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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Coverage Advisory Committee

October 6, 2005

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

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Panelists

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Panelists (Continued)

Industry Representative
Kim K. Kuebler, M.N., R.N.

Guest Expert Panelists
John S. Kirkpatrick, M.D., F.A.C.S.
Sean D. Sullivan, Ph.D.
Kenneth Koval, M.D.
Barbara D. Boyan, Ph.D.

Executive Secretary
Kimberly Long

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PANEL PROCEEDINGS

(The meeting was called to order at 8:18 a.m., Thursday, October 6, 2005.)

MS. LONG: Good morning, everyone. I am Kimberly Long, executive secretary for the Medicare Coverage Advisory Committee. The committee is here today to discuss the evidence, hear presentations and public comment, and make

recommendations regarding treatments for bone fractures that fail to progress to union. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflict of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations also disclose any current or previous financial involvement in any orthopedic device company. This includes direct financial involvement, investment, consulting fees and significant institutional support. If you haven't

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already received a disclosure statement, they are available at the table outside of this room. We ask that all presenters please adhere to the 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 in front of the stage for the next speaker, and proceed to the chair when it is your turn. For the record today, voting members present are Leslie Fried, Lishan Aklog, Marc Berger, Kim Burchiel, Harry Burke, Robert Christenson, Mark Fendrick, Alex Ommaya, and Deborah Shatin. A quorum is present and no one has been recused because of conflict of interest. The entire panel, including nonvoting members, will participate in the voting. The voting scores will be displayed on the screen following the meeting. Two averages will be calculated, one for the voting members and one for the entire panel.

Two quick announcements: Anyone

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requiring transportation following the meeting should sign up at the registration desk during the break. And also for the panel members, if you could please speak into the mike, you may have to move them since we have to share.

I would now like to turn the meeting over to our director, Dr. Steve Phurrough.

DR. PHURROUGH: Thank you, Kim, and I just want to welcome everyone to the meeting today and thank the panel for their agreeing to be part of this. We find these to be extremely helpful in our decision-making process and appreciate your participation. And with that, let me introduce our panel chairman today, Dr. Barbara McNeil.

DR. MCNEIL: Hi. I would like to welcome you as well, and what I would like to do now is do a 30-second introduction on behalf of all members of this committee, and they will indicate whether or not they have any conflicts of interest as well.

I'm Barbara McNeil, from the Department of Health Care Policy at Harvard Medical School and the Department of Radiology at the Brigham and Women's, and I have no conflicts.

MS. FRIED: I'm Leslie Fried, I'm from

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the American Bar Association Commission on Law and Aging. I direct the Medicare Advocacy Project for the Alzheimer's Association, and I have no conflicts of interest.

DR. AKLOG: My name is Lishan Aklog. I am associate chief of cardiac surgery at Mount Sinai Medical Center and I have no conflicts of interest to disclose.

DR. BERGER: Marc Berger, vice president of outcomes research and management for Merck & Company, Inc. No conflicts of interest.

DR. BURCHIEL: I'm Kim Burchiel, I'm the chairman of the department of neurological

surgery at Oregon Health and Science University, and I have no conflicts.
DR. BURKE: Harry Burke, associate professor of medicine at George Washington University, and I have no conflicts.
DR. CHRISTENSON: Bob Christenson, professor of pathology, University of Maryland Medical Center, no conflicts of interest to disclose.
DR. FENDRICK: Mark Fendrick, professor of internal medicine and health, University of Michigan. No conflicts.

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DR. McDONOUGH: Bob McDonough, Aetna, Inc., no conflicts.
DR. OMMAYA: Alex Ommaya, director at the Institute of Medicine. No conflicts.
DR. SHATIN: Deborah Shatin, Center for Health Care Policy and Evaluation, United Health Group. No conflicts of interest.
MS. KUEBLER: Good morning. Kim Kuebler, regional medical scientist for Banneker Ingelheim, representing industry. No conflicts of interest.
DR. BERGTHOLD: Linda Bergthold, Watson Wyatt, no conflict.
DR. KIRKPATRICK: John Kirkpatrick, orthopedic surgeon from the University of Alabama at Birmingham. I do have the appearance of conflicts of interest as I hold stock in Zimmer and Johnson & Johnson. Thanks.
DR. SULLIVAN: Sean Sullivan, professor of public health and medicine at the University of Washington. No conflicts of interest.
DR. KOVAL: Ken Koval, professor of orthopedics at Dartmouth-Hitchcock Medical Center. I am a consultant for Stryker and I was previously a consultant for Pugh.

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DR. BOYAN: Barbara Boyan. I am a professor at the Institute of Bioengineering and

Bioscience at the Georgia Institute of Technology and the Center for Orthopedics at Emory University Medical School. I have a grant from EDI and from Orthobiologics, which previously owned one of the electrical stimulation devices. I also own stock in Osteobiologics, which is an Orthobiologics company, and I am on the board of directors at Archer.

DR. MCNEIL: Thank you very much. I think what we will do is move right on to the presentation of the summary questions that we will be voting on, and ask Dr. Feinglass to make the presentation. I would like to reiterate what Kim indicated, and that is that we will be keeping to a very, very tight time line.

I would also encourage all the speakers to say what you want to during the morning presentation. After lunch the panel will have questions for you, but once we go into open panel deliberations, I expect that the deliberations will largely be conducted among members of the panel. There may be a rare question on facts that we would like to get from the audience. That

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said, therefore, you should put as much information as you possibly can within your time limit during the morning session. Ideally, the information should be posited towards the questions that we are going to be answering. Extraneous information is good, but if it doesn't get us to the questions, it's not going to be very helpful. Another point is that redundancy from one speaker to the next also isn't terribly helpful.

So with that in mind, Dr. Feinglass.

DR. FEINGLASS: Good morning. I think we're having a few technical difficulties with my screen; I can see it, you can't, but that should be fixed shortly.

Today we're going to be speaking about nonunion fractures and modalities used to treat them. As many of you know, there are some

controversies about the definition of nonunion and there are some controversies around about the treatments. The goals of this MCAC are to address some of these controversies.
In lieu of time, I'm going to fly through these questions, you have all seen them. There are eight. You should have picked up some

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printouts out front if you don't have them with you.
And the presenters are Karen Schoelles, who is presenting the technology assessment that is from ECRI. There will also be David Carmack, who is the medical director at Eastern Maine Medical Center. He will be discussing nonunion and the role of e-stim, electrical stimulation among other things. And finally, we'll hear from Dr. Alan Jones, director of orthopedic trauma at Baylor University. He will be addressing nonunion scan and the orthobiologics.
While I'm passing on going through all these, I'm happy that our screen is now working, and thank you for coming.
DR. MCNEIL: Karen, welcome.
DR. SCHOELLES: Thank you. Can I take her extra minute?
DR. MCNEIL: No.
DR. SCHOELLES: I didn't think so. I am Karen Schoelles, I am medical director of the evidence-based practice center and health technology group at ECRI, which is a nonprofit medical services research organization. This work was commissioned, as you heard, by CMS through

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AHRQ.
The diagnosis of nonunion was addressed in our full TA in a narrative review along with risk factors for the development of nonunion, current standards of care, and outcomes commonly reported. I am not going to go through that portion of the report, trusting that you digested

it. The systematic review is the portion that your questions are focused on, that being the evidence for the benefits and harms of bone growth stimulating devices and orthobiologics in the treatment of nonunions.
We had been asked to look for evidence regarding variations in outcomes, variations in surgeons performing the procedures, et cetera, but we're not able to find any studies that directly address how that might impact outcomes.
The bone growth stimulating devices that are being addressed in your questions, we categorized slightly differently than the categories that we had been given. Ultrasound, it's applied as an external device for about 20 minutes a day. Direct current devices are what are referred to in your questions by internal electrical stimulation, these are electrodes

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implanted at the fracture site. Capacitance coupling is an external device that conducts electrical current through to the site to promote healing. Another external electrical device is the pulse electromagnetic fields devices.
We covered shock (inaudible) therapy in our report, but we won't be discussing that in view of your questions.
We have a limited amount of information in our report on orthobiologics, the allomatrix, injectable putty, another compound prepared from allograft, and it should be partially purified human bone morphogenetic protein. And then the recombinant BMP-7 products known as OP-1.
The inclusion criteria for the systematic review portion of the report is listed on the slide. We were choosing the time period of 1990 to 2005, thinking that we were going to be thinking about these therapies against the backdrop of current surgical therapy, and knowing that many surgical techniques had changed and the other characteristics of a typical patient has certainly changed. However, we did run into some

difficulties that I will come back to later by not including earlier studies.

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We required a minimum of 20 patients in the studies, thinking that in the terms of the percent healing that is commonly described and trying to understand whether that was really different from the healing rates of patients who didn't receive the devices or orthobiologics. We spent some time doing a limited assessment of quality of the evidence, particularly focusing on the internal validity of the individual studies, and developed an a priori list of things that we wanted to be looking for in studies to decide whether they had some, or what the degree of internal validity might be. These are our criteria, they are based on a framework provided through AHRQ and the preventive services task force, but there is some arbitrariness, and we find this reasonable.

For the RCTs, we were looking for adequate randomization and an equal distribution of confounders. In the cohort studies, that at least the confounding variables would be acknowledged and either the patient group be restricted based on certain characteristics known to influence healing or that the analyses done would adjust for those. We looked for studies to

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report dropouts, crossovers, and compliance with therapy.

We wanted to be sure that the interventions were clearly defined, that loss to follow up was reasonable, so we chose less than 20 percent. In many of these studies, the nature of the treatment was such that you couldn't really blind patients and providers to the treatment assigned, so we required that, we asked that they at least be doing blinded outcome assessments, in other words, a radiologist not involved in the care of the patient be assessing the radiographs.

We wanted to be sure that they included the outcomes that we decided at the time seemed to be important, not just radiographic signs of healing but also some more patient-oriented outcomes. And in their analyses, we wanted to see whether they had adjusted for confounders. So we set up an arbitrary rating scale for the studies. We rated as good internal validity meeting all of those criteria, the fair designation for those that missed only one or two of the items, and the low designation for those that missed three or more. So this is the evidence base that we have. As you can see, we've had two RCTs that

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were both rated good internal validity. The majority of the studies were retrospective series, and for a variety of reasons were in the low internal validity category. We did have two prospective series that we rated as fair and two RCTs.
After doing the initial version of our report, it was sent out for review and we were asked to add some supplemental information into the record, but which I'm not going to be presenting in the slides, the reason for that including the fact that the reported studies of the electrical stimulation devices were conducted prior to 1990 and have not been repeated. So I'm not going to be including studies from that era in these slides, but they are in the tables and a copy of the report.
We also looked back again at abstracts and discussed some of the findings of studies available only in abstract in the report, but again, they are not in these tables.
We found a variety of definitions of nonunion in the literature. There seemed to be general agreement that lack of progression to healing for a minimum of three months was a

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necessary criterion, and that was typically

assessed on the basis of radiographs. If a patient had on physical examination movement at the fracture site, that was considered sufficient evidence for nonunion but certainly not a necessary criterion. There are a lot of differences in terms of the temporal definitions of nonunion. There was a survey conducted by Bhandari published in 2002 of over 400 orthopedic surgeon members of the American Academy of Orthopedic Surgery where he asked them a variety of questions about diagnosis of nonunion in patients with tibial fractures that have not healed. When asked how much time would have to have passed since the initial injury before you would be willing to declare a patient not to have healed, the mean was six months, but the range was anywhere from two months to a year. In the studies that we examined, the time most commonly cited as their definition of nonunion was nine months post-fracture without healing, but the rate was anywhere from the 16 weeks in the Sharrard study to some studies that had another definition, what they called established nonunion, by which they meant greater than a year.

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There are three studies of ultrasound in the study set. One of them is registry data that was required by the FDA to be kept by the manufacturers. The other is a prospective series done by the same individual who had published the registry data, and a second prospective series. The same issue will come up with all the different technologies, that patients are receiving other types of therapy in conjunction with the treatment being studied. In many cases, if it's internal devices, they have (inaudible) and the patient has failed to heal despite their presence. But in other cases surgical procedures would be done, external fixators may have been applied, new casts may have been applied. The bone types included in the ultrasound studies are probably some of the, this

is probably one of the broader range of types of bones studied, but as in all the different categories, studies of the tibia predominated. The results of the ultrasound studies will sound very similar to results in just about all the other technologies in that, as you can see in the three studies that we have, the range of results was anywhere from 76 percent to 86 percent of the

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patients healed. The relevance to the Medicare population is determined by patient age alone. All I can say is that one of the prospective series had six patients over the age of 65 and all of them healed. The registry included something less than 50 patients who were over the age of 70, and 71 percent of those patients healed. The direct current studies, there were three. The study by Brighton in which he compared, essentially a sequential series of direct current studies from 1970 to 1982 roughly, the capacity for coupling which he switched to in 1982, and he was comparing them to patients in those same time periods who underwent bone grafting. Then there were two other retrospective case series of just direct current. Direct current, again, is the implantation of the electrode into the fracture cite. Patients were receiving other therapies simultaneously, typically asked to not bear weight during their treatment, but as you know from the background information, immobilization of the fracture is critical for healing. In this group of studies, the tibia far

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outweighed the others and the results, again, 72 percent in one study, 86 percent in the other, patients who healed. We did not find any data specifically on patients over the age of 65. Some studies did include patients over the age of 65 but we were

looking for outcomes to be reported for those patients.
There was one long-term follow-up study trying to get at potential long-term failure or adverse events. One of the patients very early on had been in a gymnasium, and they didn't tell us what degree of activity was going on at that time, but there was a refracture at the site soon after the electrode had been removed. A second patient required a second device to go on to heal completely, and the other 35 patients of their original 84 patients remained united. There were a number of patients they could not locate by the time of their ten-year follow-up.
The capacitive coupling studies, including one RCT and two retrospective studies, one being the one by Brighton, again, casting, bracing, external fixators used simultaneously, bones studied, the tibia is the overwhelming one.

