relationship between the pseudarthrosis and pain in outcomes. But yet the Resnick study in the Journal of Neurosurgery in 2005 would show that that outcome doesn't exist, and we've heard other presenters say that there is very little relationship between the pseudarthrosis and clinical outcomes, so how do you connect those two?
DR. GOODMAN: This is Dr. Kwon.
DR. KWON: I think that that question is to some extent hard to reply to, and it's complicated. I think

that the association between fusion and long-term outcome, the mere fact that the Kornblum study is sort of something we really hang our hats on is a reflection of the fact that there aren't a lot of studies that generate that or establish that direct link between spontaneous solid fusion and having a good clinical outcome. I think that one of the issues is related to the heterogeneity of the population being studied. I think as a spine surgeon, the people that are getting lumbar fusions are not all the same, and that heterogeneity I think creates noise that actually does make it hard to establish that direct link between fusion outcome and clinical outcome. But certainly empirically from

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experience, seeing the patients that do need further operations because they haven't achieved a solid fusion, that, you know, when we see patients that do have pain that have a pseudarthrosis, if we really didn't believe that there was any reason for them to achieve a solid fusion, then that would actually be I think very contrary to how many of us practice spine surgery in general.

DR. GOODMAN: Dr. Baker, back to you. Did you have a follow-up to this specific question? This is Dr. Bono.

DR. BONO: Yes. I think the clarification very simply is the Resnick data didn't have, when Resnick made that statement in the guidelines, he was including most of the data with short-term outcomes, two to four years, but Kornblum did a longer-term follow-up, so the original patients that were in the Kornblum study which are in the Fishman study and the original Hergowitz OCCUR study, that do not demonstrate a correlation between fusion rate and outcome, those are the patients that were followed in the Kornblum study up to seven years, so if you follow them long enough, the pseudarthrosis may be more symptomatic.

DR. GOODMAN: And Dr. Baker, that means what with regard to your question?

DR. BAKER: Well, to me, although we're not looking at radiographic fusion as one of our clinically

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meaningful outcomes, we are dealing with pain and function, and when that graft was placed up there it showed a difference in patients with pseudarthrosis and a solid fusion in outcomes, in clinically meaningful outcomes, then that would stand in contrast with our health technology assessment, which did not really correlate a pseudarthrosis with clinically meaningful outcomes.

DR. GOODMAN: But again, the radiographic evidence in and of itself does not address our outcomes question. To the extent that you see an explicit correlation, that may be another issue.

DR. BAKER: Right.

DR. GOODMAN: And we are trying to think of pain

in our outcomes in other ways, okay. Dr. Kuntz.
DR. KUNTZ: I'd just like to address that issue from a clinical trials perspective. Addressing the issue of surrogacy is a complicated statistical process and it might be that the statistical power of looking at the radiographic fusion versus nonfusion is more powerful than that in the more quality of life endpoints of pain, and it might be an issue of power as it is in other areas. So I'm not quite sure that the lack of association means that there is no association, it may be a power issue with two different statistical sensitivities of those endpoints in
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the comparison. And because of these relatively small sample sizes overall, it would be my guess that if we had a larger sample size, we might see better correlation.
DR. GOODMAN: Thank you, although the lack of evidence does not mean that there is a finding in statistics. Yes, Dr. Baker.
DR. BAKER: The one thing I would add for the panel with regard to that, though, a number of studies do have significant reservations with tobacco usage, and even the Burkus study, I believe, had 25 percent of the study that had use of tobacco. So I think if we look at the settings a little bit more, we should be able to tease out the extent to which tobacco usage is applicable, or the use of BMP or something else.
DR. GOODMAN: Dr. McDonough.
DR. MCDONOUGH: This is a question for Dr. Ratko on something we talked about earlier on slide 38 when we were looking at the use of the OP-1 in the lumbar fusion, and this sort of illustrates the difference between the USPSTF and GRADE, a good quality GRADE study, or a good quality U.S. Preventative Services Task Force study but insufficient evidence from GRADE, and I didn't quite understand the explanation for that.
DR. RATKO: That was Vaccaro?
DR. MCDONOUGH: Yes, Vaccaro.
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DR. RATKO: So, in our consideration for GRADE a priori, we said we're going to need at least two trials, and so this was the one we had. We know it's a good study.
DR. MCDONOUGH: Okay.
DR. GOODMAN: That was the point we made earlier in the day, which is USPSTF is at least for today's purposes about single studies, GRADE is about groups of studies. Dr. Lewis is next.
DR. LEWIS: My question is for Dr. Bono if I could, please. You spoke about deliberations amongst six different professional societies with interest in this topic. My question is whether the areas of agreement you outlined in your slides constitutes a formal process and if so, what was the process behind that, number one. And number two, your last slide spoke to

indications or strength of evidence for five different spine applications; do those also represent consensus statements.

DR. BONO: To answer your first part, there was I would say very much an informal process by which we developed this agreement, this was a conference call with follow-up e-mails in order to develop this agreement slide, or these agreement slides that we had, and bullet points kept falling off the agreement slide as we went

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through the process. So this was the bare minimum of what we could agree with.

As far as the second point, that is very much not agreed upon, those are entirely from NASS.

DR. LEWIS: Thank you.

DR. SCHWARTZ: So are you going to the Middle East next?

DR. GOODMAN: Thank you, Dr. Lewis. This is an apolitical day, Dr. Schwartz. Other questions from the MedCAC panel to any of our presenters thus far? Yes, Dr. Kirkpatrick.

DR. KIRKPATRICK: Dr. Ratko, could you please help us understand what proportion of the data you saw extended beyond two years? That would help us to understand whether this fusion, nonfusion and likely follow-up is relevant to the clinical performance.

DR. RATKO: Well, we had Burkus '09, which actually came in after we submitted the draft. We had Vaccaro I think at 36-plus months. And I'm not really aware of others that go out much past 24.

DR. KIRKPATRICK: So fundamentally two articles that went beyond two years?

DR. RATKO: That's correct, if my memory serves me.

DR. KIRKPATRICK: That confirms my recollection,

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so I appreciate that. I was just looking for, was just a clarification.

DR. GOODMAN: Thank you, Dr. Ratko. Further questions?

DR. KIRKPATRICK: Yeah, a second question for Dr. Ratko. Dr. Boden's article does an excellent job of describing the exclusion criteria for their population, which if I read it, and bear with me, those using antiinflammatory drugs, steroid or nonsteroidal methotrexate, osteopenia, circulatory problems, symptomatic cardiac disease, history of cancer within five years, infection or fever, obvious, obesity, metal allergy, pharmaceutical allergy, tobacco use, anybody that has had a bone growth stimulator, and endocrine disorders. That is a very clear delineation of what their population exclusion is. I don't recall seeing exclusion criteria in several of the other articles that would be that clear so we would know what the population study was. Is that, can

you confirm or deny that?
DR. RATKO: To the best of my recollection a lot of those same criteria were applied, not necessarily that exhaustive list.
DR. KIRKPATRICK: But there were some that also include nicotine use where they excluded it, and that sort of thing.

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DR. RATKO: Correct.
DR. KIRKPATRICK: And so it's still a mixed bag, and we don't have a clear understanding of who's in the population and who's not.
DR. RATKO: I would say that's a fair conclusion.
DR. GOODMAN: A suggestion, Dr. Ratko. If you don't have it, you may want to have a hard copy of your own slides because we keep forcing you to refer to your memory for a various number of slides. I think we may have an extra copy for you with your name on it.
Dr. Kirkpatrick, in the interest of full transparency, those are very interesting questions, and I would ask you to share your opinion about what you've heard about follow-up for starters, what were you thinking?
DR. KIRKPATRICK: Well, it was an issue brought up, whether an arthrosis matters, because at two years it seems that they're similar. As a spine surgeon, I see patients at two years that have a pseudarthrosis and they're clinically doing great. They come back in three and four years and they've developed some more back pain and now maybe they've got a little bit of motion and so they've had a screw loosening, and now they need a reoperation to try and get that to fuse.

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DR. GOODMAN: So that means what for our deliberations today?
DR. KIRKPATRICK: For our deliberations we need to understand that the clinical outcome at two years may not match their outcome for their life for a Medicare recipient.
DR. GOODMAN: Thank you. And your second question had to do with all the various sort of exclusion criteria from the studies, and what might we draw from that observation?
DR. KIRKPATRICK: My Medicare population would have been excluded by Dr. Boden's study. My clinical population would not have been included in Dr. Boden's study, the Medicare patients, because all of them have at least one of those things that he excluded. And so if that's a universal criteria across the board, then I don't have good data to be able to extrapolate into the Medicare population.
DR. GOODMAN: Thank you for making those points, I hope you don't mind I questioned you on those. Those

are relevant, and I think aside from our interest in question 6.A, and B actually, we are operating in a world where effectiveness, comparative effectiveness has greater emphasis, and the kinds of questions you asked really do go into how we've been excluding people in real life from

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our clinical trials, so a point well taken that might rise when we talk about evidence gaps in the future.
I think Dr. Satya-Murti was next.
DR. SATYA-MURTI: All right, Dr. Goodman, let me see if I can convince you about the relevance of this one. Dr. Kuntz, as far as the study with some adverse effects, you said cervical swelling, but I wonder if we can draw on such data that you have in your own file that you could share. What other adverse events were noted and did these patients with cervical swelling, how did they do on follow-up?
DR. KUNTZ: Well, I think I would ask that one of my spine experts in the clinical area --
DR. GOODMAN: Dr. Kuntz, use the microphone, please.
DR. KUNTZ: I'd like to ask one of my colleagues in the spine area who may have access to that data.
DR. GOODMAN: And could you present yourself, ma'am?
DR. BARCROFT: Sure. I'm Julie Barcroft, from Medtronic. To your question about other adverse events, I think some of this came up in some of the other discussions. We have seen some other adverse events outside the cervical spine and they're all identified on the label as possible risks.

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And the second part of your question was?
DR. SATYA-MURTI: Adverse events, paucity of data was a prominent discussion point earlier, so do you have anything to share that you could that covers other adverse events that have not been published, and in particular those patients who you withdrew from those studies, how did they do?
DR. BARCROFT: Okay. Adverse events are typically followed in our trials per FDA guidelines in a very systematic formal way, right? In our cervical trial, which we've only done a pilot at this stage of the game, we have a very small pilot of 33 patients, and we didn't observe that same level of swelling that was observed post-market. We suspect that that may be somewhat related to the way the product was actually used post-market relative to our clinical trial. And as Dr. Kuntz explained, we're actually pursuing a pivotal trial now to study a more systematic approach to using the product in the cervical indication.
DR. GOODMAN: Yes, Dr. Steinbrook is next and then Dr. Schwartz.
DR. STEINBROOK: So, I think I'm following up on

the same general issue. With regard to the serious complications in cervical spine the answer may be we don't have data or it can't be shared yet, but I think it would

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be very relevant to know whether any predictors of the complications have been identified and if there are clear means to prevent them, because I know I would think differently about this in terms of the question that has to do with the cervical spine if these are totally idiosyncratic, or if there might be some learning which indicates that there are ways that they need not happen.

DR. GOODMAN: Any of our speakers care to respond to Dr. Steinbrook's question? Yes? This is Dr. Jacob.

DR. JACOB: The adverse event of cervical swelling has been reported. A number of surgeons continue to use it at a decreased dose, both in terms of concentration and absolute dose per level, although at the case report level the complication can be avoided by the administration of perioperative steroids, typically something like Epidron, which many surgeons do routinely in spine and spinal cord operations to mitigate nerve swelling, probably acting as some type of immunosuppressant, that's just guesswork, but it clinically eliminates the cervical swelling associated with that. So those two things are being done currently.

DR. GOODMAN: Thank you, Dr. Jacob. Did that answer your question, Dr. Steinbrook?