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The RCT included 21 patients.
One point I want to make about RCTs in the field is that virtually every author mentioned that they had a great deal of difficulty recruiting patients for the studies. Many of them had, I don't know whether they had done power calculations ahead of time, but most of them fell far short of their goals in trying to do RCTs.
They included only patients who had had their nonunions for at least nine months. They had an active device group and a dummy device group. Six of ten patients in the active device group healed and none of the patients of the 11.
There was not -- there was presentation of the duration of nonunion prior to the study but not a lot of other patient characteristics that I might have wanted to see to be competent that there weren't many confounding, or wasn't some confounding problems. The additional studies, one in Brighton's, we were only able to get the actual data on ten patients, seven who healed, and in the other series, 22 of 32.

There were two patients over 65 in the dummy device group in that RCT, one was 68, one was 87, and neither of them healed, and one of the

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two patients over 65 in the retrospective series. There were seven studies of pulsed electromagnetic fields. The two RCTs I'll spend the most time on, one prospective case series, and the rest were other retrospective studies. Again, long leg plaster casts, external fixators, osteosynthesis, in other words, plates and screws and such, and braces. Tibia was again predominant.

The Simonis RCT treated only patients who had their nonunion for at least a year. They excluded anyone with a metal implant at the fracture site. Both groups of patients underwent the fibular osteotomy, the idea being to shift weight-bearing to the tibia, and performance and use of an external fixator. There was an active device versus a dummy device, which in the active device group, 89 percent of the patients healed, and of the patients who underwent just osteotomy and external fixator, 50 percent healed. It was statistically significant until they adjusted for smoking.

As you know from the background information, we mention that a number of studies show that patients who smoke seem to have a lower

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rate of healing both in their initial fracture and certainly once they have a nonunion. The Sharrard study is one that generated a lot of discussion in our, going back and forth over the report. He refers to the patients as having delayed tibial union, but they were all four to eight months following fracture. They could not have had any prior surgery other than open reduction perhaps for the initial injury and cleaning the wound. They excluded anyone who had what they called severe atrophy, although, and

those who had severe hypertrophy at the site. All of the patients were treated with a long-leg plaster case. The outcomes of the study were all radiographic and there was more gradation of the results than in any of the other studies. The 12-week results for the study are what have been published. We later received some unpublished results, but these are the 12-week results, again, using just the radiographic criteria.
In the active device group, three patients had achieved full union within that 12-week period and as you can see, there were seven headed in that direction, ten who didn't change, whereas the numbers unchanged in the

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inactive device group were higher.
Dr. Sharrard presented to a Blue Cross Blue Shield committee in answering some questions that they had when they were making a coverage decision some time after the study was published, and he provided some longer term follow-up, which was two years. And it's interesting because it tells us at least that a 12-week study is probably not going to be sufficient, at least if you use comparable patients with comparable fractures, to really determine the rate of healing with various treatments. Even though only three had full union and seven had progression toward union of some degree in the 12-week period, we could see additional patients went on to heal. There were eight in the inactive device group who ultimately healed without further treatment. However, eight of them had switched over to the active device immediately after the end of the 12 weeks so we don't know what their further course might have been without that.
The other studies of this technology again, ranges from 69 percent, 76 percent, 88 percent. I'm sorry, the 69 percent was in a group in the Traina study which is a retrospective

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comparison, it examined patients getting a whole variety of different treatments lumped together in that second group.
As far as patients over the age of 65, in the Garland study, which is a prospective case series, 18 of 28 patients healed, and in the Ito study there were three patients over 65, two of whom healed.
Orthobiologics, we have four series, I'm sorry, one RCT and three retrospective case series. The Friedlaender RCT studied only tibial nonunion. All patients were treated with intramedullary reamed nailing and then randomized to either receive OP-1 or their own autogenous bone graft to be implanted into the fracture site. The measures of healing that they included in the study are even more than these, but of their combined clinical measures, you can see it looks fairly similar for the BMP-7 and bone grafting. Bridging on at least three radiographic views, fairly similar, and not requiring any further surgical treatment, similar.
They did not present any data on the patients over 65, although they did include a few.
For the retrospective case series, two

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of them were from the same group who produced their own product, they used bone allograft and partially purified human morphogenetic protein, whereas the allomatrix injectable putty took demineralized bone from allograft mixed with cellulose and calcium sulfate and used that to inject into the fracture site.
In the studies by Johnson and Urist, some patients were also receiving bone grafts at the time of treatment and the usual other treatments for stabilization. The bone study for these studies is slightly different.
Again, healing rates up around 80 to 86 percent. Dr. Johnson's group report on eight patients over 65 in one study with five in another, with high rates of healing in both.

So how does this help you with your questions? Well, it's difficult to say. The indications, I would think that ideally you would like to see randomized controlled trials with very well matched patients in the groups who had, you know, all their concomitant therapies were exactly the same with the exception of the device that you're trying to study, and you could pick out which patient characteristics determined whether

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patients need or not, these in addition to other therapies, and which patients are more likely to benefit or not. However, as I mentioned, there was a great deal of difficulty recruiting patients for the limited studies that have been done, and it may require something along the lines of a matched case controlled design to try to look at it further and tease out some of the specific patient characteristics that predict who might really benefit from these treatments as opposed to continuing just a bit longer with whatever other orthopedic therapy they're receiving. The same is true for the questions on whether the biophysical enhancement has impact on these various outcomes. We provided a table for you with the outcomes just as reported by study, that just somehow it's predominantly radiographic outcomes that were available, and not a lot in terms of patient function. Causal relationship, again, we prefer to see RCTs, but that seems unlikely to be doable in this particular field. How confident are you that there will be an important net health benefit? Well, I think you have to consider what the alternatives are. Many of the patients are facing a decision about

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whether to undergo bone grafting procedures. Some of them may be reluctant to do so, some of them may be poor candidates for further surgery, so there are a lot of clinical judgment issues that will come into your decision. And the adverse

effects of the technologies were not striking in the published studies.
The study by Friedlaender, interestingly, points out that the OP-1 implant avoided the morbidity of harvesting the bone for bone grafting, and it was curious to us that the rate of osteomyelitis in the patients who had proceeded with bone grafting was as high as they found, which was 21 percent, but nonetheless, you can tell that patients certainly would avoid the morbidity of the bone graft harvesting. That's not to say that there aren't other types of therapies in the works, there are other therapies other than bone grafting that might have less morbidity involved that are still going to be alternatives to the technologies we're examining today, and I'm thinking of the bone marrow aspirates for injection.
As to whether this will hold when no prior surgery was done, well, we just have the

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Sharrard study that only included patients without prior surgery.
And off label, we only have the allomatrix study.
The fractures -- I'm hoping that the members have a copy of these slides, but I've given you a table and as I said before, the tibia is by far the most commonly studied bone. And looking at the patients over 65, it appears I made a math error here, but that first line should be that it's something less than 56 patients included, but at any rate, we certainly have fewer than 100 patients over the age of 65 for whom we have outcomes to study.
And question eight, we didn't even consider that question and didn't see any studies on that. Thank you.
DR. MCNEIL: Thank you very much, Karen. Are there any questions for her? That was a lovely presentation, thank you again.
DR. BURKE: I have one question. Did

you get any sense for the underlying rate of bone healing in these studies? In other words, it was heterogeneous therapies, so all of them received some therapies, but did you get any sense of what

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the rate of healing would be just on its own, 15 percent, 25 percent? If you didn't do that, what's your base center line?
DR. SCHOELLES: That's a good question. The assumption had been that patients, once nonunion was diagnosed, would not heal, that, you know, if you saw it in effect once you applied one of these technologies, that it had to be the technology. Well, the problem is that patients don't get no treatment, pardon the double negative, but in the comparison groups that we have, we saw ranges of anywhere from 12 percent to 50 percent.
DR. BURKE: Thank you.
DR. MCNEIL: I had one question. You started to emphasize or mention at the end, but it wasn't on any of your slides, the result that struck me was the Friedlaender one on osteomyelitis.
DR. SCHOELLES: Yes.
DR. MCNEIL: And while there were no significant differences in anything else, that was a significant difference that favored the intervention; is that correct?
DR. SCHOELLES: It was a significant

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difference in that the control group of patients receiving autogenous bone grafting had a 21 percent rate of osteomyelitis, whereas those receiving the implant, the OP-1 implant had, I believe it was three percent.
DR. MCNEIL: That struck me as an important result and I was wondering why it wasn't on one of your slides.
DR. SCHOELLES: Well, some of our orthopedic reviewers were concerned about that

number and had raised some doubts about it.
DR. MCNEIL: Could you elaborate? I think this is a really important point.
DR. SCHOELLES: One of the points made was that a confounder for that could be use of an external fixator as prior treatment, that patients who are treated with external fixators not uncommonly contract infections, and if they go on to have intramedullary nailing following a recent impact infection, they are very prone to osteomyelitis. So he thought that the failure to report that potential confounder, they had concern about the validity of that result.
DR. MCNEIL: Other questions? Okay. Thank you very much. If not, we'll move on to

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Dr. Carmack from Eastern Maine Medical Center. Is he here?
DR. CARMACK: Good morning. The presentation that you're seeing here may not be the one that you got, the second one. Is there an AV person that might, because I'm not seeing the color. Is there an AV person here?
DR. MCNEIL: And before speaking, would you please indicate your disclosures regarding any potential conflicts? Dr. Carmack, are you here? Where is he?
DR. SCHOELLES: Should I disclose that I have no conflicts?
DR. MCNEIL: Yes, thank you. Do we have the slides?
Well, rather than wasting even a little time, maybe some of the orthopedists on the panel can talk about what they think usual osteomyelitis rate is for patients with bone grafts. 21, is that above or below the norm?
DR. KOVAL: What they didn't say was where was that osteomyelitis. If you're talking about the donor site, you know, 21 percent of osteomyelitis at the donor site after bone graft, that --

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SPEAKER: It's not the donor site.
DR. MCNEIL: It's not the donor site, so for the non-donor site, is 21 percent high or low?
DR. KOVAL: If the osteomyelitis is not occurring at the crest, it's occurring at the tibia, I assume.
DR. SCHOELLES: Right.
DR. KOVAL: She didn't say where the osteomyelitis was coming from.
DR. SCHOELLES: Right, at the site.
DR. MCNEIL: At the fracture site.
DR. KOVAL: So I think that has nothing to do, I would be more interested if that was coming from the crest site, which it's not.
DR. MCNEIL: But the 21 percent at the tibial site, is that a high or low number, or an average number?
DR. KOVAL: Very high, but it depends, they are correct, it depends whether there was a previous external fixator that could be used, so unless we know that, we don't really know, but if it was a closed fracture, that would be quite high.
DR. MCNEIL: Two other comments and

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then we're going to move on. Yes?
DR. BOYAN: I'm not sure the issue is whether or not the result was valid. It was valid if you got it and it was scientifically achieved, so it's a valid result. The issue is whether a nonsurgical technique or a less invasive surgical technique had a lower incidence of osteomyelitis than something that was surgical or repeated exposure to surgery might have caused. I think the statement, result is invalid or incorrect is a confusing statement. It was a result.
DR. MCNEIL: John.
DR. KIRKPATRICK: The other thing I would do is to immediately go back to look at the two groups to make sure they're similar, because

if there was a lot of grade three opens in the ones that got affected, that would explain that finding, as opposed to they were all closed on the other arm, and I'm not sure that their data presentation allowed for that analysis.
DR. MCNEIL: Darren, do you know the answer?
SPEAKER: The randomized procedure was quite good and it equalized most patient characteristics between the two groups, so opens,

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fractures, prior medullar reaming, it was spread between the two groups, so I believe the randomization process would equalize the patients who had prior external fixation.
DR. MCNEIL: Okay, thank you very much. Why don't we move on, and Dr. Carmack, would you indicate whether or not you have any conflicts or other kinds of things to worry about.
DR. CARMACK: Good morning. My name is David Carmack and I do not have any financial interests or conflicts in the subject matter to be presented.
I am a medical director for orthopedic trauma at a regional trauma center in Maine, in Bangor, recently transitioned to there from here in Baltimore at Shock Trauma, and I'm also transitioning out of active duty military to the civilian environment, so I thank you for the opportunity to speak to you today.
My goal is to talk specifically about physical forces in treating nonunions, i.e., electric stimulation and ultrasound, and then further modalities that we have as a practicing orthopedic trauma surgeon to treating these difficult problems. Let me talk about the normal

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fracture healing process briefly, and then again reiterate the definition of nonunion and how that is a little bit of a moving target, talk about its etiology, talk about the treatment modalities

available, and then specifically launch into the use of ultrasound and electrical stimulation for the use of that. I think we're on track and on time, so I think we're going to be fine. The normal fracture healing process, you can break it up into the following stages, impact, induction, inflammation, soft callus, hard callus, and then remodeling. Electrical stimulation as well as ultrasound affects various portions of the healing process, most commonly through the inductive phase, inflammation and soft callus, but they affect all aspects of that healing process, some to various degrees more than others. A lot of it is supported by bench scientific work, but I don't think there is one kind of target area that we're hitting, and the studies kind of point to that as well. The radiographs on the right show a typical nonunion of the proximal tibia, an open fracture initially. This one with the presence of active infection with the lack of a soft tissue

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coverage, and the treatment and evaluation of that nonunion having to deal with the various problems, the lack of soft tissue, the infection, infected hardware. And so I kind of want to put a picture out there that these modalities are good but they are a small part of the entire picture of treating these difficult patterns, and then eventually getting on to the goal of a union of that fracture below with hopefully absence of infection. Fracture environment, the hematoma phase you have proteins as well as cells, all with the goal of organizing to promote osteogenesis and cartilage formation, and then the replacement of that with bone. As well in that environment, it has been found that when the general overall electronegativity caused by mechanical type factors normally in a fracture pattern or just the environment which may further be a stimulus for osteogenesis. Two types of bone healing. It's

important to speak about contact healing versus gap healing. Contact healing is when you obtain an anatomic reduction of the fracture and essentially get replacement and extension of the bone right across that fracture gap which is

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anatomically reduced, usually with an implant or external device, but mostly implant, versus gap healing, where you go through all those stages of bone healing. And from my, you know, review of the literature and my understanding of it, I think the adjuncts are much more applicable to the gap healing phase of it.
What is a nonunion? It has been defined as failure, arrest of the bone healing process, and I think almost randomly we've landed at three months or 90 days. I personally follow the patients every four weeks, so it's a lack of progression on three consecutive monthly radiographs, which is 90 days. There's further criteria out there that it may need to be for a minimum total time period of nine months, but I think that is quite variable. So the take-home message is that the actual diagnosis of nonunion should, we hope is very objective, but in reality I think it's quite subjective, and as a practitioner when you're deciding to treat it as a nonunion, there is a lot of subjectivity that comes into play.
Delayed union for me is we're just waiting for a nonunion by the patient's variables

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and again, there's some gray zone between delayed union and the actual diagnosis of nonunion.
Etiology of injury variables, open fracture, nature of the soft tissue injuries, segmental fractures, soft tissue interposition.
The radiograph on the right shows a very clearly established nonunion of a humerus with gross motion there over about a year more clear.
Patient variables, age is certainly a factor,

nutrition, systemic hormones, presence or absence thereof, and nicotine, the majority of that being from smoking.
Further tissue variables, where is that fracture, where is that fracture, can you set it for nonunion, cancellous versus cortical bone. The cancellous fractures tend to heal better, and in some of the studies it's very hard to tease out. You can tease out the bones they are in for the location of the nonunion, but it doesn't always differentiate between the location in the bone, if it's a highly vascularized area versus the mid diathesis, which can sometimes be more challenging. If there is bone necrosis from loss of blood supply, it's hard to heal a dead bone.
Presence of bone disease, and most importantly I

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think in all this stuff is the presence or absence of infection as well.
Types of nonunions are hypertrophic nonunions and atrophic nonunions, and then we define in between there a leap of trophic nonunions which are somewhere in between. For me a hypertrophic nonunion is one such as on the right; there is a lot of callus there but it is just not making that gap to healing, so it has good biology but it needs stabilization. Atrophic nonunion is that there could be or couldn't be inadequate, some good or bad stabilization, but generally they need biology. Pseudarthrosis is more like we just showed before with that kind of false joint that's definitely declared a nonunion.
And then lastly, infected nonunion, and as a practicing trauma surgeon, this is something we are always acutely aware of and are trying to tease out before we launch into the treatment.
So you know, the use of all the adjuncts, you know, a nonunion is not just a nonunion is what I'm trying to say. And as a practicing end user of these products, there is a big variety of fractures that we are trying to put all together.

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Diagnosis, most of the time we get from plain radiographs, serial plain radiographs. If it's not clear, then sometimes we will get tomograms or CT scans, and it's very rarely bone scans.

Treatment is revised skeletal stabilization, either internal or external fixation, biologic stimuli, which Dr. Alan Jones is going to address. But specifically either, you know, the gold standard is autograft, the patient's own bone, and now with all the new proteins on the market, they are possibly replacing that. The physical force is ultrasound and e-stim.

The central hypothesis in physical forces in generating and promoting bony union is that there are electrical potentials that are produced naturally, which may be a regulatory signal that turns the cellular processes on for bone formation, promoting mesenchymal cell differentiation down into the pathway of a bone-forming cell or an osteoblast.

In ultrasound, there are very good basic studies, and some of these speakers will address that today on the actual, you know,

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science behind the use of it. But they include some increase in enzymatic activity toward the union from the ultrasound, increased calcium incorporation into cartilage, increased gene expression in the remodeling phase of fracture repair. So essentially, you know, there is good basic science showing that they turn those cellular mechanisms on and enhance them.

The clinical data, I think there are two studies which are quoted quite often in the closed and open grade one tibia fractures. They showed a decrease in union time in those treated nonoperatively, and in the distal radius study they showed a decrease in union time as well as

decrease in loss of reduction, both very important things as a practicing orthopedic surgeon, applicable and significant studies being able to relate those to our patient population. So current indications are there. They are approved for use in fresh fractures as well as approved for the treatment in established nonunions. I think there was a recent change also this year, earlier this year potentially, that the patient did not need to fail a previous surgical attempt at treatment of the nonunion.

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Electrical stimulation, as pointed out before by Karen, direct current pulse electromagnetic fields, capacitance coupling, combining magnetic fields. These have been around for, you know, a lot longer than the ultrasound has. Most of my experience is with the PEMS in short, you know, and I do think it's a useful adjunct. The basic science behind it is, again, benchwork stuff that hypothesized that a lower PO2 and rise in pH at the implanted cathode is favorable to bony formation with increased production of (inaudible) synthesis, i.e., promoting the pathway for an osteogenesis or moving in that direction. Studies show union rates for the various bones, and I won't go through all of them again, but in summary, the studies are favorable in use of the electrical stimulation direct current. They do lack prospective randomized controls clearly, and there is also a hodgepodge of different other modalities in the treatment of those fractures, such as internal or external fixation. So current indications for direct current is it's FDA-approved for established nonunion. Most commonly it's used in conjunction

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with the bone grafting procedure or hardware revision procedure because it requires an implanted cathode method, and if someone is going

to go to that effort to do the surgery they will then, you know, will or will not add that adjunct, being that surgically implanted cathode. On the pulse electromagnetic fields, the basic science behind that is, they were developed to induce the electrical fields that are similar to the endogenous electrical fields produced in response to bony strain or mechanical loads, again, promoting increased emphasis on the osteoinductive proteins, to include DBM, BMP-2 and BMP-7, which Alan will address as well, but essentially turning the switch on to promote the healing. There are many clinical studies, over 250, and some of them have found that they are comparable to surgical intervention. Certainly as an end user, my goal with these devices would be hopefully to prevent a surgical intervention if possible, and that's a very valid role. They found that dose response with healing times may need at least ten hours a day with the use of those devices, so current indications are they are

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an adjunct to standard fracture management of nonunions and failed unions as well. Capacitance couplings, the application of two surface electrodes inducing an electrical field in the environment with an oscillating electrical current turning on and off proteins such as voltigated calcium channels and having increased values of (inaudible), and again, all this theorized to promote the healing process. Clinical data, all comers, in some studies as high as 77 percent union rate, again, in prospective, not randomized, not clinically significant when you do statistics, but in their case series, showing six out of ten healed with capacitance coupling versus zero out of 11 of the ones that did not get the treatment, but again, a lot of variables in there. So current indications to include nonunion for long bone and scaphoids have been

used, combined magnetic fields, use of (inaudible) fields for transport across the cell membranes, again, increasing the production of the osteoinductive proteins. The clinical data supports its use in neuropathic joints as well as spinal fusion, I know that's not our target today,

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but they are in support of that. So from that and other studies, the current indications are the use of that for the management of nonunion as an adjunctive field as well.

So, in summary, physical stimulation to include ultrasound as well as electrical fields, to me and to a majority of the orthopedic trauma surgeon population or orthopedic surgery population, are still very useful adjuncts for treating nonunions with the theory that overall they are increasing osteoconduction and osteoblastic capabilities of the fracture environment.

I think very importantly, as will probably be brought out later, that you know, a lot of these studies come from the last 15 years. Fracture implants have changed dramatically in the past 10 to 15 years, so there are other tools available to us that we're using to treat fractures, less invasive things, better stabilization, so I think we're at a stage now where we are seeing a big shift of how we treat nonunions and if the panel is looking to these as a substitute for sound fracture management or surgery, I don't think that's where it's going. I

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think they still remain an adjunct to good clinical practice and aggressive therapy of nonunions. And just an aside, I think as our patient population changes a little bit, that, you know, certainly nine months or a year or longer waiting to make a diagnosis of a nonunion really is not acceptable anymore, patients demand better, and so we are much more aggressive in treating

fractures and using these earlier than we used to. Thank you very much for your time.
DR. MCNEIL: Thank you very much. Are there questions? A very complicated set of data. Yes, Marc?
DR. BERGER: Marc Berger. So with this array of adjunct therapies, how does one choose one versus the other, why does one choose one versus the other? Is it simply, this is what you have experience with, or what's the clinical judgment going on there?
DR. CARMACK: I think for the end user, it's in reality probably what one has had experience with in the past, as well as reviewing the literature in making that decision. I think industry plays a little bit of a part in that in presenting data to individual orthopedic surgeons

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for the use thereof. In reality, in choosing which device to use or not to use it, I will tend to use everything I can to promote union if I believe there is a positive effect from it and I can support that with some form of literature. I use both electrical stimulation and ultrasound and I use them similarly in similar patients. I don't have the case numbers to put them head to head and those don't really exist, so I think they both have literature to support their use, and it will be challenging to sort that out.
DR. MCNEIL: Bob and then Linda.
DR. MCDONOUGH: I actually had a similar question to Marc but there is also another question. As you know, ultrasound has also been studied as you mentioned, in fresh fractures that tend to progress to nonunion. Do you think those studies have any relevance to answering the question, especially with ultrasound, since we don't have randomized studies, or is that not really relevant?
DR. CARMACK: The question is, is there a role for more use, or the use of ultrasound in the acute management of fractures in general?

DR. MCDONOUGH: Well, I guess my

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question is, does evidence demonstrating, and in fact from randomized clinical studies demonstrate an effect of an intervention on fresh fractures that demonstrates a reduction in a tendency to progress to nonunion? Does it have any relevance at all? And the reason why I'm asking that question is especially in those cases where we don't have randomized clinical controlled studies looking at nonunions, is there other evidence that is randomized that we might consider?

DR. CARMACK: To my knowledge, the two studies for acute fractures were the ones that were mentioned and there was shown a benefit of decreasing, or increased loss of reduction. I think further studies that repeated those findings would be very beneficial, because certainly the role for decreasing, even if we're going to go on to a union with fracture, if that can be cut short with a decrease in morbidity and I think that's a good thing, so in short, yes.

DR. MCNEIL: Linda.

DR. BERGTHOLD: We've done some studies for variability in coverage policies among different health plans around the country, and the issue of sort of at what point after fracture you

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can begin to consider these other alternatives. And from a consumer point of view, especially if you live in Wisconsin and have the same bone fracture and wait nine months, and you can be in Texas and get some kind of treatment in three months, so the importance of having CMS establish some fairly clear cutoff points so that there is consistency, to me as a consumer is important. My question is after three months, so we have three months to a year as a period of time that these treatments could be considered. What proportion of fractures that are still, you know, nonunion at three months, or let's not worry about

nonunion, but delayed at three months, then go on to heal at six months, nine months, a year? In other words, once we've had a bone fracture for three months that is nonhealing, isn't that likely that it's not going to heal, a very small proportion are going to heal, or is there some evidence we have about that?
DR. CARMACK: You know, I think that's a great question and in essence, it would be if you take a nonunion and leave it as a nonunion and go ahead and treat one group and don't treat the other. I'm not aware of any good evidence that

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does that specifically. Usually when we make a diagnosis of nonunion, that clearly has met the criteria, the other parameters, the variables are all telling us that this is not going to heal. I think there is probably a percentage of those that will go on to union with prolonged immobilization, but with prolonged immobilization you get prolonged disability and there is a huge amount of, you know, it explodes from there. So I think, I still believe that the diagnosis is made, the clinical diagnosis, and the objective and subjective criteria is right there.
DR. MCNEIL: Sean, did you have a question?
DR. SULLIVAN: Thanks for the presentation, it was very good. I'm not sure if this question is perhaps for you or perhaps maybe even Karen, but you finished your presentation by indicating that current surgical practice now is tending towards more aggressive and very early management of nonunion fractures using internal fixators, casting more aggressively, et cetera. Are there any data, case series data or anything that would suggest to us what the healing rates might be or the time to healing for this

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aggressive usual management practice without the use of these devices or other adjunct therapies?

DR. CARMACK: I think anecdotally, people that advertise themselves or go after a nonunion market see a lot of these in referral, and what we tend to see is an established nonunion that was diagnosed a while ago but treated with less aggressive therapy, maybe an adjunct modality by itself, hoping that the problem would go away. You know, that to me anecdotally has been a position where we really end up with problematic nonunions. A nonunion diagnosed early and managed early tends to be less of a problem. So, I guess I'm not aware of any specific studies that look at that. I think just from surgeon to surgeon experience, people who are in a nonunion practice because they like that or they feel that they have the ability to provide service to their patients, I think that's what we tend to see a lot of with typical fracture patterns, not a full court press initially.
DR. MCNEIL: Linda, and then Alex.
MS. FRIED: You mean Leslie.
DR MCNEIL: Leslie, I'm sorry.
MS. FRIED: Actually, I had a similar

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question regarding your final comment, and I'm not a doctor on this panel. But when you talk about aggressive treatment, I would like you to talk about what, when you talk about taking a more aggressive role, what exactly do you mean? What procedures? A patient comes in, and let's say she or he is over 65, or is under 65 and is disabled, and therefore may have other comorbid conditions just because of who they are, can you sort of walk me through?
DR. CARMACK: It might open a Pandora's box a little bit, but --
MS. FRIED: It's open.
DR. CARMACK: If someone is referred for a nonunion, a less aggressive approach would be let's watch it, let's see what happens, give it more time, another six weeks, another six weeks. And now you're at six months so perhaps a more

aggressive approach would be a more diagnostic approach, CT scan, examine under anesthesia, document instability at the nonunion site, and from there offering early management to include revision, fixation either external or internal, bone grafting, the bio, the new proteins, osteoinductive proteins, as well as the ultrasound

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or e-stim, kind of all of that at once or a combination thereof.