DR. STEINBROOK: Yes, that was very helpful.

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DR. GOODMAN: Thank you. Dr. Schwartz, and then Dr. Jarvik.

DR. SCHWARTZ: I just want to get back to Dr. Kirkpatrick's comment about the length of follow-up and see whether Rick or Tom or anybody had information on longer-term follow-up, more than two years, because that is a very important issue to consider, and most of the studies that have been published, the ones I read, the ones that were sent us are one or two-year follow-up.

DR. GOODMAN: Dr. Ratko, I'll look at you first in case you have anything to add to what you said before about follow-up, because you looked at all the study evidence. Is there anything to add, sir?

DR. RATKO: No. I believe the Burkus study that was published in 2009 was six-plus years, that's the longest experience.

DR. SCHWARTZ: None of the other studies?

DR. RATKO: I haven't seen any.

DR. GOODMAN: Thank you, Dr. Ratko. Yes. This is --

DR. BARCROFT: Julie Barcroft, Dr. Julie Barcroft.

In our AMPLIFY trial for posterolateral use we did an analysis at five years whose data has yet to be

published, and it was on one of the slides but it got
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glossed over rather quickly. And what we did was we compared patients that did achieve fusion versus those that did not achieve fusion, and we saw what was reported by Kornblum, and then we saw an improvement in outcomes and reduction in pain, but that's not yet published.
DR. GOODMAN: Thank you for that.
DR. SCHWARTZ: But there's not much about how, how good predictors at two years predict success at four or five years.
DR. GOODMAN: I heard nothing, Dr. Schwartz, about that. Mr. Ziegler, did you have a comment?
MR. ZIEGLER: Yes. I would like to add that in 2008 Ken McCarrus et al. studied a registry database of 68 patients at three years and found 90 percent had consistent fusion results.
DR. GOODMAN: Was that a published study?
MR. ZIEGLER: Certainly.
DR. GOODMAN: Okay, thank you. Further on that? Okay. Dr. Jarvik is next.
DR. JARVIK: I had a question referring to question number six, the generalizability relating to the efficacy versus effectiveness question, and we talked a little bit about patient factors, but what about surgeon factors or hospital system factors, and how much of the data was obtained in the review in nonacademic settings,
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if any, and how might that influence outcomes that were looked at?
DR. RATKO: As far as the academic versus nonacademic, we didn't really look into that. I think there was some independent groups that have done a lot of this work, but a lot of it was done within a multicenter setting, but we didn't systematically look at it. I can defer to the surgeons.
DR. JARVIK: It's not likely to make a big difference in outcomes, would you say?
DR. GOODMAN: Dr. Jacob, if you have something to say, do you want to come to the mike?
DR. JACOB: I do. I think Burkus, the primary author of the answer study, is in private practice in Georgia, so he's not in an academic center. Some of those patients might have been recruited in an academic center, but he is not.
DR. GOODMAN: Thank you. Dr. Juhn is next.
DR. JUHN: This question really refers to the study design, especially the sample size, so the question really has to do with, I'm assuming that from looking at the studies and looking at the technology assessment, that these were really geared to the non-inferiority studies, that the gold standard was really the autograft bone approach, and that this BMP was really meant to show
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equivalency to that as a standard. I just want to make sure that I'm clear on that subject.
DR. GOODMAN: Any speaker? Yes, Dr. Ratko. I told you, Dr. Ratko, you're going to get a lot of exercise.
DR. RATKO: I think that there's a mix of that. There are some of the studies that, if I recall, it might have been Dr. Dawson's study that specified a non-inferiority, but not all of them.
DR. JUHN: Just by looking at the sample sizes, I can't imagine you could do a superiority study.
DR. RATKO: No, you couldn't.
DR. GOODMAN: Thank you. A point well made, Dr. Juhn. When we're looking at this comparative stuff, for the most part you're right, it's non-inferiority. Thank you for making that point explicit.
Dr. Kirkpatrick is next, sir.
DR. KIRKPATRICK: I hope you think this is a fair question, but we heard individual disclosures from the panel and the presenters, but we've had several that represented organizations. I wonder if there is any way that they might know or have other people to support them, and tell us how much those support organizations may have received from either the BMP manufacturer or Medicare.
DR. GOODMAN: How much support?

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DR. KIRKPATRICK: Yeah. Because most of the organizations get significant support from industry for CME, for grants, and for exhibit space. And as a business, these organizations are a business that are trying to operate, and I think that represents a potential conflict of interest that may be of interest to the panel, or it may not. I'll leave that to your discretion.
DR. GOODMAN: I appreciate your point, Dr. Kirkpatrick. Let's put it this way. For anyone who has spoken today, anyone who has spoken today should have and is responsible for having read the conflict of interest points in the disclosure form. If there's any speaker, anyone who has spoken today as an invited speaker or scheduled speaker, or our one unscheduled speaker, who wants to add anything to what they have already stated about any potential conflicts of interest, they're welcome to do so, but I'm not going to single out anybody.
DR. SCHWARTZ: Cliff, just a quick thing for going forward. From what I'm reading, a good suggestion is maybe going forward in the future is that when people represent societies that there be a report of how much the societies got, and we can't do it today, but I think going forward it's something to consider.
DR. GOODMAN: Right, and we're not going to do that today. I think there's a set of procedures that CMS

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has developed over the years, but at this time if anybody would like to add anything to what has already been stated

in their form or what they said when they spoke, Dr. De Long, would you like to approach the microphone?
DR. DE LONG: Well, I would just like to say that I have no disclosures personally, and there was no influence on me by the American Academy of Orthopedic Surgeons; they asked me to develop some evidence and that was it.
DR. GOODMAN: Thank you very much. Okay. Dr. Baker.
DR. BAKER: I guess as an answer to two points. One is, I thought in the hallway whether I should disclose that I'm president of the North American Spine Society. That may be or may not be relevant, but I recused myself from any discussions within the society about that. I do know the answer to your question, and that is that the North American Spine Society abides by the Rothman PMA guidelines that came out in JAMA, a less than 25 percent interest.
DR. GOODMAN: Okay. Any questions now for our presenters this morning, thus far? No further questions at this point for our presenters about -- yes, Dr. Rao.
DR. RAO: Just a quick question for Dr. Glowacki. From a biological standpoint, Dr. Glowacki,

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we've heard how autograft has, or it becomes lower quality as we age, and that's primarily related to a lower number of stem cells, quality of stem cells in autograft bone as we age. What is the presumed biologic mechanism when we use BMP? BMP is supposed to work by stimulating osteoblastic differentiation from the sentinel stem cells. What is the number of stem cells we know is less as we get older, so what is the presumed mechanism of action in BMP in an older patient who presumably has a lesser number of stem cells? That's one question.
The second question --
DR. GLOWACKI: Can I answer that one before I forget it?
DR. RAO: Sure.
DR. GLOWACKI: Because I think there's multiple parts already.
DR. GOODMAN: Please proceed.
DR. GLOWACKI: I think that the mechanism is supposed to be able to, even if there are smaller numbers, to make sure that they maximize the potential, that's the theory behind it.
DR. RAO: How would that be different from just the autograft potential?
DR. GLOWACKI: It --
DR. RAO: Is BMP an extra --

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DR. GLOWACKI: It wouldn't be --
DR. RAO: -- in an elderly patient with fewer stem cells?
DR. GOODMAN: Dr. Rao, just, I'm looking out for

my favorite court reporter in the whole world, who is having trouble with the back and forth conversation. So let's lay out your question and get an answer, and then we can come back to you for a follow-up. Dr. Glowacki.

DR. GLOWACKI: I've published rather extensively on the age-related decline in the osteoblast potential in marrow from humans, and I've also looked very very hard to find the evidence of decreased fracture healing, graft incorporation as a function of age, and there's very very little evidence to support that if you look at age alone. If you look at diabetes, smoking, other factors, other drugs, other symptoms, you cannot isolate the age effect. That is why I think it's reasonable to assume that it's a question of maximizing what the potential is there in those numbers themselves.

DR. GOODMAN: Thank you, Dr. Glowacki. Dr. Rao, did you have a follow-up question?

DR. RAO: Not a follow-up, but a slightly different line of thought again dealing with biology, and since you're the biology expert. We know that BMPs stimulate osteoblast function. With osteoblast function

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we get radiodense bone. They don't do much with osteoclasts. Osteoclasts are important for the remodeling and the proper formation of good bone quality. We know that there's another disease that's physiologically somewhat similar called brittle bone disease or osteoporosis, where the primary physiologic deficiency is one of osteoplast function. How would you say brittle bone disease where fractures are more likely, where the quality of bones is suboptimal, compares with the bone or radiodense tissue that's created by the use of bone morphogenetic proteins?

DR. GLOWACKI: I think all of the animal and radiographic or clinical evidence indicates that there's a normal turnover of bone that is induced by any material such as AAA bone or BMPs, that it's not sclerotic bone, it's bone that undergoes remodeling at a normal rate, so there's no pathology to the osteoplasts that are recruited to it.

DR. GOODMAN: Thank you, Dr. Glowacki. Let's take one more question before we break. Dr. Satya-Murti.

DR. SATYA-MURTI: My question is for any spine surgeon. The patients who go on to receive BMP, some would have had a hardware placement already and some would have gone to BMP without a prior hardware placement or

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failure of hardware, is that not correct? So this would be a mix of two different kinds of population, and if that is in fact a fact, can we separate the data as to who does better, those in whom the hardware has failed versus those in whom the BMP was put in de novo without the hardware?

DR. GOODMAN: This is Dr. Bono.

DR. BONO: If I understand your question correctly, what is the difference in the outcomes of performance of BMP in a redo operation or a pseudarthrosis operation, nonunion, versus a primary fusion, and I don't think that that comparison has been made. The only evidence that we have of BMP use in pseudarthroses are that we do scenario, or very limited case series, case reports, all of the primary data we have is on first-time lumbar fusions. So no previous surgery, and that's usually one of the disqualifications under the exclusion criteria for these studies.

DR. GOODMAN: Thank you, Dr. Bono. Dr. Kirkpatrick, on that point?

DR. KIRKPATRICK: Yes, just further to help you understand. The posterolateral fusions that were done in most of these studies were accompanied with hardware. The anterior on-label use is with hardware, but it's a cage that is interposed within the disc space. So none of them are just put in the place to get a fusion without some way

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of augmenting the stability of the spine.

DR. SATYA-MURTI: By hardware you mean the pedicle screws and such, not the cage?

DR. KIRKPATRICK: Posteriorly would be pedicle screws typically used with BMP. Anteriorly, frequently it's a cage alone with the BMP. Sometimes people are now doing, as you saw, two other categories of fusion, posterior lumbar interbody fusion and transforaminal interbody fusion, and those are also done with hardware typically.

DR. GOODMAN: Thank you for that clarification, Dr. Kirkpatrick.

It's 12:01 and I think we've pretty much exhausted the questions for the presenters at this point. So when we come back from lunch, we're going to start with our questions. And what we'll do, starting with question one, is have a brief and focused discussion about matters pertaining directly to the question, and it does have multiple parts, and we will proceed to take a vote on it, and then we'll do the same for question two and so forth. So do come back prepared to address in a concise fashion questions, and we will take the voting that way.

I would like to thank our speakers thus far this morning for their excellent presentations and timeliness. Speaking of timeliness, I've got 12:02 now, but we'll

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start directly at one p.m. after lunch, not 1:01, one p.m. The cafeteria, for those of you who don't know, is down the hall and downstairs, and we'll see you at one p.m. Thank you all very much.

(Recess.)

DR. GOODMAN: Panel, we're going to proceed now to discussing our questions, of which there are seven, six voting questions and one discussion question, and just a

few reminders here about what we're going to do. First of all, pretty soon we will find out about our new voting system, so do you want to do that now, Maria, or wait until -- we're going to have some discussion and then move to question one, so do you just want to do it then?

MS. ELLIS: It's up to you, whichever.

DR. GOODMAN: How long is it?

MS. ELLIS: A minute.

DR. GOODMAN: Why don't you hand those out to folks, and let me go on while you're doing that, and then when it comes time to vote, we can deal with that. On these voting questions, remember a few things. We're going to have some discussion, so we're not voting in the next 20 seconds. Some reminders here now. Do have ready your voting question pages, which will help direct you to what we are doing, and here are some

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reminders. Remember that for all of those voting questions we're looking at the three general types of meaningful health outcomes that CMS has laid out; they are pain, patient function and adverse events. We've talked a little bit today about what those mean, and you know with respect to adverse events we had a discussion before lunch, our intent on that and so forth. So pain and patient function, we're not talking here about intermediate lab markers, unless you have a real, real strong understanding that those are strongly related or correlated to one of our outcomes. We're going to be talking about on-label uses as well as off-label, keep that in mind, so that's an important distinction. We're going to be talking about premarket approval, which we will call PMA, as well as humanitarian device exemption, HDE, and we've got some supplemental material in the appendix that describes what those are. Just keep in mind in general, as was noted before, HDEs do not contain a requirement for demonstrating efficacy, so there's a different threshold, if you will, even for regulatory action, with regard to HDEs, as opposed to PMAs. You will notice that there are three bulleted examples of off-label use of lumbar, and we are going to

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get to those. Now, what we've asked CMS staff to do is repost on our screen, on the screen you will see the synopsis of the indications, I should say the descriptions of the use of the PMA and HDE respectively, so those are the respective descriptions that go with the PMAs and HDEs, and the indications of lumbar, open tibial fracture and so forth. So basically there are a bunch of points of reference here while we're doing this. You may also recall, panel, that in the

materials sent to you ahead of time was a more detailed, should you need it, a more detailed summary of some of the FDA actions on BMPs for PMA and HDE, and so forth. So what you see on the screen is a synopsis of this more detailed information that you were to have looked at earlier.

All right then. Any questions at this point about how we're going to get started? Let's do this then. In general we're going to talk about each question and then we'll vote on it and proceed. And we want to make sure that, there are paper ballots on the table before you vote, but let's make sure that people are pretty much ready to vote on something and no big chunks are missing, and we will try to proceed that way. Do remember that we will have some discussion period at the end to pick up

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where the evidence gaps may be and what evidence may be required to get us past them.

Okay. Question one, then, asks about the adequacy of the evidence. This is one where you don't say what the evidence tells you, it's is there enough evidence to go on, and sometimes we don't need to go any further. So question one asks, how confident are you that there is adequate evidence to determine one way or the other, to determine whether or not use of BMPs in each of the following indications improves at least one of the clinically meaningful health outcomes?

So for example, 1.A(1) is lumbar spine, so we're asking here for lumbar spine, is there adequate evidence to determine whether use of BMPs improves any one of those three outcomes. And by the way, lumbar spine, the on-label of that is described on the screen and in your paper up there. As a matter of fact, I'll just use a laser pointer here to show you on the screen, you see where it says PMA there at the top, and you'll see spinal fusion for degenerative disc disease up to Grade 1, so forth, L4 to S1. By the way, we had anterior or anterior laparoscopic approach. So that's the PMA description on label there and the second and third entries there are supplements, you see an S there, an S there, so those are supplements to the original PMA, and I just wanted to make

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that clear. So when you're asking about what indication you're talking about here, it's the one shown at the top here, on-label lumbar as described there.

Below the PMA, there's the HDE here. So the first three entries are the PMAs for lumbar, and the next two are for HDEs, also lumbar. Dr. Kirkpatrick.

DR. KIRKPATRICK: If we could please clarify the question from the CMS standpoint. It says improves one of the three outcomes. Are we talking about improves relative to the natural history of the disorder, or improved relative to the control that was studied in the data analysis.

DR. GOODMAN: The question is asked of CAC staff, so we'll ask Dr. Louis Jacques to approach the microphone.
DR. JACQUES: Hi, I'm Louis Jacques, I'm the director of the coverage group. In general when we say improves, it's improved compared to whatever would have happened to the patient if they hadn't had that particular intervention as a part of the strategy. So we're not necessarily restricting you to this versus something else in some sort of head to head manner. It's is the patient better off if they do this than if they didn't do this or use this, so you have a little bit of flexibility there.
DR. GOODMAN: Thank you. Dr. Steinbrook was
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next.
DR. STEINBROOK: If one is concerned about adverse events and when looking at the cervical spine, the word improves is giving me problems in terms of what we're building on. If you think that there's substantial evidence about adverse events, I'm just saying it this way to make my point, but it doesn't improve, I mean, you're just basically -- I think what we're being asked is whether there is enough evidence to have an opinion on what the evidence says, and I'm getting confused by this improves as it relates to adverse events, because I don't think adverse events are an improvement.
DR. GOODMAN: Well, a couple points. One, you're right, and question one is about the adequacy of the evidence, are there, what have you, RCTs or other strong studies that measure the kind of thing that you're interested in. And then if there is adequate evidence, subsequently we will figure out what you think the evidence says.
With regard to adverse events improving, we're looking for fewer adverse events, the patient is better off this way vis-a-vis adverse events than he or she would have been otherwise, as Dr. Jacques indicated. So improvement in adverse events is not more adverse events, of course.
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DR. STEINBROOK: Well, I'm still confused, and I think I can perhaps defer this to the later question if we get to voting on it about the cervical spine injuries. But if one is concerned about adverse events as an issue, I'm having difficulty as to how one discusses that in terms of the numbers. We can defer that to later.
DR. GOODMAN: Okay, good. You can exercise your judgment as an expert panelist. Dr. Rao.
DR. RAO: Even to determine whether there is adequate evidence, we're talking about two grossly divergent groups. One is the ALIF PMA group and the second is the HDE group which is used for difficult posteriors. Would you like us to kind of compile and add the sum total of evidence, would you like us to give you

two separate opinions?
DR. GOODMAN: Well, we are supposed to go with the on-label FDA indications as described on the screen. Does that not suffice for your purpose?
DR. RAO: Not really. They are two completely different groups. One is the anterior lumbar fusion, which is a PMA group, and the other is the revision posterior lumbar group which is the HDE group. Both of them are on label.
DR. GOODMAN: Okay. Now I'm sure we can handle this. Even though you might think you want to split

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those, we're looking for anything that might register as adequate evidence in question one, it could be either of those, and then when we get to the subsequent question, we can hit on the one for which you thought there was adequate evidence, if you would like to do it that way. If not, we might consider splitting it.
Dr. Baker, did you have a comment?
DR. BAKER: I'm going to echo the comments by Dr. Rao. I think that in this case the two groups are very different, so although you can just lump them together for the first question, you can end up having to tackle it in part two, and if you get to part two if you split them. So I would be in favor of splitting those into the PMA versus the HDE.
The other is, I was completely on board with you on everything including the lower evidence required for an HDE, I understand an HDE and the lower evidence required, but for today's discussion are we separating out the fact that an HDE has a device decision, with lower threshold evidence perhaps?
DR. GOODMAN: Here's the thing. CMS is fully aware of what FDA's requirements are, but CMS is not bound by those. When CMS here today is referring to a PMA or HDE, it's referring to those for the purposes of helping us understand which indication is on the table for

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discussion, which type of application, and those are described as well as can be in this statement here. So this is not a discussion about whether CMS's thresholds are higher or lower than FDA's. It was mentioned earlier about what an HDE means so that we know, at least as I understand it, to satisfy the requirements of an HDE, you need not demonstrate efficacy, that's the difference.
DR. BAKER: Okay.
DR. GOODMAN: Okay. Dr. Baker just suggested that we split 1.A(1), lumbar spine, into the PMA versus HDE indication, would the panel like to consider that? I see a lot of heads nodding yes. Dr. Kirkpatrick, that's an affirmative?
DR. KIRKPATRICK: Yes.
DR. GOODMAN: Thank you. We'll do it, PMA versus HDE, everyone okay with that? So we'll split that

one and discuss it coming up now. So if that's the case then, remember from the screen or your handy-dandy handout what those mean, right? And this is Dr. Bozic.
DR. BOZIC: For clarification, the HDE we're talking about is both the BMP-2 and BMP-7, and for the PMA is only BMP-2.
DR. GOODMAN: We're talking about the way they're described on the screen, yes, sir.
DR. BOZIC: And so given that there are two

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lumped into the HDE category, if the evidence is sufficient for either, we would answer that we're confident.
DR. GOODMAN: Right, we'll take either one. It's your understanding of what the evidence adequacy is, and then we will proceed.
(Discussion off microphone.)
DR. GOODMAN: So as far as I understand, we have to consider what's up there and what's happened with the FDA. Thank you. Any other considerations? Dr. Rao, on this point?
DR. RAO: Just to clarify, the HDE only refers to OP-1 and not to BMP-2.
DR. GOODMAN: Also helpful, thank you for noting that.
All right. Does anybody want to start off with discussion, or we can always just jump to the vote if nobody has anything to say about it. When we're looking at lumbar, starting with PMA, lumbar PMA, adequacy of the evidence for any one of the three types of health outcomes. We're thinking now about not what the evidence says, but how strong is the body of evidence there? Remember the USPSTF scores on the individual studies, the different GRADE scores on the studies and so forth. Any discussion about that? Dr. Kirkpatrick.

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DR. KIRKPATRICK: I'm going to ask you to suspend your recommendation for me to hold until after when we talk about future studies, and I think it's important as we think about the data to make sure everybody understands that issue about pain in patients.
DR. GOODMAN: If you believe it's relevant now, we'll be glad to hear it.
DR. KIRKPATRICK: I believe it's relevant to understanding the data as presented.
DR. GOODMAN: Great.
DR. KIRKPATRICK: The data as presented did not differentiate between specific indications for fusion. The reason that's important is if we looked at a global analysis of fusion for low back pain, the clinical results are somewhere between 50 and 60 percent favorable. If we look at a global analysis of patients that have spondylolisthesis, and those patients are actually closer to our Medicare age group, the results are more in the 80

to 85 percent success rate. So what they've done with most of the presentations we've heard is putting all those together. And so you know, for future direction and for understanding this data, we can't determine exactly which ones are going to have high clinical benefit and which ones are not.

DR. GOODMAN: That's a point well taken, and I'm

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sure CMS will address that in the future. If any of the panelists think that that has a bearing on answering questions, please let it bear on the question. Thank you, that's a good point, Dr. Kirkpatrick.

Any discussion or observation about, again, lumbar spine on the PMA description, the PMA use of lumbar spine, telling you something about pain, patient function or adverse events? I don't see anybody making a comment. Dr. Lewis, did you want to make a comment? No, okay.

Let's, I think what I'll do is keep going here and we'll discuss all the 1.As. Anything having to do with the HDE side, HDE for the lumbar, adequacy of the evidence. You're going to say to yourself, what confidence do you have that the evidence is adequate, one would be you don't want to go forward with this, five would be high confident, the evidence is sufficiently adequate, you do want to proceed on it.

Would the panel like to vote on this now or do you want to take it by group? I'm seeing now. Dr. Sloan, did you have a comment? No? Okay. I don't see any further hands, Maria, so you need to tell us about how to vote 1.A(1) into the PMA and HDE parts, so that's going to complicate your electronic recording, is it not?

MS. ELLIS: I should point out that the gentleman that will set it up is on his way over. If you

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want to lump them together, that way we can --

DR. GOODMAN: Is he on the way over like today or tomorrow? It's a big building. Yes, Dr. Satya-Murti?

DR. SATYA-MURTI: I was wondering if we could go ahead with 1.A(2).

DR. GOODMAN: That's what we're going to do.