DR. MCNEIL: Alex and then Ken.

DR. OMMAYA: My question is regarding the site of injury. Does that play a role in your choice of therapy approach? And then my other question is in terms of combination therapy, is that ever an option, for example, ultrasound and electrical?

DR. CARMACK: A site is absolutely a predictor of difficulty in healing a nonunion. The tibia is a very difficult bone to heal. Bones that have a less abundant blood supply tend to be more problematic fractures and we tend to be more aggressive in those bones, i.e. with surgery, than we would in something like the femur, which is very well vascularized. The location of the fracture in the bone, as we alluded to, makes a difference as well as far as the vascularity of that.

As far as combination of modalities, I personally don't mix ultrasound and e-stim. I do mix ultrasound with bone grafting, e-stim with bone grafting. I mix, you know, some autograft with that, so yes, I mix them, but I don't mix

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those two.

DR. MCNEIL: One final question. Kim.

DR. KOVAL: It's more of a comment for the panel, that we have to be careful that we just don't start lumping nonunions into regular unions and delays. If somebody has broken hardware and they have a crooked leg, you don't want it to heal

just the way it is, so just putting an ultrasound or electrical stimulator on is not an option because the patient doesn't want the crooked leg to heal that way, so you'd have to do surgery on that patient. So it's sort of adjunct to surgery, because surgery is going to be required to straighten the leg up, so we have to remember that as we go through these discussions.

DR. MCNEIL: Great, thank you. Okay. Dr. Jones, and would you please indicate any conflicts that you might have?

DR. JONES: First, I would like to thank you for the opportunity to be here. My name is Alan Jones, and I am the director of orthopedic trauma at Baylor University Medical Center in Dallas. Like Dr. Carmack, though, I was also in Baltimore and the chief at Shock Trauma in orthopedics up until a couple years ago, and I'm

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going to talk about the use of some of the orthobiologics -- I'm sorry. I have been involved in research in orthobiologics for more than a decade and I have received institutional support from both Wyeth and Medtronic.

So, this morning I would like to talk about the use of bone morphogenetic protein in the treatment of nonunions, and I would like to thank Dr. Carmack for sort of an overview of what the nonunion, I'm going to try and touch on that, give you a two-minute synopsis of what a bone morphogenetic protein is, or BMP is, and some of the rationale for using it in some nonunions, and then hopefully review the clinical evidence to support its use in nonunions.

First off, you have already heard that a nonunion is basically a fracture that has failed to heal in an expected time, and depending on the location, that may be a few months to even as long as a year. And I think the other thing that you heard is there is usually a period of time where really nothing has happened and that can be for a variety of reasons.

So to simplify, I think we can say that some of them are for mechanical reasons, like this

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gentleman who decided he wasn't going to wear his cast, he has a nonunion and a very malaligned leg and when he walks, it just sort of bends when he puts weight on it. Well, obviously we don't want it to heal this way, and the fracture healing hasn't happened because of the lack of immobilization, and so he has a mechanical problem.
As opposed to this patient with a gunshot wound, a lot of scarring, poor vascularity, gross motion of the fracture, and just frank bone missing from the area of injury. This patient has both a mechanical problem and a biologic problem. There is no bone there, there is not a healthy tissue environment to help progress to healing.
In both of these patients, if we give them no interventions, they are not going to heal, pretty much no matter how long you wait. So for the mechanical problems, we use mechanical solutions, straightening out this gentleman's leg, placing an instrument or a nail, allowing him to weight-bear solves his problem and he goes forward with a straightforward mechanical solution.
For most nonunions, however, many of

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them are biologic and have a mechanical element, where it's not just a plate or not just a bone graft, but a combination of a biologic intervention such as bone graft and a plate to provide stability, combine to provide treatment.
So most nonunions, at least in general, have both a biologic and mechanical problem, and both have to be addressed in most cases.
And then as Dr. Carmack pointed out, infection is a big part of treatment and with an established infection, that has to be eradicated before you even contemplate the next intervention.

So what about BMPs? Well, bone morphogenetic proteins are osteoinductive proteins, they are found in all animals, and there is very little difference between a rat BMP and a human BMP, and they have a number of roles in bone growth and development of your skeleton, and cartilage development. But if you take a BMP and isolate it, and put it in either an animal or a human model, it will increase bone formation. So if you place it in your body, it will make bone. And how they do that is they basically take or differentiate (inaudible) stem cell and tell them to follow an osteoblast, along an

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osteoblastic cell line, primarily in the osteoblast, so those cells turn into bone-forming cells. Now, they have a number of other different processes that will stimulate, including (inaudible) systems and other things, but for the most part they differentiate the cells. So, they are available in a recombinant form and so the rationale is that DBMs may be used for osteoblast system differentiation, and provide a biologic, not mechanical, but biologic stimulus to promote healing in a nonunion for a fracture, and of course they could be combined with other modalities, either internal, external or bone restorative issues, bone grafts. So the question then is, do they work? Well, as Dr. Schoelles pointed out, there are currently two bone morphogenetic proteins available in the United States, BMP-7, which is marketed under the trade name OP-1, and BMP-2, which is marketed under the trade name INFUSE. So I'll try to take them separately, because I think the evidence is separate on both of them. BMP-7 is currently available for use in the United States in nonunions under a humanitarian device exception and is available for

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recalcitrant nonunions in long bones that have

failed treatment, and particularly in patients who are not candidates for bone grafting or have already failed bone grafting. So this is for a subpopulation that is based on the Friedlaender study that you have already heard some about, basically a prospective randomized unblinded study of established nonunions of the tibia, treated initially by nailing and randomized to either bone graft or OP-1. It was a multicenter study, and as I think Dr. Schoelles alluded to and you may hear from some of the others as well as the investigators in this study, the tibial nonunion fracture is a difficult thing to treat, it's a difficult patient population, and recruiting 124 patients with typical nonunion and randomizing them is a gigantic task. You have to understand, this is not something you could go out and do again.

They used a definition of a minimum of nine months post-injury for the big range, no healing over a three-month period, and they had to be a candidate for a nailing or bone graft. There was no randomizing to allow the patients to know whether they have a bone graft or not, and the

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doctor knows whether he did it or not. They did have a blinded radiographic analysis. They had a number of different end points including radiographic bridging on either side of the bone or three out of four sides of the bone, or probable need for retreatment as well as physician and patient perception. They defined their end point at nine months but followed the patients for two years.

One of the questions that was brought up was whether there was a difference between the groups. When you look at severe open fractures at higher risk for infections, it was not statistically different between the groups. The failed bone grafting, not statistically significant. An amazing difference against the OP-1 was the higher proportion of patients who

were smokers in the OP-1 group. There is not specific information on external fixation as far as I know that was reported.
So, how were their outcomes? Well, if you look at some of the combined clinical gains, weight-bearing scores, I think they are possible. If you look at the blinded radiographic analysis you can say, well, maybe there are some

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differences where an autograft is slightly judged to have more bridging of bone than the OP-1. But to me what makes the difference is patient improvement, did the patients require another operation or not, and basically it was either slightly in favor of OP-1 or in reality, statistically no difference between the two, so 90 to 95 percent for the OP-1 and autograft groups respectively.
Now you also heard overall equal numbers of serious adverse events, a much higher rate of osteomyelitis at the nonunion site in the autograft group compared to the OP-1 group, and of course without a donor site, they had no donor site adverse events, compared to 20 percent of the other patients.
So, I think you can summarize that by saying I think there is good evidence that OP-1 is at least comparable to bone grafting in combination with nailing in a very challenging patient population.
I have one example from this study, it's a 34-year-old male who had a nonunion going on 33 months, he had a nail and bone graft, so he failed all sorts of things, and here's his x-rays

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immediately following the nailing and the placement of the OP-1. Here he is at nine months, looking very healed, and at two years he was able to have removal of his nail with a well-healed fracture and a good result.
So to summarize OP-1, I think there is

good evidence that at least in the tibia, which is probably the most challenging group, a very challenging recalcitrant population, there is good evidence to support its use at least as an alternative to bone grafting as a biological stimulus.

Well, what about BMP-2 or INFUSE? It's currently FDA-approved for the acute treatment of open tibia fractures as an adjunct to healing, and that brings up really the concept of the nature of nonunion, or preventing a nonunion. Tibia fractures overall don't always heal, particularly the group of open tibia fractures where the bones come out through the skin, there's significant soft tissue injuries and risk of infection, maybe 40 percent of that overall group will go on to have a secondary surgery as treatment for either a delayed union or nonunion. So not quite half, but a big proportion of patients who come to us with a

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tibia fracture end up with delayed union or nonunion and further treatment or surgery.

So this study, which has been published in the Journal of Bone and Joint Surgery by Govender and all, also known as the BESTT study, basically looked at a big cohort of patients with open tibia fractures and randomized them in a prospective randomized single blinded study of open tibia fractures in which they took 450 patients, three cohorts, and followed them for 12 months in about 49 centers worldwide. And basically they took tibia fractures treated with nails and then they made a treatment decision at the time of wound closure and treated with one or two doses of BMP-2 at the fracture site.

So here's what it looks like on a sponge, here's one of my patients from a different study, identical procedure, where we see a big soft tissue injury, the bone is stripped, and there is not a lot of soft tissue blood supply to foster healing there. So you put the BMP-2 on the sponge, you just put it around the fracture, and

then the rest of the patient's care is identical to the patient that you're not treating. Now, what the BESTT study found was in

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fact at every time point measured, there were more patients healed in the higher dose BMP-2 group than in the control groups and there were fewer secondary interventions. And so to put it all together, the proportion of the patients in the control group that went on to secondary surgery, it was actually about half, compared to 37 percent in the BMP group, so it reduced the rate of nonunion by about 29 percent, so there is some evidence from this study for the use of BMP-2. Secondarily, there is a study that we presented at an Orthopedic Trauma Association meeting in 2004 that has been accepted but not yet published in the Journal of Bone and Joint Surgery, a prospective randomized comparing BMP-2 in combination with allograft, compared to autogenous bone grafting for treatment of traumatic bone loss associated with open tibia fractures. This is a relatively small group of tibia fractures where the surgeon determines that the patient has enough bone loss like in this example, so the patient is not going to go on to healing, basically this is a nonunion that can be identified at phase one. So most of these, or all these patients have a planned intervention, bone

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grafting somewhere between the sixth and 12th week period after injury. Patients were randomized to either a combination of BMP-2 with allograft or autogenous bone grafting and again, called for nonhealing for a year or more. Here is an example of a patient with a tibia fracture. You can see there is a fair amount of bone missing from the open fracture and there is an open fracture with a gap all the way around, so this patient without intervention is not going to heal no matter how long you wait,

and so there's no reason to wait a year, and so the surgeon decides I'm going to intervene with some intervention to provide both bone and some biologic stimulus. This patient was randomized to the allograft, that's the allograft and the bone, there's the BMP-2 on the sponge that you saw placed over that, and then -- I'm sorry, we should have had a picture where he went on to heal, but I'll show you another one.
So in the BMP-2 group, 13 out of 16 patients went on to heal, there were two patients that went on to secondary intervention, compared to 10 patients in the autogenous bone group, and four of them underwent secondary interventions,

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and one was not healed at the one-year period and I don't believe, I don't know the status at this point.
And here's an example of what this patient showed. There he is after his injury and before any treatment, and there he is at 12 months with a healed fracture. And I think if we look at this close-up view, it's pretty interesting to me that you can take something out of a bottle, put it in there, have bone formed, fracture healed and restore those muscles. So I think from that study, I think comparing BMP-2 in combination with allograft, we had comparable rates of healing. We had, because there is not a donor site just like in the Friedlaender study where there is no donor site, we had less blood loss, shorter surgery duration, and you're doing less surgery, and I think this is a reasonable alternative to bone grafting.
So, how are BMPs being used in the United States? Well, to me, the current rules provide a biologic stimulus in selected nonunions. I think that orthopedic surgeons tend to use either one of these BMPs for their most difficult or recalcitrant cases, they are not the chip

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shots, and this would include those patients who are both elderly and in the Medicare population, but would also include patients who are not candidates for bone grafting for whatever reason, they already had a bone graft, they are osteoporotic, or at risk for other reasons. Just as Dr. Carmack pointed out, it is not a substitute for correcting the mechanical environment or other things. If you haven't gotten rid of infection, if you haven't stabilized the instability, it doesn't matter what you put in there, it's not going to work.

And I think overall, to summarize the orthopedic surgeons' common experience nationwide, is that it's overall positive but still considered anecdotal. But I will reiterate, we tend to use them for our most difficult cases.

This is an example of a 54-year-old female, this lady had had probably at least 11 or 12 surgeries for her femoral nonunion. She'd had bone grafting, electrical stimulation, ultrasound, electrical stimulation with a variety of different devices, and has a persistent nonunion. It's obvious she doesn't have a lot of mechanical instability or mechanical misalignment, she just

doesn't have any biology, and she has been going on more than two years, actually probably two years since this nail was put in, before she came to me. So I did a replacement of her nail, primarily because I was afraid her nail was going to fracture after two years of being loaded, and then a placement of BMP-2 in this case, and that was just enough biology stimulus to get her to go on to heal. She is now walking pain-free and doing well.