All right. Keep in mind the score, you may want to write it down, what you had in mind for 1.A(1) lumbar fusion and 1.A(1) for HDE.

Let's open the discussion for the open tibial fracture, the open tibial fracture, and the adequacy of the evidence there. You will see on the screen or if not, on your handout -- oh, there it is. Thank you for being so adroit, Mr. Man Behind the Screen. You'll see at the bottom the description, the PMA description of open tibial, treating acute open tibial shaft, stabilized with IM nail fixation after appropriate wound management, and it must be applied within 14 days after initial fracture.

Any comment or question about open tibial fractures with regard to adequacy of evidence? Keep in

mind, you think there's no confidence or low confidence in the adequacy, or high confidence in the adequacy. Dr. Schwartz.
DR. SCHWARTZ: Cliff, you know, there just wasn't much discussion of that in any of the presentations
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we were talking about here, and so that's really the larger question there. It seems that the discussion that was there was generally accepting, if not favorable, but there wasn't much discussion, and I don't think this one's going to go very far, just given the nature of the literature.
DR. GOODMAN: Yeah, I think I concur that there's not overwhelming evidence there. I do recall in the summary of the HTA made some reference to what looked like pretty meager evidence, as I recall, about that. So you're right, Dr. Schwartz, you didn't hear a lot more about it, but it was addressed.
DR. SCHWARTZ: It was addressed, and you don't say that very often.
DR. GOODMAN: Did I? Okay. So, any comments, then, about anything else on open tibial here? I don't see any.
Let's move to recalcitrance of long bone nonunion, and that you will see is also shown on the screen toward the bottom, you see it next to the HDE there as an alternative to autograft in recalcitrant long bone nonunions when use of autograft is unfeasible and alternative treatments have failed. Any comments about that one, recalcitrant long bone nonunions?
Oh, by the way, I should have spoken earlier
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when I was looking at the types of evidence.
Dr. Schwartz, with regard to open tibial, I recall that the summary had stronger evidence, and the weak evidence was with regard to recalcitrance as I recall, and I see heads nodding. Thank you. Dr. Bozic.
DR. BOZIC: There were two RCTs for the open tibial that were included in our materials for the acute open fractures.
DR. GOODMAN: Yes, and I corrected myself on that. That was in the health technology assessment done by the EPC, and it was recalcitrance where there was less evidence. Yes, Dr. Davis.
DR. DAVIS: I think the comment was also made about the open tibial studies about the number of patients, and actually in the one randomized control trial there were 150 patients in each group, so it was actually quite a large study, not a smaller study.
DR. GOODMAN: Thank you, Dr. Davis, good point.
Dr. Rao.
DR. RAO: If it's on label, I think the only on-label use of BMP for tibial fractures is open fractures. The second study wasn't for acute open

fractures, so I think it was primarily one study, if I'm not mistaken.
DR. GOODMAN: For the open tibial?

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DR. RAO: Yes. The other one was for a defect at the fracture site but not for an acute open fracture. The FDA on-label issue is acute open fractures of the tibia, so it's just basically one study, which is the Govender study.
DR. GOODMAN: Dr. Bozic.
DR. BOZIC: According to my summary notes, and I'd have to go back and look at the literature, the second study was for Type III open fractures.
DR. RAO: That's a subgroup of the first study, you're right.
DR. GOODMAN: There were two RCTs, the patient population of the second was a subgroup of the first, correct, Dr. Baker?
DR. BAKER: That's true.
DR. GOODMAN: Thank you, Dr. Baker. Dr. Rao.
DR. RAO: The second study was an extraction of data, not a separate RCT, it was an extraction of data from the first study.
DR. GOODMAN: Also true, Doctors?
DR. BOZIC: Yes.
DR. GOODMAN: Different primary indication but not different patients, a subgroup of the same group of patients, correct? Thank you, Dr. Rao. Dr. Davis.
DR. DAVIS: No, I don't agree. While there was

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a subgroup there was also an additional group of patients that are from, I believe from an unpublished study, so I think it combines some patients from the first study and some additional patients.
DR. GOODMAN: This would be a good time to ask Dr. Ratko if he would like to weigh in on this.
DR. RATKO: Yes, we have the BESTT study, which was the pivotal trial, that's the 151 plus 150, and we have the subgroup analysis which gave us the underlying refractory fractures from the BESTT study plus 60 additional patients, and then one that has not been published, called the US study, handled at the ten level one trauma centers, identical selection criteria.
DR. GOODMAN: Thank you, Dr. Ratko. I think we got that one finally. Okay. At this point, other comments about recalcitrant long bone nonunions? I don't see any. Dr. Lewis.
DR. LEWIS: I just want to go back to the hardware part of our discussion earlier about how to set these, and it is virtually impossible in a clinical setting at this point to adequately break these down. And I make the point only in that when faced with one of these very difficult problems, there aren't a lot of alternatives. And so my question, I guess, is sort of a

question of clarification to CMS, and that is what happens
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if there is equivocal evidence of efficacy, in this case it's an HDE, but from a coverage determination standpoint, what are the implications of a decision on this?
DR. GOODMAN: That's a very interesting question, though I don't think germane to our question today. There's not an NCD on the table, and our job is to try to deal with this imperfect world which you described so well. Doctors and patients have to make decisions, and the payers have to make decisions every day. Yes, Tamara.
MS. JENSEN: Just a reminder, there is no national coverage decision on this particular item, and so I think you have more flexibility in how you want to interpret all of these questions. And you know, what you decide today, what you discuss today, we are all taking that in to make a decision on what our next step will be, so we may never open a coverage determination, so there is more flexibility than if we had one open, and this is one reason for letting you decide how you want to interpret this.
DR. GOODMAN: Right. Do recall what Dr. Jacques said, though, and he talked about looking at BMPs in comparison to what would happen otherwise, so it's not what will happen two, five or ten years from now, it's what would have happened otherwise in the context of the current evidence. Dr. Kim.
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DR. KIM: Yes, thank you. Just to follow on that, I think that where we are, we (inaudible, off microphone) flexibility in determining the alternative to BMPs, which would be no treatment whatsoever or the comparators within the RCTs. Now, how we evaluate -- that's sort of at the level of is there enough evidence, so we're sort of evaluating the quality of the evidence to inform improvement of health outcomes, and we're examining to have to get aligned on what the alternative is.
DR. GOODMAN: We're looking at the adequacy of the evidence that was presented to us and summarized and so forth. We're not taking a lot of guesses here, we're trying to understand based on the available body of evidence, what can you say about these questions. And the available body of evidence may not include some considerations that one might include in the future. It's imperfect, we're asking for your judgment here. This will not satisfy a lot of statisticians, but we do have a lot of choices here. Dr. Baker.
DR. BAKER: When you talk about strategy and risk that CMS asked us to do, we're potentially left with what is the improvement that occurs as a result of the strategy, and (inaudible, off microphone) and to me that is not versus natural history or interpretive management in light of the trial that has been done, that we have
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evidence cohorts, (inaudible, off microphone) the use of the BMP.
DR. GOODMAN: Okay. I'm turning to my left now to see how we are on our fancy new electronic system.
(Discussion off the record.)
MS. ELLIS: With the control pads, with the voting pads that you have in your hand, you are voting one through five, the same as usual when you're holding up the number, so you just hit that when it's time to vote, and also, if you could, say your name and say your vote for the record, and we'll keep it going as smooth as possible.
DR. GOODMAN: To satisfy the needs of the staff, we're going to go down here, and what I'm going to ask you to do, I'll just point to you, if you don't mind my impolite action, and ask you to state your name as you push your button, or say your name and what, Ms. Ellis?
MS. ELLIS: And vote.
DR. GOODMAN: All right. Let's try it with my trusty cochairman here, the gentleman to my right, Dr. Satya-Murti.
DR. SATYA-MURTI: On 1.A(1), lumbar spine PMA, I vote four.
DR. GOODMAN: Dr. Baker.
DR. BAKER: Ray Baker. I vote four.
DR. GOODMAN: Dr. Bozic.

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DR. BOZIC: Kevin Bozic, four.
MS. DARLING: Helen Darling, four.
DR. DAVIS: Charles Davis, three.
DR. JARVIK: Jeffrey Jarvik, three.
MS. KENDIG: Susan Kendig, three.
DR. KIM: Edward Kim, three.
DR. LEWIS: Courtland Lewis, four.
DR. MCDONOUGH: Tom McDonough, three.
DR. SCHWARTZ: Sandy Schwartz, four.
DR. SLOAN: Andrew Sloan, four.
DR. STEINBROOK: Robert Steinbrook, four.
DR. JUHN: Peter Juhn, four.
DR. KIRKPATRICK: John Kirkpatrick, three.
DR. RAO: Raj Rao, four.
DR. GOODMAN: And this is just a reminder. The chair does not vote, and we're going to keep separate tallies for the voting members and the MedCAC as a whole, correct?
MS. ELLIS: Correct. Two people didn't hit the key pads.
(Discussion off the record.)
DR. SCHWARTZ: While we're waiting, I did have one other disclosure I wanted to make. I did have some research on adherence in an unrelated area funded by Pfizer the last two years, and I understand that they have

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a company marketing agreement with Medtronic, and I wasn't aware of that.

DR. GOODMAN: Thank you. Ms. Ellis, are we fixed?
MS. ELLIS: We're good. Let me mention, do not forget to record your votes also on the sheet of paper that was in your folder.
DR. GOODMAN: All right. Thank you for your patience, all, this has been the first run of this technology, do we call this beta testing? Now, Dr. Davis.
DR. DAVIS: Ms. Ellis, since one is broken out, on the sheet of paper, how do you want us to indicate that?
MS. ELLIS: You can just do an indication of PMA and HDE.
DR. DAVIS: Thank you.
DR. GOODMAN: Thank you all for your patience here. I'm wondering if I liked the old version better. We'll find out. Let's now move to -- yes, Dr. Satya-Murti.
(Discussion off the record.)
DR. GOODMAN: Okay. We're still on lumbar and now we're looking at HDE, correct?
MS. ELLIS: Correct.
DR. GOODMAN: So it is adequacy of lumbar, HDE.

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Adequacy of evidence, lumbar, HDE.
DR. SATYA-MURTI: Satya-Murti, two.
DR. BAKER: Ray Baker, two.
DR. BOZIC: Kevin Bozic, two.
MS. DARLING: Helen Darling, two.
DR. DAVIS: Charles Davis, two.
DR. JARVIK: Jeffrey Jarvik, one.
MS. KENDIG: Susan Kendig, one.
DR. KIM: Edward Kim, one.
DR. LEWIS: Courtland Lewis, two.
DR. MCDONOUGH: Tom McDonough, one.
DR. SCHWARTZ: Sandy Schwartz, one.
DR. SLOAN: Andrew Sloan, two.
DR. STEINBROOK: Robert Steinbrook, two.
DR. JUHN: Peter Juhn, one.
DR. KIRKPATRICK: John Kirkpatrick, two.
DR. RAO: Raj Rao, two.
DR. GOODMAN: Thank you all. Ms. Ellis, are we all on?
MS. ELLIS: We're missing two.
(Discussion off the record.)
DR. GOODMAN: Okay, open tibial fracture.
DR. SATYA-MURTI: Satya-Murti, three.
DR. BAKER: Ray Baker, three.
DR. BOZIC: Kevin Bozic, three.

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MS. DARLING: Helen Darling, three.
DR. DAVIS: Charles Davis, four.
DR. JARVIK: Jeffrey Jarvik, four.
MS. KENDIG: Susan Kendig, three.