So to summarize, I think fracture nonunions, as stated by Dr. Carmack and myself, requires individualized treatment depending on the mechanical, biologic and infectious processes presented. I think BMPs as a group create an efficacious biologic method for the treatment of

nonunion to promote healing, and I think it's an alternative to autogenous bone grafts.
So, I will finish with that, and I will be happy to answer questions.
DR. MCNEIL: Thank you, Dr. Jones, that was very nice. Are there questions? Yes?
DR. AKLOG: Given the results of the Friedlaender trial, it seems that OP-1, you know, was comparable to autogenous bone grafting and you

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had the benefits of avoiding the harvest site. Why do you think the manufacturers were unable to achieve a broader approval from FDA?
DR. JONES: I don't want to speak for the manufacturers and I think we may hear from some of them later. My impression was that the FDA put a lot of their focus on the blinded (inaudible) analysis, which was, it favored autogenous bone grafting. So I think if I can summarize, the FDA felt it was safe, but they didn't really look at superiority, and so they basically said well, for those patients who can't have a bone graft, this is a reasonable alternative. What they didn't say is what to tell the patient who doesn't want a bone graft and which probably doesn't need one.
DR. AKLOG: Just as a follow-up, does that mean a significant portion of the use is occurring off label?
DR. JONES: The difficulty is with the HDE as I understand it, off-label use is really not allowed, you need to go through your institutional review board, you need to meet the criteria in the labeling to be able to satisfy your IRB. So, does any off-label use occur? I'm

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sure it does. I personally am unwilling to use it off label. Of course the other side of that would be if you have an acute indication, you use that for a nonunion, it is off label, and of course we're doing a lot of things off label, but I am

not going to tell my IRB we are doing one thing and then do another.
DR. KIRKPATRICK: Alan, thanks for that presentation. Could you give us what you feel are the specific indications for those two products, the BMP-2 and BMP-7? You presented one that -- well, actually both of them, some of it was acute and some of it was nonunion, so can you tell us whether there is data to back up, for example, INFUSE in a nonunion model as opposed to an acute fracture model, and if so, what are the specific criteria for that, and the same thing for the OP-1.
DR. JONES: As I said today, other than that sort of (inaudible) patient with a tibial defect that I presented, there's not a good study with good, you know, type one evidence to show efficacy of BMP-2 for nonunion. So right now, although I use BMP-2 in nonunion treatment, I don't know, there is no clinical evidence that I

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can show you a series for. I'd put together a series of, you know, a couple hundred tibial nonunions with reasonable similarity between groups, but randomizing something in the face of the bone grafting is a very difficult model to do. It's probably ahead for the manufacturers of BMP-2, but it hasn't been done yet.
DR. KIRKPATRICK: If I could just clarify, I was asking also for your expert opinion on what you think would be reasonable use indications for a nonunion for each of those products.
DR. JONES: I think for me, what's reasonable use for either one of these products is very similar. So for BMP-7, OP-1, it's essentially on-label use, so it's a long bone nonunion failed treatment in a patient who is either not a candidate for or has failed bone grafting, so on-label use to me is appropriate for BMP-7. On-label is appropriate use in a nonunion for BMP-2 as well, so a patient with a nonunion

who needs biologic stimulus or maybe has a bone defect who needs restoration, who either does not want, can't have or has failed a bone graft, and most nonunions are tibial, maybe with secondary

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femur and humerus.
DR. KOVAL: Alan, would you consider a nonunion in an elderly person an indication for using OP-1 because they do have a bone graft, but going to the iliac crest on a 70-year-old person is rather unfulfilling, because there's nothing there. So, would you consider that as one of the indications where you could use OP-1 because even if the person has a bone graft, it's not usable?
DR. JONES: I personally would consider the elderly population or the osteoporotic population regardless of age as someone who is not an ideal or suitable candidate for autogenous bone graft. So whether, I think you said 70, I think in an older patient who, the blood loss associated with a bone graft and the pain and morbidity of it and the reality is if you go inside their pelvis, there's nothing in there but a little fat and a lot of bleeding, what you get out is not, to me not as efficacious and the risks to the patient are higher. So to me, I think that patient population puts you in that more likely to use a biologic such as BMP-2 or 7.
DR. PHURROUGH: Alan, this sort of expands on that same question. If you've got this

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osteoporotic bone which typically is going to be the iliac crest, is that osteoporotic bone in the elderly patient going to respond to one or any of these? Is there evidence that says you're not going to get an old osteoblast to do the same thing as a young osteoblast?
DR. JONES: It's a good question and again, I think I can summarize, and Scott Bowden, who has done more work on this than I have, and he and I have talked about this quite a bit. But

what we can say is if you look at elderly rodent studies or in the handful of patients who were in the elderly population and have been treated in any of the studies, there is no evidence. Obvious their healing potential is somewhat diminished, the older you get, the less everything works, to conclude in your fracture healing, but there is no evidence to suggest that with BMP-2 or 7, you get less effectiveness in an older population. The bones seem to respond to that in the same way. To me, I sort of look at it in the other direction. They are the group that needs more stimulus because they have less on their own.
DR. BURKE: I just want to focus a bit on some of the control population, so in the

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Sharrard study and unpublished data, it looked like 30 to 50 percent healed without further treatment, in the unpublished study. Then in the INFUSE, 50 percent in the controls, and then in your study, 10 to 15 healed with the graft, and of course Friedlaender showed that grafts worked quite well, that's the bottom line of their study. So what is the gold standard here, in other words, what are we comparing against? It looks like, you know, even the controls were getting some pretty good results.
DR. JONES: Well, remember that the INFUSE study was for acute tibia fractures without, talking about the BESTT study, without bone loss. So these patients were felt to have a reasonable chance of healing, they weren't nonunions, they were acute fractures but they were in a high risk group. Now in Friedlaender's study, to me, none of those patients without intervention, they had already failed, if you did nothing to them, not a single one of them would have healed. You have to understand that bone grafting is a big deal.
DR. BURKE: Is that the gold standard? In other words, what are we comparing this to?

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DR. JONES: Well, probably autogenous bone grafting in combination with whatever mechanical stabilization is the gold standard.
DR. BURKE: So that's what we should judge things against at the end?
DR. JONES: Yes, but you have to understand now, that gold standard has a lot of morbidity.
DR. MCNEIL: Okay. Kim and Mark, and then we'll break.
DR. BURCHIEL: This question might be better for Dr. Schoelles from the TA, but I'm trying to find the BESTT study in your analysis. Is it there and I'm not seeing it?
DR. SCHOELLES: Not as in the adjective, the acronym is what you're talking about?
SPEAKER: No, that was fresh fractures. The only thing you'll find in our TA is on nonunion.
DR. MCNEIL: Mark.
DR. FENDRICK: Along those same lines, I am very encouraged to see prospective randomized trials, but as Dr. McNeil knows, I am particularly troubled by your final slide and final point that

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your experience is overall positive, and this is what I come to. Why is that? I think that given the lack of uncertainty of some of these interventions, I find that the reviewer of the TA says these things are hard to do, and I know you just finished one which is very impressive and certainly contributes a lot to the literature. I think that if you were committed as a field to tell your patients you have a lot of questions that need to be answered, and to answer them you need to appropriately control your studies, you probably would get enrollment. Are they just saying they won't do it?
DR. JONES: Well, you have to understand that in many cases they are saying they

won't do it. You also have to realize that most of these patients have already had a number of surgeries. For most patients, anybody who has ever had a bone graft, it's very difficult to talk them into another one, because they are very painful.
So to take, like I said, the Friedlaender study, they had 124 tibial nonunions to be treated. The treatment was the same fixation and randomizing the group was a huge

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undertaking. So that's not like cardiac surgeons or thoracic surgeons or something, and if you remember, this is a population of open tibia fractures, and we had a nice study that (inaudible) published, and this is a challenging socioeconomic and behavioral group. The majority of the patient score in the low to extremely low (inaudible) do anything either, so it's a very challenging group of patients. So can it be done, yes. Will it be done? The reality is you've seen all of the randomized controlled studies to date, there is just a handful of others. So it's not an easy undertaking and unfortunately, it takes a gigantic organization and resources to accomplish that.
DR. MCNEIL: That seems to be a common problem, as Mark has identified several times. I would like to thank the speakers from this morning, I think they all did a spectacular jobs in presenting a very complicated bit of information to us, or bits of information. What I would like to do now is take a break and really get back here at 10:15. Otherwise, I'm worried that we won't get through all the planned speakers. So thank you very much, back at 10:15.

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(Recess.)
DR. MCNEIL: Why don't we get started.
We have three members of the committee who would like to amplify their conflict of interest

statement and the fact that they were contacted by some industrial representatives, so, let's see, Linda, did you want to add something?
DR. BERGTHOLD: Yes. As the consumer representative I'm allowed to be contacted and respond; is that right?
DR. MCNEIL: Yes.
DR. BERGTHOLD: So I was and I did. I was contacted by John Gould, of Arnold & Porter. Is it Gould or Gold?
MR. GOULD: Gould.
DR. BERGTHOLD: Representing, not Smith & Hockett, Smith & Nephew.
DR. MCNEIL: And Kim, you also were contacted?
MS. KUEBLER: You have the contact, I don't have that. I don't have it with me. I was contacted this week but I don't remember the name. I can get it for you if you need it.
DR. MCNEIL: Okay. We'll put that in the record. And Deborah Shatin.

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DR. SHATIN: I would like to make a correction, that I have stock in Medtronic and also J&J. Thank you.
DR. MCNEIL: Thank you for clarifying that. So here we are for a kind of jam-packed session. We have Randy Davis from Osteotech as our first speaker. We have six scheduled speakers, actually seven, but there's going to be a combination with one person giving two talks, and each speaker will have eight minutes, and will be cut off regretfully sharply at eight minutes, whether you're at slide one or slide 30. So, thank you. Dr. Davis.
DR. DAVIS: Good morning. I'm Randy Davis. I am up here in Baltimore, I work at Johns Hopkins, and I work at the Baltimore-Washington Medical Center, a community hospital by the airport.
I'm here to talk a little bit about bone fractures, fracture nonunions, and the use of

alternatives. The other speakers talked about problems associated with autograft and I share that concern. 30 to 40 percent of patients, almost of any age, who face autologous bone grafts have significant pain and disability, and we don't

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have any good reason for this, so I think we have been looking for better alternatives for a long time.

Fracture nonunions, Dr. Jones spoke about, they require a number of things. They require carpentry and they require chemistry, the body healing. You can be a good carpenter but if you don't have the right biology, these fractures unfortunately will not heal. It requires several things. It requires cells, it requires a matrix to support the bone to be able to grow there, and then it requires signals or what I call the seeds. We have a variety of things becoming available now but it's incumbent upon us, as you all pointed out, to basically prove that these things are working.

And the growth factors, there's a variety of ways they could be established but in demineralized bone matrix, which is one of the things I've used for many years now, there are growth factors, there are bone morphogenic proteins and are other growth factors in demineralized bone matrixes that have been prepared.

There are a variety of studies, most of

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which as you all pointed out here, because I'm a big believer in evidence-based medicine, most of these are retrospective studies and case series, this is what it has been based on for a hundred years, but we're trying to do better and we have to use a triangle.

But these studies basically talk about the use of demineralized bone products to treat a variety of difficult conditions. Virtually all of

these have shown healing to a certain degree, but they are not done in prospective fashion. It has been to a point, though, where almost all orthopedic surgeons that I know who use and treat fracture nonunions and spine surgery, they virtually are all using demineralized bone matrix in some form or fashion.
It's our job here also, for me as the director of the spine center at the hospital where I work, to think about cost as well, and a number of the products that you hear about today are very, very expensive. I think that's one of your concerns.
Osteoinductivity is the ability to grow the bone, and I use this slide to show what I call the triangle of evidence. In talking about

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research, one of the best ways we have, since it's very difficult to do prospective blinded studies on humans, you have to do that in lower models. So you can start out in cell or test tube, move up the triangle to rabbits, rats, move up to primates, and we found these to be very effective, and many of them can mimic the model of a human. So for example in this model, you've got a rabbit lateral spine model where if you put the material that's not inductive, you have virtually no healing, but if you use an inductive product such as Grafton, then you have comparable healing, which is like 60 percent, which is just like the control if you use only autografts, and that has been shown in several series.
If you take an interesting study done by the folks from Europe where they operated on patients who had what are called Coventry osteopathies, they have arthritis, you basically take a wedge out of the bone when they have arthritis, and then you also have to take a chunk out of the fibula so that you can close that down, so they want that to heal eventually. And basically they were able to randomize a variety of products. They could put in collagen alone, they

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could put in demineralized bone products, or a variety of things, or BMP and OP-1, which shows over a period of time here, if you put nothing in there, nothing grows, that's your control. If you put BMP, yes, there is a lot of bone but the mechanism is different, and we can see that when you use demineralized bone matrix that forms from the center as opposed to a BMP product which calcifies from the periphery.

So there are a variety of papers that have been presented at a variety of meetings, trauma associations to discuss specifically demineralized bones. In your white paper, which I was quite impressed with, the very detail, they go through a number of these, and describe them as not being class one or two studies, and that is indeed true. But I think we have to have decent papers to proceed with the prospective studies, and it will give us as orthopedic surgeons the ability to go ahead and proceed to decide what's best for our patients.

For example, here's a study that compared OP-1 with Grafton, which is a demineralized bone matrix, in that human fibula defect that you talked about. It's actually 24

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patients, and there are four groups as it says, blinded radiologic analysis at a variety of time phases. The amount of bone and bone density in the groups as you follow them over time, it appeared very, very soon, but it obviously continues to increase in both the BMP group and the demineralized bone matrix group.

There are significant issues associated with the economics of using these products in the hospital, and I think that's something you all will have to address as time goes on.

Here's an example of that slide to show you. Indeed, BMP products will form bone in my experience clinically, they form in a different

physiologic nexus, and there is some calcification on the periphery as opposed to when using demineralized bone matrix products, which are usually used to fill a void or a defect as a bone graft extender, and it forms in different fashion. So, retrospective, there are a number of problems, but it's a big group. Even in smokers when you do blinded radiologic evaluations, it will help, but in a variety of studies, you can get overall healing with up to 87 percent of patients in a trauma model and with

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nonunions up to 91 percent, which is better than no treatment alone, and certainly comparable to autologous studies. So, I'm getting the red light, but again, here are groups using demineralized bone matrix products that have been presented. So I believe that it's incumbent upon us, and everybody has said it's very difficult for anyone, and especially Medicare patients, to take iliac crest autografts. My goal is not to take any by the time I finish my career, and I have been doing this for 25 years. I think that we can use demineralized bone matrix products as an adjunct and extender, and hopefully not use the patient's own bone. We all know the risks of failure and I think we have issues of economics which have to be pursued at meetings such as this. I thank you all very much.

DR. MCNEIL: Thank you very much, Dr. Davis. Before you go, I neglected to ask you for your affiliations and potential conflicts with regard to this presentation. I notice that you are representing a company?

DR. DAVIS: Yes, I am here speaking for Osteotech, which makes the Grafton demineralized

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bone matrix product. I'm also a consultant on the speaker bureau for Medtronic.

DR. MCNEIL: Okay. And just to clarify

for new members of the committee, while you did mention cost as something that we need to consider, that is not something we're allowed to consider.
DR. DAVIS: I apologize.
DR. MCNEIL: At least not today. So it's nice information to have, but just so that everybody is clear, we will not be considering relative costs for any of these materials, all we are looking at is the evidence and its effectiveness. So, thank you very much.
Dr. Dickson, please.
DR. DICKSON: Well, I'm particularly grateful to be here. It's the first time I have left southeast Louisiana since Katrina and the first time I have slept on a real mattress in over 30 days. I have no conflicts of interest, but Stryker OP-1 will pay for this trip, hopefully.
I'm going to basically talk about treatment of nonunions and specifically bone morphogenetic proteins. I'm a professor at Tulane as well as chief of orthopedics at Charity

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Hospital Trauma Center and Tulane, but I'm not sure where that stands right now.
This is who I am. I think the important part is that I'm a referral physician, I don't take any primary care, I get other orthopedic surgeons that send me my cases, and as Dr. Koval and Dr. Jones maybe can attest, there is probably nobody in the world that treats more nonunions than I do, between 30 and 50 a year.
How do I look at nonunions? Well, most fractures do heal. Some of the questions, I mean, they're all good questions, but they are difficult. Most fractures do heal. I think there is an important distinction between delayed unions and nonunions. If I had a delayed union that may potentially heal or there's comorbidities associated, out of all the studies there's only one study that I quote in that Sharrard study, and I know that's controversial.

But these people were not operated on, they were treated with a cast, and they went from a 30 percent success rate to a 50 percent. Not a great success rate, but in those patients that aren't ready for an operation, that's what I possibly could do for them. In those other

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patients that go on to a nonunion that aren't going to heal, those generally need some kind of fixation and bone graft, that's the gold standard. Those people that have failed that treatment, with a recalcitrant nonunion, those are the ones that I believe are the ones that are important. So for a nonunion, I don't use any of the other devices. I think that you have to be careful, the literature is very confusing, because a lot of times they will give you something, you use it for three months, you say it doesn't work, you take it off, you do surgery. Yet, the paper comes out with a 90 percent success rate and there is no information because there are criteria that the patient has to use it for four months, and there is no intention to treat or that denominator that's so important. These are all the good things that you want when you treat a nonunion, and what I've emphasized or left out is the demineralized bone protein. That has an order of ten to the sixth less material than BMP-2 and BMP-7, so these are the same as autografts, but BMP-7 is the only one that's FDA-approved for recalcitrant nonunions. When I think of nonunions, I think of

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the mechanical treatment and the biological treatment. In elderly patients, both of those are a problem, so the BMP basically gives me the biological stimulus that I may need in these recalcitrant nonunions. This is essentially the FDA report and what I want to emphasize is, this is approved for recalcitrant nonunions, that is our purpose here.

This is, you have heard enough about this Friedlaender study, it was a very difficult study to do, but essentially their conclusion was that OP-1 offers the advantage of highly inductive molecules, an excellent safety profile, and lack of donor morbidity, and these are just some of the slides that you've seen already.
Interestingly enough, my personal opinion is that there is something specific about this that we need to evaluate. It has been shown both in the BMP-2 and the BMP-7, there is some protective thing happening with infection and that's something that needs to be looked at further.
In terms of the elderly, the problem is that when you go to the iliac crest and all that's in there is fat, and in those cases where there is

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not really bone graft available, I think the OP-1 is really a must for some of these nonunions.
I'm going to go through some of my own case studies. This is an 82-year-old, bad osteoporosis, two previous failed surgeries with bone graft. We did a definitive fixation with a locked plating and OP-1. There was presence of callus at seven weeks and full weight-bearing by six months, and you can see the ten-month x-rays of that.
This was a study done from Canada by McKee and what you see here are seven of them. We have over 30 nonunions of the humerus, a common problem in the elderly, and this patient had four surgeries, nonunion for 66 months, which is quite debilitating. And his conclusion was OP-1 does not require an additional operative site and was found to have a lower perioperative risk in terms of blood loss and rate of infection. This is of particular importance to patients of advanced age suffering from osteopenia and other significant medical comorbidities.
This is one of my first patients when I got to Tulane about ten years ago. He is a

35-year-old with 17 previous surgeries for

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everything that you can imagine, scheduled for an amputation. Treated it with OP-1 in 1995 and in six months he began having pretty good callus, he was full weight-bearing by nine months, and here's his ten-year x-rays of follow-up.
In conclusion, like many of the private and governmental payers, I think OP-1 is very important for the recalcitrant nonunions. I think it's especially important in those patients that don't have bone grafts, some of the elderly who don't have good bone graft, those patients that are high risk for failure as Dr. Jones talked about.
Sometimes you have to remember what our treatment goal is. My longest patient had a 20-year nonunion with 17 different surgeries, and these groups of patients are really disabled, and they are probably my most appreciative patients and in the meantime they are very important, but to get them back to independent mobility is a real goal. Any questions, I can take them.
Unfortunately, this number is under water, so if you guys want to take down my cell phone number, it's the same area code, 628-3352. Thank you.
DR. MCNEIL: Thanks very much,

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Dr. Dickson. I think what we'll do is just move through all of the speakers and then if we have a couple minutes left at the end of the scheduled public comments, we'll take general questions. We will move on to Dr. Laurencin from Virginia.
DR. LAURENCIN: Thank you. I want to thank the Medicare Coverage Advisory Committee for allowing me to speak today. I'm a professor of orthopedic surgery and also a professor of engineering at the University of Virginia.
DR. MCNEIL: Don't forget any potential conflicts.
DR. LAURENCIN: I want to disclose that

I have been a consultant for almost every major orthopedic device company, and I and my partner receive research grants from Stryker, Zimmer, and a few other companies. I also own stock in the Zimmer companies. I'm also on the board of directors for a company called Orthopedics Technology, and (inaudible) Company paid my travel expenses today.

What I would like to do is bring you some of the high points of what should be in your binder. There is a binder of information that has been presented which has papers and also copies of

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my presentation that I believe should have been submitted to the committee, and in the time I have, I want to review some of the high points.

The first high point is the current status of ultrasound. My belief is that the more one knows about ultrasound, the more one appreciates its importance and power. The three points that I want to make there is, one, there was a large body of evidence which was recently presented to CMS, and as a result of that they expanded the use of ultrasound for the treatment of nonunions.

Now why do I believe the coverage should be expanded even more? There are two reasons. First, there is an extensive amount of research showing that ultrasound accelerates all phases of fracture healing. And second, there's excellent clinical data demonstrating that ultrasound accelerates all phases of the fracture healing process. With two placebo prospective, placebo-controlled randomized double blinded multicenter studies, the FDA (inaudible) in 1994 for acute fractures. Working with the FDA, three prospective multicenter self-paired control studies were conducted consistent with the FDA's

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guidance options for determining future efficacy for fracture nonunions.

There has been a lot of discussion about a randomized controlled trial. I just want to make it very clear that in the case of ultrasound, the company went to the FDA and utilized the guidance document for industry for an established nonunion fracture study, and I think there is a copy of that in your binder. That guidance document states, in a clinical study to evaluate the efficacy of a bone graft device for treating established nonunion fractures, the patient may serve as his own control. It was with that guidance document that the studies that were conducted by the Old Town companies to determine the efficacy of ultrasound.

And third, again, in 2000 the FDA provided an approval for nonunion.

So I'm going to move through a number of other areas, because I think Dr. Carmack and Dr. Dickson actually talked about the control cuts very well, in terms of whether nonunions are a problem. We know they are, and what I would like to do is talk about how we're working on them clinically. Again, we know nonunions are a

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specific problem and we also know that in the elderly Medicare population, it has been recognized that noninvasive techniques can have an important advantage for patients. We know, again, from what Dr. Dickson stated, that from the patient's perspective, that there are break points in terms of quality of life.

We talked about nonunion definitions and I'm not going to go into these areas. And we've also, I think, touched upon fractured healings and nonunions in terms of different stages that occur. Where does ultrasound affect the healing process? Well, the answer is it affects the healing process at every level, and there is a great body of basic science information, really a very broad base of science information on this area, from the (inaudible) proliferation to the areas involved in enhancing

(inaudible) with vitamin D, (inaudible) synthesis, and stimulating exercise making it turn over. So there is really a very, very nice body. There's some new work that has demonstrated that EXOGEN or ultrasound can accelerate the patient's healing process and this is summarized in a large number of papers

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published over the last ten years. Now just to take a step back, when we talk to you about low intensity ultrasound, we mean 1.5 megahertz of mechanical pressure wave; it's low intensity, it's safe, it's similar intensity to fetal ultrasound, and it's of course much lower than physical therapy ultrasound. How does ultrasound work? Now, I have a CD that's also included in your materials that has a summary of the mechanisms of action, but again, it enhances the normal activity. Pressure waves are transmitted through the skin and soft tissue. Sheer waves are then transmitted to the bone and then a number of different mechanisms that we detailed before take place, which again enhance the normal intracellular process to take place. And again, the mechanism of action is summarized in the CD that was sent to you. I need to emphasize again that in April of 2005 we went to CMS, Smith and Nephew went to CMS, and a detailed review of all the clinical and scientific data was performed, and that resulted in an expanded nonunion coverage, and that expanded nonunion coverage was a caveat that surgical procedures did not need to be performed.

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And so recently, I had a review of the ultrasound therapy with CMS and that's actually resulted in the broadening of the coverage of ultrasound. Also interestingly in terms of the orthopedic community, I recently moderated a session at the (inaudible) society which included orthopedic surgeons, to examine the evidence.

There was one question. Is the evidence compelling in terms of to support (inaudible) for fracture healing and again, in a live audience preimposed, over 80 percent agreed that it was. Now, what I would like to do now is go through the questions and talk about some of the questions that you will be facing today. The first question is how will this current scientific evidence support well-defined indications in the use of these technologies? In terms of ultrasound, I believe it's high confidence. For the PMA, an extremely rigorous review was performed, over 5,000 subjects were in the PMA registry with three or four very, very large trials. These were expert reviews, publicly available, expert reviewed by the FDA, and peer reviewed literature. Again, case controlled studies that were consistent with the data and

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consistent with the draft guidance document that was utilized for the study. In terms of core data, again, high healing rate, 80 percent healing rate, all bones, all fracture types, all fixations, and again, these fractures that were enrolled were true established nonunions, 21 months since fracture, and at 15 months an average of 2.4 had prior failed intervention, and we got 80 percent. And we were looking at nonunions that really had not healed, not delayed unions three to four months out that could heal, did not heal, but at long-term nonunions with other procedures that were performed.

We examined other data that was great evidence in terms of use by the Medicare population, 80 percent heal rate in terms of Medicare population. A number of different bony areas were in this described area. Almost every bony area has shown success using ultrasound, and also in terms of multiple fracture sites and all different patient types in terms of the use of these areas.

The peer reviewed literature of

nonunions is particularly robust in terms of self-care control, again, through the FDA, at

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least in terms of their discussions. But as I say, there is also robust information about fresh fractures in terms of fresh fracture indications, and again, to say that we're not ready to do a great amount of randomized trials, we've done them for the fresh fractures, but for the others we have not.

DR. MCNEIL: One more minute, Dr. Laurencin.

DR. LAURENCIN: One minute, thank you. In terms of how confident are you in terms of outcomes based on the evidence, high in terms of the low morbidity and also safety, radiographic healing was being performed. In terms of confidence in terms of the biological enhancement, high in terms of these areas.

I just want to close with the, again, in terms of the number three, the positive health outcomes, again, the 80 percent healing rate that we demonstrated shows that. And again, in terms of the Medicare population, again, I think it's very important, in terms of generalizing fracture types it's very likely, because we've demonstrated so many different fracture types that are there, and also in terms of nonunions, in terms of

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providers and in terms of the Medicare population, as I've shown. And so again in summary, I think that ultrasound has demonstrated itself to be outstanding for nonunion, demonstrated outstanding efficacy, it's FDA-approved, and recently came to CMS for an additional indication. I think the 20 minutes per day factor is very important in terms of ease of use, and it has an excellent safety profile. Thank you.