DR. KIM: Edward Kim, three.
DR. LEWIS: Courtland Lewis, four.
DR. MCDONOUGH: John McDonough, three.
DR. SCHWARTZ: Sandy Schwartz, four.
DR. SLOAN: Andrew Sloan, four.
DR. STEINBROOK: Robert Steinbrook, three.
DR. JUHN: Peter Juhn, four.
DR. KIRKPATRICK: John Kirkpatrick, three.
DR. RAO: Raj Rao, two.
DR. GOODMAN: Now we will move to recalcitrant long bone nonunions.
DR. SATYA-MURTI: Satya-Murti, two.
DR. BAKER: Ray Baker, two.
DR. BOZIC: Kevin Bozic, two.
MS. DARLING: Helen Darling, two.
DR. DAVIS: Charles Davis, two.
DR. JARVIK: Jeffrey Jarvik, one.
MS. KENDIG: Susan Kendig, two.
DR. KIM: Edward Kim, two.
DR. LEWIS: Courtland Lewis, two.
DR. MCDONOUGH: John McDonough, two.

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DR. SCHWARTZ: Sandy Schwartz, two.
DR. SLOAN: Andrew Sloan, two.
DR. STEINBROOK: Robert Steinbrook, two.
DR. JUHN: Peter Juhn, two.
DR. KIRKPATRICK: John Kirkpatrick, two.
DR. RAO: Raj Rao, two.
MS. ELLIS: We're missing three. Thank you.
DR. GOODMAN: We'll keep pushing through, and this is still adequacy of the evidence, not what the evidence says. So we've done 1.A(1), (2) and (3), including lumbar for both PMA and HDE, so we'll proceed now to 1.B, and we're on off-label use now. Off-label use we're going to consider cervical, lumbar, and a category called all other.
Before we vote, because we didn't have a chance to discuss these yet, any points of discussion with regard to the adequacy of the evidence now? It says the adequacy of evidence on cervical spine. First, any comments on that? Dr. Satya-Murti, and then Dr. Sloan.
DR. SATYA-MURTI: I made an assumption with regard to swelling as a complication, it's not the cervical cord that is swollen, it is the cervical soft tissue. Isn't that correct, anyone, because cervical cord swelling would be even more serious.
DR. GOODMAN: Dr. Sloan.

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DR. SLOAN: So when we're talking about the evidence, we're talking about the evidence that it improves the clinical endpoints, not just evidence in general?
DR. GOODMAN: The evidence for improvement along any of the three dimensions of pain, patient function or

adverse events. That's what it is for cervical spine. For all of these questions it's pain, patient function or adverse events. Dr. Bozic, yes.

DR. BOZIC: I think what Dr. Baker was talking about was is there adequate evidence to determine, so if the evidence is that it does not improve outcomes but there's adequate evidence, then I would give it a higher score, because there's adequate evidence to determine the answer to that question.

DR. GOODMAN: Yes.

DR. BOZIC: So it does not have to improve outcomes, it could demonstrably not improve outcomes, but there's adequate evidence to show it.

DR. GOODMAN: For the purpose of the current question, we're not looking for whether it did or did not improve outcomes, we're looking for you to tell us if the body of available evidence might enable you to draw some conclusion. I see heads nodding, I think people got it, okay? Anything else on cervical spine?

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Now, would the panel like to vote now on cervical spine? I see heads nodding. Okay. For cervical spine, again, this is off-label use of cervical spine, adequacy of evidence, not the answer but adequacy of evidence about an impact, a favorable impact on any of those that we've talked about. So if you think there's adequate evidence to make a judgment about the impact on any, pain, patient function or adverse events, you should vote a certain way. One, no confidence, five is high confidence. Are people ready to vote and press their buttons? Dr. Schwartz.

DR. SCHWARTZ: Just one comment here, and that is, I might vote that there's adequate evidence but that doesn't mean that there's sufficient evidence. There might be adequate evidence to make a determination that it's beneficial, but it may, we may not know enough for example of follow-up period, so we have short-term information, so maybe at the very end we could comment on what CMS should try to focus the information on despite our vote.

DR. GOODMAN: That is an excellent point, because the questions do not specify after one year, after two years, after five years or so forth, but you as a clinician and researcher might have an opinion about the impact that you would judge a favorable impact ultimately

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on the scale here.

DR. SCHWARTZ: And more importantly, me as a patient.

DR. GOODMAN: And for all current and future Medicare patients, of course. Okay. Cervical spine, is the panel ready to vote on the adequacy of the evidence, starting with Dr. Satya-Murti?

DR. SATYA-MURTI: Satya-Murti, four.
DR. BAKER: Ray Baker, three.
DR. BOZIC: Kevin Bozic, four.
MS. DARLING: Helen Darling, three.
DR. DAVIS: Charles Davis, three.
DR. JARVIK: Jeffrey Jarvik, three.
MS. KENDIG: Susan Kendig, two.
DR. KIM: Edward Kim, three.
DR. LEWIS: Courtland Lewis, three.
DR. MCDONOUGH: Bob McDonough, two.
DR. SCHWARTZ: Sandy Schwartz, two.
DR. SLOAN: Andrew Sloan, two.
DR. STEINBROOK: Robert Steinbrook, three.
DR. JUHN: Peter Juhn, two.
DR. KIRKPATRICK: John Kirkpatrick, one.
DR. RAO: Raj Rao, three.
DR. GOODMAN: Thank you all very much. Now

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we're going to move to off-label use in the lumbar spine, and I apologize for the broken record treatment here, but again, this is the adequacy of the evidence, not whether or not it improves outcomes, but if you've got enough to go on to later make a decision or a finding about impact on those outcomes. This is lumbar spine. Any comments or questions at this point about lumbar spine off label, any clarifications about evidence that you might want to raise before we vote? I just remind you that we have, our speakers are still in the room and our technology assessment folks from Blue Cross Blue Shield are here. I don't see any hands, except Dr. Kirkpatrick.
DR. KIRKPATRICK: Just one other question for actually any of our presenters. On the posterolateral lumbar fusion, which is the lumbosacral spine issue that we're talking about, can anybody comment on the uniformity of dose per level of BMP that's used either with OP-1 or with BMP-2?
DR. GOODMAN: Okay. Dr. Ratko, I would ask you to come back up here, and if you wouldn't mind, I neglected to raise this earlier, but if we could have the presenters back up front in your usual chairs in case we do need to refer to you or ask you questions, so would our main five presenters please come to the front once again.

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Dr. Ratko, from the EPC.
DR. RATKO: We look at Table 23 and the range of doses is quite substantial, anywhere from the labeled dose of 40 milligrams per patient, so it's quite a range.
DR. GOODMAN: Are you okay with that, Dr. Kirkpatrick?
DR. KIRKPATRICK: As long as we understand that, and there's no disputing that with the other presenters, correct?
DR. GOODMAN: I see none approaching the

microphone, thank you, and that is understood, it's a good point that you made. Thank you, Dr. Kirkpatrick. Other points here on, this is lumbar? On lumbar. Okay. Let's get ready to vote here. Lumbar spine, off label, adequacy of evidence, any of the three clinical areas.

DR. SATYA-MURTI: Off-label lumbar spine, one, Satya-Murti.

DR. BAKER: Ray Baker, three.

DR. BOZIC: Kevin Bozic, four.

MS. DARLING: Helen Darling, three.

DR. DAVIS: Charles Davis, two.

DR. JARVIK: Jeffrey Jarvik, three.

MS. KENDIG: Susan Kendig, three.

DR. KIM: Edward Kim, three.

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DR. LEWIS: Courtland Lewis, three.

DR. MCDONOUGH: Bob McDonough, two.

DR. SCHWARTZ: Sandy Schwartz, two.

DR. SLOAN: Andrew Sloan, four.

DR. STEINBROOK: Robert Steinbrook, three.

DR. JUHN: Peter Juhn, four.

DR. KIRKPATRICK: John Kirkpatrick, two, and I need to tell you that I pushed one first by mistake.

MS. ELLIS: That's fine. The last response is the one that counts.

DR. RAO: Raj Rao, three.

DR. GOODMAN: What's our batting average, Ms. Ellis, did we get them all?

MS. ELLIS: Yes.

DR. GOODMAN: Thank you. Now we move to what is described here as off-label use in all other, and all other can be just about any other, to tell you the truth, so I think you will recall, at least I recall when the technology assessment was presented that there was at least one table with quite an extensive list of -- oh, that was cervical? Okay. Dr. Baker.

DR. BAKER: So we're going to be looking at off-label uses that we never really discussed, although the technology assessment mentioned this, so it would be one -- I mean, it's off label but it's on one of our

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questions, so would this be augmentation?

DR. GOODMAN: These are off-label uses. Your point is well made, because that is an example of something that was specifically addressed in the HTA but was not specifically noted here, except for something under off label. Thank you, Dr. Baker. So in this case, to look at voting for this thing that's called all other, which I really think should have said any other, the adequacy of evidence on any of those other, for any of those other off-label uses on any of the three types of outcomes. So you've got to probably be thinking now, did I see any evidence that looked pretty

substantial on any other off-label indication and if there was one, you can, one or more you can answer one way, and if there was none, you can answer a different way. Comment or question? Dr. Satya-Murti.
DR. SATYA-MURTI: Satya-Murti, one.
DR. BAKER: Ray Baker, one.
DR. BOZIC: Kevin Bozic, one.
MS. DARLING: Helen Darling, one.
DR. DAVIS: Charles Davis, one.
DR. JARVIK: Jeffrey Jarvik, one.
MS. KENDIG: Susan Kendig, one.
DR. KIM: Edward Kim, one.
DR. LEWIS: Courtland Lewis, one.

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DR. MCDONOUGH: Bob McDonough, one.
DR. SCHWARTZ: Sandy Schwartz, one.
DR. SLOAN: Andrew Sloan, one.
DR. STEINBROOK: Robert Steinbrook, one.
DR. JUHN: Peter Juhn, two.
DR. KIRKPATRICK: John Kirkpatrick, one.
DR. RAO: Raj Rao, one.
DR. GOODMAN: Okay, thank you. Now we're going to move to question two, and in voting on question two as I understand it, we're going to need some feedback from CMS, is that correct, Dr. Satya-Murti, because it says at the bottom of our first page, questions two through six should be addressed only for those indications where the panel's confidence that there is adequate evidence, which is defined here again as a mean vote of 2.5, to consider the question. So for example, question two is referring to lumbar spine for, first of all, the indication for PMA on-label use, and as I recall, the mean average for that was greater than two and a half, but the average for others was probably less than two and a half. So what we're referring to now back in question 1.A(1), which was lumbar, and we subdivided it into PMA and HDE, and now we're asking about PMA for lumbar.
(Discussion off the record.)
DR. GOODMAN: I think we're going to find that

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2(a) is on the table, which is lumbar spine, the PMA on-label use, and now we're asking, since we've determined the evidence is adequate, now what we're asking indeed --
(Discussion off the record.)
DR. GOODMAN: Now what we're asking here is, since we've decided the evidence is adequate to come to some finding, does it indeed show that we can determine that the use of BMPs for lumbar spine improves at least one of those three clinically meaningful health outcomes. So for the FDA's PMA on-label indications for use of BMPs in lumbar spine, do they improve, is the evidence strong enough to show that it improves any or all of pain, patient function or adverse events. That's the question. Ms. Darling.

MS. DARLING: I have a question. These seem like fairly sweeping recommendations, and yet we heard from a number of people who were much more specific about when they thought it would be indicated. So this seems to be kind of a universal endorsement if you say anything about the intermediate or above.
DR. GOODMAN: Right. I think what I would say to that, this is a pretty broad, this is broad rather than quite specific, and the fact that it says improve at least any one of those clinically meaningful health outcomes, if you register on one of any of these three, you can score

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accordingly. Dr. Lewis.
DR. LEWIS: Doesn't this get back again to the issue of specificity, because the PMAs are only covering anterior interbody fusion, I know that we've said that, but I think we should be very clear that we're talking specifically about the existing PMA.
DR. GOODMAN: Yes, and unless CMS staff tells us otherwise, we're going to go with the definition that we've got in front of us, which I know does not fully represent the clinical spectrum, but by our discussion, and by your point just now, we want to make sure that CMS considers, and in any future consideration takes account of that, but right now we're pretty limited to the anterior, correct?
MS. JENSEN: Yes.
DR. GOODMAN: I got a confirmation. Given that, lumbar spine, PMA, on-label use, if the evidence is adequate to make some sort of finding about whether or not it improves at least one of the outcomes, low confidence one, high confidence five. Dr. Satya-Murti.
DR. SATYA-MURTI: Yes. For the narrow indication I will go with four, Satya-Murti.
DR. BAKER: Ray Baker, four.
DR. BOZIC: Kevin Bozic, three.
MS. DARLING: Helen Darling, three.