DR. MCNEIL: Thank you very much, Dr. Laurencin, for that rapid run-through. Let's see. We now have Dr. Marotta, and I gather he is

presenting for two people; is that correct, Dr. Marotta?
DR. MAROTTA: Yes, it is.
DR. MCNEIL: So maybe you can indicate what you're doing and your conflicts, potentially for both you as well as for Dr. Kuklo.
DR. MAROTTA: Certainly. My name is James Marotta. I work for Medtronic, a manufacturer of these products. Dr. Kuklo was scheduled to give a presentation as well, he works for Walter Reed Army Hospital and has no conflicts that I'm aware of.
So the goals of my presentation today

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are twofold. The first half of the presentation is to suggest to the panel that when voting on these osteobiologic products that they segment them out based on those products, because they are all not the same and they don't all have the same levels of evidence associated with them.
The second half will be Dr. Kuklo's presentation which will be looking at the evidence that supports BMP and its use in nonunions.
If we look at the tech assessment, there is a good definition of these phrases or for these terms. Osteogenesis is the active action of cells making bone at that nonunion site.
Osteoinduction would be the induction of bone, that is growth factors or protein stimulating stem cells, attracting to the site, and then differentiating them into bone-forming cells so those cells can then make bone. Osteoconduction is a property that bone grafts have, which is purely just a scaffolding, a passive response; it sits there and holds it so that bone-forming cells can move in there and replace that scaffold with new fresh bone over a period of time.
And so when we look at bone grafting materials, we can classify them into two different

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categories. They are either purely

osteoconductive, that is, they have no activity whatsoever, you put them into small bony voids and hope that the body can bridge that void. Then there are the inductive materials which we have talked about quite a bit today, which are the demineralized bone agencies which have mild induction because they have small minuscule amounts of BMP in them that come from the allograft sources. And then there is the recombinant bone morphogenetic protein products out there, the OP-1 and the BMP products that are out there.

So one thing that I would propose is that if you're going to vote on osteobiologics, you not vote on them as a whole, since in voting on them as a whole you would have to vote on conductive materials, inductive materials, and then purely other materials that don't even have approvals and aren't even on the market yet, and if you voted on that, how could you vote on the level of scientific evidence when some of them have no evidence whatsoever, and others do have a small amount of evidence supporting them?

So I would propose osteoconductive

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materials, which your tech assessment has shown no evidence whatsoever using those alone by themselves to treat nonunions. Osteoprogenitor cell products, those are the bone marrow products or those patient derived therapy products that we hear a lot of press about, but they're not necessarily approved yet or on the market, or regulated by the FDA, and there is very little evidence that supports them. There are other demineralized bone agencies, of which there are probably 20 or 25 of those on the market right now, and there is some evidence that is shown in your tech assessment, but also in your tech assessment there are a couple abstracts that show that certain demineralized bone agencies in certain areas and environments leads to a high complication rate, a high infection or

osteomyelitis rate. And then there are the BMP products that other speakers have talked about. So in conclusion, I think that the committee should not look at orthobiologics as a whole, as one big voting block, because that would be difficult to vote in any way. They should separate them out into separate categories and I have listed those categories here. And I would

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just emphasize that BMP has the most scientific evidence supporting its use and its ability to induce bones in the body. So going on to the second half, BMP is a treatment for nonunion fractures. We've already had some of the history, but BMPs were discovered in 1965 by Marshall Harris. He then discovered that you could extract BMPs from allograft tissue, and that when you extracted these BMPs, they were active and they could induce the body to grow new bone. And the first published report of using BMP was in fact in the treatment of nonunions, it was in 1988 using human extract of BMP from allograft bone. And so Johnson and Harris at UCLA had a number of patients that they published on. Two of these were summarized in your tech assessment, but if you look at the history as a whole, human extracts of BMP placed in a nonunion consistently were able to heal those nonunions over a period of time in these case series. BMP approvals we have talked about a little bit. BMP-2 is under the trade name INFUSE bone graft, it has two approvals. It has an approval in 2002 for interbody fusion, that is inducing bone in the spine to fuse the spinal

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elements together. It has another approval in 2004 for the same product, it has gone through two PMA processes where they've done clinical trials to gain approval from the FDA showing that they're safe and effective. The second approval is for open acute tibia fractures.

BMP-7, as a product it's called OP-1 implant, and it's also called OP-1. The first has a Medicare device exemption for recalcitrant long bone nonunions, and the second one has an exemption for residual fusion, and as Dr. Jones has stated, HDE products cannot be used off label unless it's an emergency situation and you get prior approval by your IRB, and that's very different from PMA approval products like INFUSE bone grafts, which the Supreme Court and the FDA have affirmed that through the practice of medicine, physicians may use fully approved products like INFUSE in an off-label manner.

So just going over briefly some of these studies, INFUSE bone graft has been the subject of 14 prospective randomized clinical trials, the great majority of them have been in spine fusion, but it has involved more than 1,750 patients, more trials are continuing. Medtronic

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has a commitment to do prospective trials on BMP-2 to gain further indications and more abilities to help patients by treating them with BMP-2 products. But this was the first time that they gained the approval in the spine, 279 patients randomized against autograft. They did the spine trial, but this trial was able to prove that INFUSE bone grafting, the use of the two products was equivalent to autograft to induce bone in the spine, induce the spine and have good successful clinical outcomes.

We have also just filed a second PMA on the spine, it was just filed last week, and that is yet another trial, 480 patients, prospective randomized trial against autograft, randomized against autograft, and that will eventually allow us to have a second indication in the spine, again, where BMP-2 has been able to prove that it's equivalent to autografting induced bone, and in this case it's addressing the posterior spine as opposed to the interbody spine.

Dr. Jones has talked to you about the

best study which was published, it was a prospective randomized trial. I just want to highlight that in that trial, one thing that they

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did find was a 44 percent reduction in the incidence of infection when BMP-2 was used. This is, as Dr. Dickson has said, something that we don't fully understand yet, but it is a consistent result that we see in many of our clinical trials, and that is when BMP-2 is there, the risk of infection or the incidence of infection goes down. It seems to be some indirect cause, maybe through antigenesis, maybe the ability of the body to heal at an accelerated rate, but for some reason bacteria is not able to get a foothold and infect those sites when BMP-2 is used in a local area. Dr. Jones did show this 30-patient randomized trial that he and others were involved with, and I just want to highlight that in two weeks from now at the OTA, Dr. Kuklo will be presenting on 52 patients, similar type patients. They are tibia fractures, soldiers coming back from Iraq with tibia fractures with large traumatic bone loss, treated with BMP-2 and allograft bone and he is getting very good successful outcomes compared to the first Gulf War, that is the Gulf War back in 1991. But comparing the Walter Reed experience in the first Gulf War to this Gulf War, the difference being

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that BMP-2 is being used in those open tibia fractures with traumatic bone loss, he is seeing significant improvements. There are two unpublished case series that we're aware of right now in long bone nonunions. 19 patients by Dr. Race at Loyola, which was a poster presented recently. Dr. Hicks at Fort Lee has also, or will be presenting data on 46 nonunions, and this data will be published eventually. I predict in the next year or so, there will be many case series on BMP-2 in

nonunions published in the literature out there, and so many more studies are ongoing and will be out there.

I just want to highlight finally, one thing that should have been delivered to you that was alluded to by Dr. Jones, but Dr. Scott Jones from Emory University has created a white paper looking at the evidence of the effectiveness of BMP-2 inducing bone in older individuals. In that he looked at not only animal data where they used very old primates and used BMP-2 in there, and have shown the ability to induce bone, and that bone looks like good young healthy bone in those old primates. But also in this case, this was a

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spinal fusion study, a randomized prospective spinal fusion study where we looked at the patients that were over 65, and in there there were eight patients in the BMP-2 group, nine patients in the autograft group, and at 24 months both groups, 100 percent healing, but at six months, faster healing with the BMP-2.

So just in conclusion, BMP-2 extract has been used for more than 20 years. BMPs do induce new bone formation, there is a compelling body of evidence that BMP-2 can induce bone formation in a clinical setting in numerous prospective trials, and certainly the majority of those are the spine, we also have some in oral surgery, but we do have some from the fresh fracture and in those traumatic fractures with large amount of bone loss, and BMP-2 is being widely studied with many future indications to come.

DR. MCNEIL: Thank you very much, Dr. Marotta, particularly for filling in at the last minute for your colleague. We very much appreciate that. So, Dr. Aaron, from Brown.

DR. AARON: Thank you very much, I am Roy Aaron, and we have the wrong slides

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unfortunately. I am a professor of orthopedic surgery at Brown Medical School. I am a consultant for EDI, they paid for the trip, they do fund research in my laboratory. I have no stock, royalty or other relationships to speak of with EPI.

It's not my purpose to summarize or repeat any information that you have had but rather to highlight certain areas which I think are of interest, and my role really is to emphasize some aspects of the science, so I will touch very briefly on preclinical studies, very briefly also on mechanism of action, and some clinical studies and the relevance to Medicare beneficiaries. And I may use the phrase EMF but I really am referring to pulse fields, capacity coupling and combined magnetic fields.

If we had the slides I would be able to show you that in terms of preclinical studies, there are quite a number of in vitro and in vivo reports, both cell and organ culture, as well as the animal studies which demonstrate that these devices actually increase extracellular matrix, particularly cartilage and bone, and you can see here there are a variety of models that have been

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looked at, mostly different kinds of progenitor cell models, and a variety of different outcomes in terms of cell differentiation, proliferation, depending on the cell cycle position of the stimulating tissues.

Now in long bones, again, there have been a variety of, and this is just samplings, of course there is a much larger total there. Here is one of the delayed union models on the right using the stimulation techniques, and the important thing here that I want to get across is that in both bone and cartilage, not only do we see accelerated extracellular matrix production, but also increased stiffness and strength in both bone and in our laboratory now, in cartilage, and the take home message is in a sense that there is

a great deal of both in vitro and in vivo evidence that these are biologically active devices and the biological activity is to enhance bone formation. Now in terms of mechanism, I think this scenario is particularly interesting because years ago, this was thought to be kind of a clack box and nobody really understood the mechanism of these devices. Over the past five to seven years, there has been a great deal of work, and I'll

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quickly go through it, to indicate that indeed, very well-known and very well-worked-out mechanisms are now in place. Now it's true that not much is known about the physics of interaction of the cell membrane, but that's not unique. It's the same for all physical stimulation, heat, mechanical strain, fluid flow, things that we understand are biologically active. In my opinion, the best worked-out mechanisms concerns the stimulation of receptor activity, particularly parathyroid hormones as recently demonstrated in some Italian studies, and it's pretty clear that these receptor populations are efficiently activated. Our lab has shown that this leads to activation, ultimately activation of the transcription path which you see with OP-1, and eventually an upregulation of genes for extracellular matrix, notably collagen and (inaudible). Now, there have been an enormous number of studies looking at the role of growth factors and the amplification and mediation mechanisms of electrical stimulation. A lot of this was started by the (inaudible) group working with biomagnetic fields and they demonstrated increase in IGF-2,

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and probably the first demonstration of receptor activation by fields in bone. Barbara Williams' group did excellent work looking at both the BMP and TGF Beta, and in fact has looked at nonunion cells, human nonunion

cells, and has demonstrated that TGF Beta is regulated by a sodium field. We have looked at the same type of thing in the endochronal bone model and have shown that these growth factors are upregulated but the physiology is not disorganized.

Now, for those who are here who are pharmacologists, they will be interested to know that there is clear dosimetry of these fields in terms of amplitude, frequency and exposure duration. So there are around the world at least ten laboratories which have shown detailed internal consistency that is reproducible and relevant mechanisms of action.

And then the question concerns the clinical aspect of things and the levels of evidence that we have heard about early on. I think that this technology notice really improved on the FDA in the 1970s when longitudinal cohort studies were the standard of evidence, and it was

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felt that longstanding recalcitrant nonunions rarely healed and certainly could serve as controls after a period of time, and I think most people believe that that biological situation remains today. So the technology was approved and the post-market studies confirmed that somewhere between 75 to 85 percent of these fractures that were nonunion would heal with electrical stimulation.

And so in the '80s and early '90s, a state of echo poise did not exist and without that it became very difficult to do randomized clinical trials, very difficult to get an IRB to approve patients, and you've heard others speakers allude to this as well. So in essence, there are not a lot of randomized controlled trials because the documentation of efficacy predated these standards.

Now having said that, let's look and see what level one and two evidence actually exists today. These are studies not of nonunions,

but of bone healing in osteotomy and in spine treatment, and I will just concentrate on these. These are Italian studies, they are all randomized controlled studies and they do demonstrate that

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indeed, exposure to pulse magnetic fields stimulate bone formation in a model of healing. Now with regard to delays and nonunion, I should first talk about a study done by Gotling. It is not a true metaanalysis, but a compendium of 28 studies that looked at nonunited or healed fractures treated with pulse fields, compared to 14 studies of similar fractures treated with bone graft with or without internal fixation, and the success rate was exactly the same, demonstrating equivalence of the techniques. There are many observational studies and a variety of different models with a variety of stimulation techniques, and you hear numbers coming out of those observational studies, 86 percent, 80 percent, 87 percent healing rates. I know of four randomized controlled trials, two placebo controlled and two controlled against grafts. The studies where the controls were grafts demonstrated equivalence between pulse field techniques and the graft, and in the two placebo controlled trials, in the Sharrard trial the overall numbers, 45 percent healed versus placebo device, and in the other study, 60 percent healed versus zero.