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DR. DAVIS: Charles Davis, three.
DR. JARVIK: Jeffrey Jarvik, two.
MS. KENDIG: Susan Kendig, three.
DR. KIM: Edward Kim, four.
DR. LEWIS: Courtland Lewis, four.
DR. MCDONOUGH: Bob McDonough, three.
DR. SCHWARTZ: Sandy Schwartz, four.
DR. SLOAN: Andrew Sloan, four.
DR. STEINBROOK: Robert Steinbrook, three.
DR. JUHN: Peter Juhn, five.
DR. KIRKPATRICK: John Kirkpatrick, three.
DR. RAO: Raj Rao, four.
DR. GOODMAN: Thank you all. The next one would be 2.B. My recollection is that those votes are probably inadequate, less than 2.5, unless staff tells me otherwise. That was the HDE on label for lumbar.

MS. JENSEN: That's a no.
DR. GOODMAN: So we don't deal now with 2.B, correct. We're going to move to 2.C, which is the lumbar for off-label use. That's a yes, so we are going to address that.
MS. JENSEN: Yes.
DR. GOODMAN: So now we're talking not about the adequacy evidence, because we have shown that it is adequate. This is lumbar spine off-label use, that is to

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determine if the use of BMPs in lumbar spine for that off-label use indication improves at least one of the three clinically meaningful outcomes, one to five. Ready to vote? Dr. Satya-Murti.
DR. SATYA-MURTI: Satya-Murti, one.
DR. BAKER: Ray Baker, two.
DR. BOZIC: Kevin Bozic, three.
MS. DARLING: Helen Darling, one.
DR. DAVIS: Charles Davis, two.
DR. JARVIK: Jeffrey Jarvik, one.
MS. KENDIG: Susan Kendig, two.
DR. KIM: Edward Kim, three.
DR. LEWIS: Courtland Lewis, two.
DR. MCDONOUGH: Bob McDonough, two.
DR. SCHWARTZ: Sandy Schwartz, two.
DR. SLOAN: Andrew Sloan, three.
DR. STEINBROOK: Robert Steinbrook, two.
DR. JUHN: Peter Juhn, four.
DR. KIRKPATRICK: John Kirkpatrick, two.
DR. RAO: Raj Rao, one.
DR. GOODMAN: Thank you very much.
MS. ELLIS: I need everyone to hit the key pad; everyone did not vote.
DR. GOODMAN: Thank you. We'll move to question three now, and question three concerns recalcitrant long

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bone nonunions, it concerns the FDA HDE on-label use of the BMPs in recalcitrant long bone nonunions. Are we voting on this question? This one did not meet the threshold, correct?
MS. JENSEN: No.
DR. GOODMAN: So we're not going to address question three. Thank you very much.
We'll proceed to question four now, and question four concerns the acute open tibial fractures. These are the open tibial fractures, FDA PMA. Are we answering question four?
MS. JENSEN: We are answering question four.
DR. GOODMAN: Any discussion on question four with regard to anything that you need clarified from our presenters this morning or among the panel members? These are acute open tibial fractures. Dr. Baker? No, okay.
Ms. Ellis, would you mind if we started at the other end of the table this time, would the electronic system

countenance that?
MS. ELLIS: It's not a problem.
DR. GOODMAN: Good. I have just a nagging feeling that Dr. Satya-Murti, Dr. Baker, Dr. Bozic and Ms. Darling are so influential in the field that they might sway someone else's vote, so why don't we start at the other end of the table to try to get a little bit of

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different effect here.
So this is the open tibial and we're going to start with Dr. Rao. Is everyone ready to vote? Dr. Rao.
DR. RAO: Raj Rao, two.
DR. KIRKPATRICK: John Kirkpatrick, three.
DR. JUHN: Peter Juhn, five.
DR. STEINBROOK: Robert Steinbrook, three.
DR. SLOAN: Andrew Sloan, four.
DR. SCHWARTZ: Sandy Schwartz, four.
DR. MCDONOUGH: Bob McDonough, three.
DR. LEWIS: Courtland Lewis, four.
DR. KIM: Edward Kim, four.
MS. KENDIG: Susan Kendig, four.
DR. JARVIK: Jeffrey Jarvik, three.
DR. DAVIS: Charles Davis, four.
MS. DARLING: Helen Darling, four.
DR. BOZIC: Kevin Bozic, three.
DR. BAKER: Ray Baker, three.
DR. SATYA-MURTI: Satya-Murti, three.
DR. GOODMAN: Ms. Ellis, are we okay?
MS. ELLIS: Yes.
DR. GOODMAN: Great, thank you. So we will proceed to question five now, which concerns cervical spine, and this is the off-label use of BMPs in cervical spine, whether the adequacy of the evidence to make a

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conclusion about whether or not it improves at least one of the clinically meaningful health outcomes. Off-label cervical spine improves any of the three, and we are voting on this question. Any discussion at this point?
I know we discussed it before with regard to the adequacy of evidence to make some kind of determination. Any discussion about what that determination might be or how the evidence weighs in and so forth, what it might say? Seeing none, Dr. Rao, could you please start us off again, sir?
DR. RAO: Raj Rao, one.
DR. KIRKPATRICK: John Kirkpatrick, one.
DR. JUHN: Peter Juhn, one.
DR. STEINBROOK: Robert Steinbrook, one.
DR. SLOAN: Andrew Sloan, one.
DR. SCHWARTZ: Sandy Schwartz, one.
DR. MCDONOUGH: Bob McDonough, two.
DR. LEWIS: Courtland Lewis, one.
DR. KIM: Edward Kim, one.
MS. KENDIG: Susan Kendig, two.

DR. JARVIK: Jeffrey Jarvik, one.
DR. DAVIS: Charles Davis, one.
MS. DARLING: Helen Darling, one.
DR. BOZIC: Kevin Bozic, one.
DR. BAKER: Ray Baker, one.

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DR. SATYA-MURTI: Satya-Murti, one.
DR. GOODMAN: That was cervical spine, off label.
MS. ELLIS: We're missing one vote. Thank you.
DR. GOODMAN: You have it now?
MS. ELLIS: Yes.
DR. GOODMAN: Okay, thank you very much. Now having looked at adequacy of evidence for various uses of BMPs on label and off label at various anatomic sites, adequacy of evidence and what they actually said in your judgment, now we're going to move to question six, which is that aspect of generalizability, external validity it's sometimes called, and we had various discussions today about this, because we learned and thought carefully about how the particular age may not be so important this time, but we will also remind ourselves that the Medicare patient population is usually but not always age 65 or older. We talked about how this might be done in practice, different practitioners and so forth.
And so question 6.A, again using the scale of one to five, where one is low confidence and five is high confidence, now is saying that if you sort of integrate under the curve all the previous questions one through five, how confident are you at this point that these conclusions that you drew heretofore are generalizable to

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the Medicare patient population, the Medicare patient population. And before we vote on that, we want to make sure that any panelist doesn't have a question or some point you would want to raise that will help inform on your voting. This is generalizability to the Medicare patient population. Yes, Dr. Bozic.
DR. BOZIC: I just wanted to clarify that although there is a significant portion of the Medicare patient population that's under 65, I think that they are uniquely different in terms of their comorbidities, they tend to have many more comorbidities and they tend to be in a lower socioeconomic status, both of which influence outcomes in the populations we're talking about. So I would not assume that the studies that included patients under 65 are somehow generalizable to the population of Medicare patients that are under the age of 65.
DR. GOODMAN: Thank you, point well made. It also recalls the earlier discussion we had regarding exclusion criteria, does it not, in some of the trials, which was very informative. Dr. Kirkpatrick.
DR. KIRKPATRICK: The organizations that presented had pretty much agreement that certain

comorbidities were things that should be thought about as indications. I'm wondering if any of them have data that shows that BMPs are better in those indications or equal
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in those patients, or if it's just an intuitive sense that since these patients are predisposed to nonunion, we think BMP is better.
DR. GOODMAN: Presuming that everyone understood the question, I think I understood it, does any presenter want to address that issue raised by Dr. Kirkpatrick? This is Dr. Bono.
DR. BONO: I think it's a good point that Dr. Kirkpatrick has, and listed among those comorbidities are things like renal dialysis, we're not inclined to perform spinal fusion procedures on patients like that. I think that the one that's most identifiable is the patient who has had previous crest, who has been overly harvested, doesn't have any autograft left, that's one that we're aware of, but we don't have any data, it's just case reports and case series of individual patients.
DR. GOODMAN: Case reports and case series of individual patients, thank you. Any other comments in response to Dr. Kirkpatrick? Dr. Kirkpatrick, I've asked you this before, but what's our takeaway from your question and the response we just heard, what might be added for us.
DR. KIRKPATRICK: I'm conflicted as a clinician, because we're being asked about the adequacy of evidence, and what you've just heard from Dr. Bono is fundamentally
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the grade of evidence is very low to justify that special group that the organizations are advocating for. As a clinician I think it's an important group to consider. As a person being asked to evaluate the evidence, I have to let everybody else decide whether that's adequate to make a decision.
DR. GOODMAN: Thank you. And we are just talking about that external validity in this case, but you're right, there's a large swath of the population out there. Thank you. Was there another point on that? Thank you, Dr. Kirkpatrick.
All right, then. Question 6.A, we're going to ask you to vote from one to five, and we're going to pick on Dr. Lewis here, we'll start with moving in this direction with regard to the voting. So Dr. Lewis, how confident are you that these conclusions are generalizable to the Medicare patient population, reviewing the whole body of evidence here, but 6.A, Medicare patient population.
DR. LEWIS: Courtland Lewis, four.
DR. GOODMAN: Dr. Kim is next.
DR. KIM: Edward Kim, three.
MS. KENDIG: Susan Kendig, three.
DR. JARVIK: Jeffrey Jarvik, two.

DR. DAVIS: Charles Davis, one.
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MS. DARLING: Helen Darling, two.
DR. BOZIC: Kevin Bozic, one.
DR. BAKER: Ray Baker, two.
DR. SATYA-MURTI: Satya-Murti, two.
DR. RAO: Raj Rao, two.
DR. KIRKPATRICK: John Kirkpatrick, two.
DR. JUHN: Peter Juhn, three.
DR. STEINBROOK: Robert Steinbrook, two.
DR. SLOAN: Andrew Sloan, three.
DR. SCHWARTZ: Sandy Schwartz, two.
DR. MCDONOUGH: Bob McDonough, two.
DR. GOODMAN: Thank you all.
MS. ELLIS: One more. Got it.
DR. GOODMAN: Thank you. We're going to move now to question 6.B, which is another form of external validity, this time in community-based settings. And, you know, when you look at various topics that have come before MedCAC before, sometimes more, sometimes less the evidence is applicable to community settings. I think we heard some mention made of that today and we will ask you to consider about the confidence that the conclusions that you've derived from questions one through five are generalizable to community-based settings. Any comment or question at this point prior to voting? Dr. Kirkpatrick.
DR. KIRKPATRICK: Comment. When I reviewed the
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literature, there was a good mix of both university or non-community-based settings and community hospitals that were participating in the studies. Did you guys even look at that when you looked at your analysis?
DR. RATKO: We didn't look at it systematically but our observation would be the same in looking at where the studies came from, but we didn't do a systematic analysis on that.
DR. GOODMAN: So you did not do the slice and dice on the source, but thank you, sir. Dr. Schwartz.
DR. SCHWARTZ: Just a caveat. I agree with that, but that doesn't preclude that there still could be a difference, because the studies did not stratify by the nature of the practice in doing the analysis.
DR. GOODMAN: So we really don't know actually.
DR. SCHWARTZ: At least there were a lot of patients involved, so we don't know if they were all done on a referral-based practices, or referral of a referral already.
DR. GOODMAN: Understood. Dr. Bozic.
DR. BOZIC: Just a point of clarification. I've always made the assumption that RCTs in general are reporting on efficacy and not effectiveness, and therefore they're not necessarily generalizable to the way medicine is practiced in the community regardless of whether it's
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done in an academic center or a community hospital. I interpret this question to mean can you generalize the results of a randomized control trial where patients are treated in a specific way and followed very closely to practitioners that are practicing out in the real world that are not following their patients as closely and not treating their patients the same way. That's how I interpret this question.

DR. GOODMAN: Your point is well taken, if you will allow me to add clarification there. Most randomized control trials, most but not all RCTs involve carefully selected patients with very specific inclusion and exclusion criteria, very specifically defined intermediate and long-term outcomes, often under special conditions of care and so forth. So typically when something is an RCT does not necessarily mean that it's what we sometimes call an efficacy trial. There are pragmatic control trials that are randomized, other simple trials that might involve randomization. So just because something's an RCT does not mean it only addresses efficacy. Usually it does and usually it derives from the fact that a large body of evidence of RCTs comprises studies done for purposes of receiving FDA approval for drugs, and typically those I would suggest, not equating RCT with efficacy, but some RCTs may address effectiveness in a rural setting. It's

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up to you, Dr. Bozic, to judge whether the evidence you heard today, whether it's RCT or any other study design, about this efficacy versus effectiveness type of evidence. Dr. Jarvik.

DR. JARVIK: Just by way of clarification, if there are other study designs that were taken into account such as observational data, we should take that into account in making this decision?

DR. GOODMAN: Absolutely, yes. Not all the evidence we heard today was RCTs, and quite often RCT evidence is complemented by evidence from other sources that may shed light on what happens in clinical practice. Observational studies may consist of claims data analyses, registries and other forms of study. Thank you, Dr. Jarvik. Dr. Kim.

DR. KIM: This brings up a question for Dr. Ratko. Could you comment on more findings within the observational studies regarding community-based academic studies, the overall strength and directionality? We didn't hear much about it except for that handful of well designed clinical trials.

DR. RATKO: I guess I really can't address that because we really didn't look.

DR. KIM: So many of the things you mentioned this morning were on the radar, but yet they didn't meet

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the standards for inclusion in the review?

DR. RATKO: Correct. We were looking for

directly comparative evidence, peer reviewed studies.
DR. GOODMAN: By the way, comparative studies might not be RCTs either. Thank you. Dr. Lewis.
DR. LEWIS: Another question, Dr. Ratko, sort of a corollary. Did you look at the disclosures in publications by authors, whether or not they were related to academic institutions?
DR. RATKO: We looked at them just as part of studying the papers but we didn't analyze that at all.
DR. LEWIS: You didn't specifically analyze whether the authors who were involved with these particular studies, whether they were community-based or academic facility-based as part of the disclosures about the companies that funded the study and that sort of thing?
DR. RATKO: Well, I can say disclosures were provided for most of the papers, and probably about 90 percent were industry sponsors.
DR. GOODMAN: I just want to add, in some evidence appraisal schemes or tools, there may be a question that deals with who funded the study in the disclosure statement, but it doesn't sound like the technology assessment looked at that specifically, or

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analyzed it, I should say.
DR. RATKO: We didn't analyze it but we did note it in the USPSTF, so that is in the report.
DR. GOODMAN: So the USPSTF does ask that.
DR. RATKO: Yes.
DR. GOODMAN: Thank you. Dr. Kirkpatrick.
DR. KIRKPATRICK: One other question that would lead to generalizability is whether centers that have a lot of experience doing a procedure would be different than those that just had a few in the studies. I think we had a presenter from Medtronic, I don't know if they were involved in the IDE studies on either the tibia fractures or the original anterior lumbar fusions, but if they could comment as to whether they saw a difference in the centers that had multiple patients versus the ones that had few.
DR. GOODMAN: Would that be Dr. Kuntz or someone else from that organization? And would the gentleman approaching the podium identify yourself?
DR. KENNER: I am Jason Kenner, I work at Medtronic, and perhaps you're referring to Dr. Fon. Dr. Fon had a family emergency and left at lunchtime. I do not believe he was a participant in either of those studies, though.
DR. KIRKPATRICK: I don't have a perfect memory, but on the FDA panel the subanalysis when it was presented

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was that there's no difference between high volume centers versus low volume centers, but I can't remember perfectly from a long time ago.
DR. GOODMAN: Well, whether it's high volume or

low volume may be of interest to CMS in the future, but I don't think we heard much about it today. Thank you. Dr. McDonough.

DR. MCDONOUGH: In that FDA, was there any analysis of whether the surgeons themselves had had a financial relationship in the outcomes?

DR. KIRKPATRICK: Again, it's a vague recollection because it was many years ago on the anterior lumbar fusion, but I seem to recall that when they looked at those that did have involvement such as consultants and that sort of thing versus those that did not, there was not a difference in the success rates.

DR. GOODMAN: Thank you. I am hearing, just for the record, quite a bit of interest among our panel members about funding sources and potential conflicts of interest. Dr. Bozic.

DR. BOZIC: Again, I just want to get back to the point of what evidence was considered in this review and what was presented. I completely agree that large observational cohort studies and registry data are useful tools in gathering information on effectiveness, and I

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also agree that they were not excluded in the analysis that was presented today, but the analysis presented today included RCTs, 50 percent RCTs and the other 50 percent were relatively small case series or case reports. They were not large observational cohort studies or registry studies included in the data which we considered today. So I just wanted to make that clear indication about the generalizability and making conclusions about effectiveness on the data we considered today.

DR. GOODMAN: Dr. Ratko is nodding in the affirmative. Dr. Ratko, so of the comparative studies, comparative studies, for most or all of those RCTs, were there comparative studies?

DR. RATKO: I will give you an answer.

DR. GOODMAN: Dr. Ratko is perusing his report for an answer. I believe there were, were there not, 41 comparative studies?

DR. RATKO: 41 studies total.

DR. GOODMAN: 41 comparative studies total, right?

DR. RATKO: Right. And of those, six were BMP-2 RCTs, two were BMP-7 RCTs, and that's the on label, and in the off label, nine for BMP-2 were RCTs, and seven for BMP-7 were RCTs.

DR. GOODMAN: Okay. My quick math tells me 24

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of the 41 were RCTs for one reason or another, correct?

DR. RATKO: Correct, 24.

DR. BOZIC: Of the total studies, slide 26 says there are 41, and it seems to me -- are you saying 24 of the 41 are RCTs?

DR. RATKO: Correct.

DR. BOZIC: And then out of the non-comparative studies, the numbers are, they would be case reports and case studies?
DR. RATKO: Yes.
DR. GOODMAN: Thank you very much. So of the comparative studies, a little more than half were RCTs, but there were other comparative studies that weren't RCTs, thank you.
Okay. 6.B asks about, how confident are you that these conclusions are generalizable to community-based settings, community-based settings? And everybody has their handy dandy little data thing there ready to punch in a number. Let's start with Dr. McDonough this time, and we'll move to his right, which would make Dr. Schwartz the second person. Dr. McDonough.
DR. MCDONOUGH: Bob McDonough, three.
DR. SCHWARTZ: Sandy Schwartz, four.
DR. SLOAN: Andrew Sloan, four.
DR. STEINBROOK: Robert Steinbrook, three.

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DR. JUHN: Peter Juhn, two.
DR. KIRKPATRICK: John Kirkpatrick, two.
DR. RAO: Raj Rao, two.
DR. SATYA-MURTI: Saty Satya-Murti, two.
DR. BAKER: Ray Baker, three.
DR. BOZIC: Kevin Bozic, two.
MS. DARLING: Helen Darling, two.
DR. DAVIS: Charles Davis, two.
DR. JARVIK: Jeffrey Jarvik, two.
MS. KENDIG: Susan Kendig, two.
DR. KIM: Edward Kim, two.
DR. LEWIS: Courtland Lewis, two.
DR. GOODMAN: Thank you all. Batting a thousand, thank you. That covers our voting questions, one through six. Thank you especially for being our guinea pigs for the new voting technology. We'll have some discussion later on about which we prefer.
We have one more question, by the way, which is our discussion question, and that's question number seven. This is not a voting question. And here what we're going to ask you to do is go back up to 30,000 feet and sort of look down on all the evidence we considered today, and consider what kinds of research are needed to fill some of the evidence gaps.
So the first obvious question here is, do you

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think you see any obvious evidence gaps, any obvious important evidence gaps, and if you do, what sort of research may be necessary to address those gaps. And I will just ask you, let's try to stay within the general bounds of BMPs and the kind of anatomic sites we talked about today, another limitation is PMA versus HDE, so try to stay in the same ball park, if you will, but what are some of these important evidence gaps and ways you think

they ought to be filled. And I might add that this is intended not only to be helpful to CMS, but we hope that this is helpful, and instructive perhaps, to those who are preparing research agendas in the public and private sectors, anybody who's got something in the pipeline that they might want to consider presenting for third-party payment at some point, it's probably smart if you listen to hear about what sort of evidence the independent experts think might be addressed. Dr. Schwartz had his hand up first, I believe. Dr. Schwartz, an evidence gap that might need filling.

DR. SCHWARTZ: A couple quick ones. One is I think long-term follow-up. The groups, two is in the patients who are at high risk, the numbers for this spoke about them with very little information about knowing, whether steroid use or osteoporosis, things like that, whether this helps us know what -- we know they're at

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higher risk for having poor results. Third is, I think we need some better measures of surgical approach where relevant, for example in the neck whether we're doing anterior or posterior.

For some of these, for example, I mean just Louis from Medicare, I think these might be things that are required before making coverage decisions if we ever get to that, other things like whether we have meaningful outcomes might be a good thing to specifically put in, because what's out there isn't very good, and, you know, we will need that information.

DR. GOODMAN: Thank you, Dr. Schwartz.

Dr. Sloan.

DR. SLOAN: Thank you. I second everything that Dr. Schwartz said, but I also, I'm really struck by really how little we seem to understand biologically. My understanding of the basic science on this particular issue is limited largely to what was presented, but, you know, it seems like there are a lot of BMPs, we only looked at two of them. The best animal data showed that the fusion was much better when you combined them, and yet none of the studies here ever attempted that. Now obviously you've got to have single-agent use before you can go to two-agent use, but I think we really don't understand very well the basic biology here.

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There's not even been much mention of even what the receptors are, so are the proteins, you know, we know that stem cells in the older patients are diminished in number and seem to have decreased capacity, but what about the proteins, what happens to the receptors, how do the steroids affect those. I think that one could possibly make the case for doing some basic studies using human tissues in some of these patients, at least when they go (inaudible, off microphone) they're going to be there anyway. People at the NIH and NCI did something called

the Cancer Genome Atlas project looking at thousands of genes. (Inaudible, off microphone) important problem, and one could look at a small number of proteins perhaps.

DR. GOODMAN: Thank you, Dr. Sloan. So there's some interest here, if I could summarize that into mechanism of action. Thank you, sir. Dr. Bozic.

DR. BOZIC: I think one of the gaps in evidence is the lack of generalizability of the data that we heard today to real world practice and/or to the Medicare population, and I think the way to address that evidence gap is to include large observational cohort studies and analysis of administrative claim data in future analyses to determine the true effectiveness of these procedures. That's one gap.

The other gap I think is, we really have a poor

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understanding of what are the clinical, demographic and procedural covariates that most influence the outcomes of interest in this particular population, and we would need to do multivariant progressions to look specifically to see for this population, what are the covariates of interest.

DR. GOODMAN: Excellent point, and that was a very specific and helpful way to address the gaps about generalizability. Dr. Baker.

DR. BAKER: You know, we have a number of different indications that might be useful for BMP, but again, Dr. Schwartz, to echo your point, we have scoliosis patients, we have (inaudible) patients, we have patients who have osteoporosis, on dialysis, patients with tobacco usage, steroids, and we don't really have a clear understanding among those cohorts of which ones are going to have improved outcomes, and so I think that's going to echo the point.

Although we don't have a really good idea of the dose-response curve, with posterolaterals we use up to 40 milligrams and in the anterior you're using, you know, 48, and when it comes to the risks that are involved, the (inaudible, off microphone) tumor risk, we really need to do that, which brings me to the harms point.

And that is, as pointed out in the health

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technology assessment, there was a poor standardization of how harms are collected or stratified within the data, so if you could in a more systematic way as you're doing these trials, which are very expensive, make sure that we take care of harms and look at that.

The last thing I'll say is that, although I could not use this at all to date to look at my decision-making, I found it very interesting, the AHRQ HTA looking at the costs, looking at the cost to quality and looked to the value of ICER. We're moving into a time where we're going to have to ask ourselves, what is the incremental benefit of this technology in patients, so I

found that very compelling, not today, I didn't include that, but I think certainly this is a precursor of things to come that we need to be taking into consideration.
DR. GOODMAN: Great comments, Dr. Baker. By the way, you made reference to the ICER. That's the incremental cost effectiveness ratio which is typically defined, though not always, as cost to quality of best care, correct, Dr. Baker?
DR. BAKER: And you take a particular delta cost over (inaudible).
DR. GOODMAN: Very good, sir, thank you. Dr. Kim and then Dr. McDonough.
DR. KIM: I just want to follow on with what Dr.

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Baker said regarding the dose range, and secondarily to address some of the issues around generalizability to the Medicare population looking at the dose range, what is a minimally effective dose and an optimal dose across different age ranges with the different covariates that have been mentioned before that could mediate the benefit-risk of BMPs, but also when compared to the effectiveness of BMPs versus the alternative, which might be an autograft.
DR. GOODMAN: Excellent point, thank you, very helpful in terms of guidance for future evidence. Dr. McDonough, and then Dr. Davis.
DR. MCDONOUGH: I think one of the things that our discussion, some of the questions from CMS have brought up, are maybe better evidence about what are the effects of BMPs on outcomes that matter to patients, because so much of the evidence is focused primarily on radiographic evidence of improved fusion.
I think we also have found that we need better evidence on adverse effects, and that's going to require follow-up in large clinical databases, perhaps registries or some other source.
The issue about the harms of autogenous tissue harvesting and to be able to quantify that and put parameters on that, how much of that is a problem, how

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important is that as a problem considering the potential benefits.
And then the question of industry funding, you know, can we get more studies where there might not be a relationship with industry, and can we get to some studies involving clinicians that might not have links to industry, and see if there's any outcome differences there.
DR. GOODMAN: Thank you, Dr. McDonough. Dr. Davis is next.
DR. DAVIS: I think it would be beneficial to see some studies that looked at comparison of demineralized bone matrix, and again in comparison to BMPs. If not moved to the BMPs, it may be that

demineralized bone matrix would contain local BMPs and perhaps other factors that would facilitate bone growth and fusion may be more effective than isolated BMP, and certainly a large supply available of them.
DR. GOODMAN: Thank you, Dr. Davis. Dr. Juhn is next, and then Dr. Satya-Murti.
DR. JUHN: So as the industry representative, my comments really are directed at my colleagues in the industry, and I think really two suggestions. The first is from a methods perspective, from a study design perspective, to really think about the difference between
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a non-superiority design versus a superiority design. And you're already spending millions of dollars recruiting patients into these trials, and if you really incrementally just added a few more patients to specific groups, you could actually make a superiority claim, and I think that is something that I would just seriously ask that the industry companies consider.
The second suggestion I have is to review this technology assessment to see where you have fallen short. So for instance, the various indices that are used, like the USPSTF, you should really ask yourself why you did not get the highest grade, and really ask what's the delta between the way that the studies that were described in the TEC assessment were rated that way, and what does it take for you to actually get those high ratings. Because I think as you know, that we'll just have a repeat of these types of situations that come before the panel and you have lots of data, but the data is not really adequate given the criteria that we're using.
DR. GOODMAN: Thank you, Dr. Juhn.
Dr. Satya-Murti.
DR. SATYA-MURTI: This is just a point about, three times earlier this was brought up. All of our fusion patients come in needing some type of fusion, that's the starting point. But if you go backwards in
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time, the types of indications for which fusion was needed is in fact multiple and diverse, and in going forward for future studies I would like to see comparison trials or RCTs that further classify patients into those that were due to scoliosis, to trauma, and other types of indications, rather than lump them all together. That just seems like too broad a category to assess them.
And the other question I have is this bone graft pain that we heard much about today, that's in the immediate postop period as mentioned, but that pain that occurs post-grafting is not so tangible, so what is the natural history, are we looking at it in such a short interval and then comparing it to BMP results, or is it sustained at the iliac crest site? And then we heard about nerve damage, and I don't know what kind of motor nerve is in that vicinity. So we just don't know enough

about what the natural history of left-alone graft pain would be.
DR. GOODMAN: Thanks, Dr. Satya-Murti.
Dr. Steinbrook is next.
DR. STEINBROOK: Just a couple of points, I'll try not to duplicate some of the comments that have already been made. I think that the whole area of study design is ripe for consideration. I think to the extent that these studies are being done, it seemed like there
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was an issue of, not directly in the field, of course, but an understanding of how to correlate radiologic findings with clinical information, and that that probably is something that could be addressed in a consensus sort of way, ideally I would think in a consensus sort of way independent of those who have interests in particular products, and to sort of raise the bar on study design to get more effective information out of studies.
And the other point I will make, which is somewhat different, but if we look at this from 30,000 feet and we're looking at this in terms of Medicare beneficiaries, and I'm not a surgeon, but at some point you begin a process where you have to decide okay, does this situation lead to a surgical intervention or some other course for a period of time, because that will start happening once you start to use these things. And I think that part of this in terms of the best treatment is when do we want to start down these paths, and you need to think about that as well.
DR. GOODMAN: Excellent point, we need to think about how to manage patient care over time, excellent.
Ms. Kendig, I think.
MS. KENDIG: Yes. Just to build on some of the comments that have already been made, in terms of, someone made the comment about more longitudinal studies, but I
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think also clinically looking at what those long-term effects are. We heard a little bit about that this morning, but probably more study is needed in terms of long-term effects past the two years.
And also in terms of generalizability for the Medicare population, looking not only the medical conditions, the medical variants or the effects of such things as smoking, but also some of those social determinants of health such as socioeconomic status, et cetera, in terms of outcome, support to adhere to the prescribed clinical arrangements postoperatively, that sort of thing, and other social determinatives of health.
DR. GOODMAN: Thank you, Ms. Kendig. Dr. Lewis is next.
DR. LEWIS: I think those comments are well said and we do need to put more focus on patient-centered outcomes. I know the Oswestry score includes some of those elements. Certainly arthroplasty surgery, and I'm

not clear whether it's used in other spine surgery as well, but we use the Short Form 36 and its multiple variants to see if there's sensitivity to change the outcome, and that might be helpful to us in this particular kind of situation, so I raise that as a possibility.
DR. GOODMAN: Great point, thank you. Dr.

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Jarvik.
DR. JARVIK: Another potential outcome to focus on would be reoperation rates, and we heard a little bit about that today, but I think that would be a ripe area to focus on.
DR. GOODMAN: Thank you, sir. Dr. Kirkpatrick, a short comment?
DR. KIRKPATRICK: I would just say that all the panel comments I would also back up, they're all good suggestions. With regard to basic science mechanisms, I think looking at the specific input from synergy. We're looking at two molecules out of 20-something, and naturally occurring 20-something, you can't replicate with just one. So there may be synergy among the different molecules and, you know, heaven forbid if two companies get together and see if the two work better together, but who knows. But that's one thing I think in basic science should be looked at.
And then the other thing that was brought up under comorbidities are the ones that we think are actually worse, which were brought up by some of the association speakers, was things like renal failure, other sources of osteopenia and osteoporosis. Are those specific things better with graft or BMP, versus not as well.

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DR. GOODMAN: Thank you. And I believe Ms. Darling, you have the final comment. Ms. Darling.
MS. DARLING: This is actually about the assessments, and I think to me since one of our questions will always be what will be the impact on Medicare beneficiaries, that actually Medicare is one of the few places in the world that has detailed data on its population at all times, including medical outcome studies. So I would suggest that as background material that we would have a detailed report. More recently, there's data that suggests that disability rolls are growing, so we're going to probably have a slightly different population to look at as well because of the recession and the impact that had. So the kind of distribution of age, morbidity, disabilities, you know, a lot of detailed information would allow us to do a much more rigorous job ourselves of looking at what's the population that we're trying to serve.
DR. GOODMAN: Great point, especially what Ms. Darling said about how this population is evolving now,

thank you. Dr. Schwartz, this will be the final words.
DR. SCHWARTZ: I just wanted clarification about one thing. I think if we're going to do long-term follow-up it will be important to look at functional status in particular, because fusion may not be fusion.

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In other words, these things may affect the functional outcomes that one gets from different, whether using allograftic or non-allograftic ways of approaching this. And then the other is just on the harms that were mentioned, and I would just like to clarify. It always surprises me how we view particle compounds and assume that their only impact is going to be at the target organ that we're concerned with. And if we're going to be using these in large numbers of people, which we will, I think it is incumbent upon us to sit down with biologists and the people who understand how these things work, and make sure that we have an understanding that we're not causing other problems or, if so, that they're problems that we're willing to deal with.
DR. GOODMAN: Okay, thank you, Dr. Schwartz. In closing then, this panel today took a very careful look at the current terrain of evidence, and we covered the four corners of this terrain of evidence for various indications, for various regulatory requirements, and I think there was some pretty clear voting on our voting questions. We appreciate the panel's effort on clarifying what those questions ought to be and what we're considering.
This is today a very strong example of how this MEDCAC process as implemented by CMS is a public hearing

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of the available evidence in an explicit transparent fashion, and judging by the comments I just heard over the last 15 or 20 minutes with regard to evidence gaps and ways to address them, I hope no one leaves the room thinking that there is some evidence that we don't need to take a closer look at. There are a lot of evidence gaps that need to be filled. We need to consider carefully what sort of study designs among the many types we discussed today need to be used to address those.
So this meeting gives some pretty clear and I hope very helpful signals to researchers, practitioners, patients, innovative companies and others about the kind of evidence that we hope you will be thinking about putting into the pipeline so that as this particular clinical problem doesn't get any smaller, including a lot of us here on the panel, that this problem doesn't get any smaller, we will have better ways to address this very important clinical problem. It ought to be evidence-based, it can inform patient and doctor decisions, it can inform third-party payer decisions, it can inform further research.
Thank you all very much, it's been a superb day,

we very much appreciate your attention to the evidence. Thank you very much to our presenters who did such a superb job under time constraints. And thank you finally

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to the superb staff here at CAG at the Centers for Medicare and Medicaid Services. And our trusty court reporter, ever vigilant, thank you, sir. Thank you all very much.

(Whereupon, the meeting adjourned at 2:49 p.m.)