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So the question comes up then to me, what is the generalizability of this data to the Medicare beneficiaries? And it would seem to me from looking at the data that when you look at comparison studies, there really is no significance when you break this out for age, and that these techniques work equally well regardless of age. Of course there is no morbidity in the sense of surgical morbidity which can be as high as five percent, and graft has a reoperation rate

of ten percent. And this is a group which, as you know, is very intolerant of complications. So in summary, I think we have a technique with excellent preclinical data, well understood mechanism of action, a reasonable amount of level one and two evidence of clinical efficacy, and I think particular relevance to the Medicare population. In fact, because these techniques have minimal morbidity, they can restore function, and since the Medicare population is not particularly tolerant of surgical morbidity, I think these actually have a special applicability to the Medicare population. Thank you.
DR. MCNEIL: Thank you very much,

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Dr. Aaron. So, Dr. Whitman.
DR. WHITMAN: I'm Skip Whitman, I'm a general orthopedist, been in practice for 18 years. I do provide consulting services for Smith & Nephew in the area of government affairs. I have no stock in any company that provides orthopedic devices, and I don't have any agreements with any of the treating companies. As I sat here today and saw everybody and listened to everyone talk, I wondered why am I here. Well, I guess you might think of me as representing the silent majority. I probably represent 80 percent of the orthopedic surgeons who see patients. I am not in a medical center or tertiary care facility, I know my patients' first and last names. I order x-rays, I do their exams, I see them in the grocery store, they go to my church, and I treat their kids, somewhat different than everyone you've heard up here before. So my talk, therefore, is going to be a little different.
How does ultrasound, how does that affect me and what I do in my practice? And I don't just use ultrasound, I have used electrical stimulation, I've used demineralized bone matrix,

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and obviously I use surgery. So I use whatever I think will get the best result for my patient. And my patients walk in or are transported into the emergency room or off the street, they are not referred by another orthopedic surgeon, at least in eight out of ten surgeries. I'm looking for something that's not invasive. I have to sit down and discuss these things with my patient. I want low risk, I want it to be easy. If it's easy for me and easy for my patient, I find that it's a lot more successful. I want something that's going to give me a faster healing response, less morbidity, early return to work, and I always look for a win-win situation. I'm just going to skip through this mechanism of action, I think you've heard enough science today for that. It's a cute little slide, but you can tell who I am. Okay. Safe and effective technology delivering a significant health benefit. I really think that when it comes to ultrasound in my practice and why have I gravitated towards it, it's a noninvasive treatment for my patients, many of which, the vast majority are Medicare patients,

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and I think that's true for most practitioners who are general orthopedists in the country today. I would prefer to do something that's nonsurgical for my patients. My elderly patients don't handle surgery as well as my young kids that I treat, so I want to give them something that's going to be easy for them to get to and yet have good results. Get them back to their normal activities. I find that really important. One of the first things they ask me after surgery is, can I go to Wal-Mart? I mean, can I go to Wal-Mart. They want the simple things in life. They don't want to spend time in the hospital, they don't want these surgeries. It's safe for me in my hands. It's

easy, it's safe, and it's easy for my patients. And especially my Medicare patients, if I try to get too complicated on my octogenarians, they have a hard time understanding and keeping with the treatment program and the protocol. I use it a lot in my fractures that I feel are at risk in my practice. We've seen the data in the handouts that you have, advanced age, smoking, diabetes, open fractures, medications, steroids, fracture type, energy, all those things,

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osteoporosis, they all go into effect when we're making a decision as a clinician, and my Medicare population especially has a lot of these comorbidities. You've seen the science, it's well documented, ultrasound affects the healing at all levels of the fracture healing process, it accelerates the normal process of healing. And we've already talked about the recent CMS decision after reviewing all the data to expand coverage. Now I have a couple of case studies, sorry these aren't scientific studies, it's anecdotal information from a small town practicing orthopedic surgeon. A 76-year-old patient that had first surgery actually by one of my partners, came to me and already had been a year after the first surgery, a lot of delay in trying to get this to heal. He did a second surgery. When the patient came to me after the second surgery, I put on ultrasound, I put an EXOGEN on this patient. I realized there were still mechanical issues with this, so I took the patient to the operating room and did an osteotomy and put a locking plate on, continued the ultrasound, and three months later the patient is ambulating, full weight-bearing,

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with very strong healing response. A very happy patient that happens to go to my church. Now, based on that experience, I had an 85-year-old patient who came to see me with a very

similar proximal tibia fracture, and I put the EXOGEN on her right away, day one. She got the EXOGEN day one. Did I expect to get paid for it or to bill for it, no, I didn't, but this is what my patient needed. And I put the EXOGEN on her, and here she is with x-rays at three months, she's ambulatory, she's weight-bearing, she's getting back to her normal activities with an excellent healing response at her fracture site. I think that that patient, versus the patient that went through three years of a lot of trauma to try to get healed.

Distal pilon fracture, I do think that these are at risk oftentimes, certainly this is a Medicare-aged patient, but when I did the surgery on this patient I placed the EXOGEN on it immediately postoperatively, because I thought he was at risk. Eleven months post-op, hardware out, patient is walking pain-free.

Scaphoid fracture, as everybody in the business knows, they are difficult fractures to

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heal. This patient had three months of symptoms and no treatment prior to walking into my office. I'm not sure when this patient fractured his scaphoid. First visit, nonsurgical, put the patient in a cast, placed on EXOGEN. Four months later, no scars, fracture completely healed. And it's proximal on this, so it's even more difficult.

66-year-old patient here with an open distal radial and ulnar fracture. Initial debridement, placed an external fixator, I felt that internal fixation at the site was too high risk for infection, so in order to assist that, I put EXOGEN on the patient. Three months, fixator off, invisible therapy, already getting back to her normal activities with a good solid clinical union.

In short, I like the EXOGEN because it's safe, it's easy. I can sit there with my patients and say would you like me to give you a

device which you wear ten hours a day or would you like me to give you a device that you can wear for 20 minutes, or would you like me to do an operation where I can do a surgery and put in some demineralized bone matrix or bone graft. Most of

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my patients choose the 20-minute device. I choose the 20-minute device in my practice in this small area and small world of what I do. It's been effective for me, it's worked for this surgeon in private practice, it reduced my rate of nonunions and the number of patients I have to send to a number of my esteemed colleagues here who do it a lot better than I do. It decreases my need for surgical interventions, and it plays a critical role in my practice and I think it makes it easier for me to see my patients in church and in the grocery store, because they're happy for what I do.

DR. MCNEIL: Thank you very much, Dr. Whitman, that was very nice. What I think I would like to do now is take the chair's prerogative and instead of moving right on to the public presenters, take a few minutes while these previous presentations are fresh in our mind and ask the panel if they have any questions for them. We will obviously have time after lunch, but I think we will start now. Yes?

DR. KIRKPATRICK: I have a couple of questions, one for Dr. Laurencin. You mentioned a number of times that the data presented to the

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FDA, and unfortunately I didn't see that in our packet, we don't have the details of this study, so I'm wondering why hasn't it been published in the literature and why wasn't it submitted to the panel for their deliberations.

The other issue on Dr. Laurencin's presentation is, you quoted the standard for the guidelines that the FDA put out, and I would like to comment that that's more than likely a minimum

standard and that when you're dealing with electrical devices, the FDA certainly would have very much welcomed a randomized placebo trial.
DR. LAURENCIN: Well, thank you. A couple points. The first question, if you look in your binders, you will see there is a summary --
DR. MCNEIL: Just if I can interrupt, Dr. Laurencin, I gather from Kim that the committee did not get everything that you submitted to the staff and instead got the presentations only, so referring to the binder is a little moot.
DR. LAURENCIN: There is a summary of that information that was submitted to the FDA, a large registry study and was actually submitted as a part of some of the materials that were

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submitted to the committee, number one. A portion of that registry information was actually published as a study that was peer reviewed.
The second point that you asked, yes, the point of what I'm saying is that, one, it is a guidance document that says if you want to perform a clinical trial in this way, you know, this is a guidance document that we have for you, and so this concept of doing randomized controlled trial versus a nonrandomized controlled trial, doing a case study trial, my belief is that for nonunion, recalcitrant nonunions out there for 20, 21, 22 months, I believe that patient self-control is valid.
While I have the podium in terms of answering that question, as an answer to that question, I think Dr. Burke's question was very important in terms of what do these rates mean and what do the studies mean in terms of what is the rate of nonunion that occurs, what is the potential for these fractures to heal on their own. In one study by Sharrard, they found three out of 25 healed. Now, the thing to remember is that these were delayed unions, not established nonunions, they were delayed unions. Some were

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only three to four months old in terms of their timing. So what that study said was for delayed unions, a certain number of delayed unions or slower healing unions will go on to union. And the other study by Simonis where they looked at patients, they had a 60 percent rate, but those patients all received a surgical intervention and the electrical stimulation intervention. They received a surgical intervention and the electrical, and their control was a surgical intervention at that point. That study said that with surgical intervention at that point, 50 percent would heal. In the case of the ultrasound study, it's very interesting. Those studies that were presented, the patients who did not receive an additional surgical intervention, if they had a rod placed and they were 24 months out from that rod being placed, they did not have an operation performed at that point and they just had the ultrasound device placed. And so the numbers in terms of using it, these patients actually were going on their same, had their same clinical course, and the only intervention that was placed was the ultrasound device placement. Thank you.

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DR. MCNEIL: Other questions? Yes.
DR. BERGTHOLD: Did the ultrasound treatment, the 20-minute-a-day treatment, right, and it's set in the doctor's office in terms of the setting of the controls, I'm just interested in the outcomes in terms of an elderly patient, how difficult is it for them when they get home?
DR. LAURENCIN: That's a great question. And first of all, all these modalities are great, and so what I don't want to do is get into a lot of comparisons. But the 20-minute-a-day administration really ensures that there is high compliance. Once it's set and once it's on, you just place it on for 20 minutes a day and it's

off the rest of the time. So there's high compliance in terms of the Medicare population. There is also very high compliance, and one of the things that Dr. Aaron said is very true in terms of nonunions, there is a lot of noncompliance that makes these studies very difficult. And so if you're administering an apparatus for 10 hours, 15 hours, you know, 10 or 12 hours a day, when you have a 20-minute-a-day administration, they're all great modalities, but the 20-minute-a-day administration has some

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particular advantages in terms of compliance, and I think Dr. Whitman also alluded to that earlier.
DR. MCNEIL: Yes.
DR. AKLOG: You just mentioned something that I think was brought up before as well, and that is an initial concern is that we were talking about multiple modalities, some of them are very different, all of which seem to treat similar disease processes. It hasn't really been made clear to us and certainly to me what indications are for individual ones. So in a sense, you know, generally speaking when you have multiple different treatments for the same thing and one has not risen above the other, it doesn't really give the strength of the evidence for any individual ones. Do you have an algorithm as to when you would use ultrasound versus some of the other ones?
DR. LAURENCIN: Well, I think there are three reasons why there are multiple different modalities for treatment of a disease process. Number one, they all work; number two, none of them work; or number three, the fact is that some of them are better than others and so it's not really coming out. I think one and three are the

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case. I think that a number of these modalities do work and do have clinical efficacy. I think that some of the modalities such as the BMPs

obviously, remember, we're talking about approvals for BMPs that just occurred over the last few years, and we have had (inaudible) for the BMP-7. In terms of ultrasound, the ultrasound is a growing area in terms of this, we've got great scientific data, great clinical papers, a couple papers in 2001 and 2003 that have come out, so that's a growing area in terms of use. Where it's all going to shake out, I think we're going to see over the next few years, but I think they all have good clinical efficacy in these areas. I obviously have personal biases and so on, but I can see how individuals may have differences there. What would be very interesting to see is some comparison studies from a scientific point of view utilizing all these modalities in terms of nonunions and see what shakes out.

DR. MCNEIL: Let's see, Mark or Kim? Kim, go ahead.

DR. BURCHIEL: I wanted to ask possibly Dr. Dickson, and Dr. Marotta, I think you also commented about the potential morbidity of the

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osteobiologics. We haven't heard anything about hypertrophic responses of these agents, and I know that's been a bit of concern in my area, and I wonder if you would want to comment on that.

DR. DICKSON: In terms of the studies, safety has been fairly good with them. There was, in the BMP-2, there was a case where it formed too much bone around the spinal cord and that's certainly a concern if that BMP leaks out. Comparing with all the BMPs, the other thing that is of concern is whether it's a cancer-producing thing in terms of taking a cancer and making it worse. In all the BMPs that have been used, there hasn't been anything shown to say there is an increased risk of cancer. There have been patients with cancer and it seems to make them more differentiated, so it actually makes them a little bit better in terms of looking at all the patients that received BMP.

The other thing that's a concern to me and I don't know the answer, it probably is nothing, but there is about a 38 percent result with BMP of forming antibodies to the BMP and where that's going to go, it seems to go away, but I don't know what that means exactly.

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DR. MAROTTA: In terms of the fresh fracture studies done with BMP-2, there was very little incidence of hypertrophic ossification between the study group and the control group, and in fact there was no difference between the two, using it or not using it. There was that one spine study where there was some bone seen behind the cage, but that spine study was actually using an inferior technology spine treatment, and they're now using what's called stand-alone cages, where the cables are coming in from the back all by themselves without any pedicle screws whatsoever, and in those situations it's very difficult to get the cage countersunk deep enough. So it was seen on CT scan that there was bone in the back of it. We also saw that in the autograft group too as well, the growth of bone in the back. All the patients did well in that study and had good successful outcomes, but it was a concern of the surgeon, and they stopped enrollment in the study and followed the patients out to two years and published the results just last September. And they hypothesized as to why they saw that bone, and the major hypothesis was stand-alone cages, the fact that they weren't

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countersunk and the fact that some of those cages might have actually slipped forward, even though they had the cage in place, which is why the implant is still in use, we now have these stand-alone cages with pedicle screws to keep it from slipping forward.
In terms of cancer, there is a warning on both BMP-7 and the BMP-2 that we haven't

investigated either of those in cancer patients and so we shouldn't be using them on cancer patients. There have been numerous cell culture studies where we've exposed cancer cell lines to the BMP products and we have not seen any proliferation of those cancer cell lines, but we have not done any clinical studies to look at, you know, to use it in cancer patients, is there a higher incidence of cancer. It has been used very frequently in the spine with very, very few adverse events coming in, reporting in from the field.

In terms of the antibodies, the antibodies do form, they seem to form a little bit higher in the BMP-7 than in BMP-2, and that may just be due to the clearance rate of the body, but they are transient, they go away by six months.

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And again, we don't know how that interacts with humans, so there is this warning not to be used in pregnant women. But we've had hundreds and hundreds of litters of rabbits and rats where we have induced antibodies in those rabbits and rats and haven't seen any issues with those litters, but again, no clinical studies other than in the spine studies where the women actually got pregnant after their spine fusions using BMP-2 and there were issues that were pregnancy-related.

DR. MCNEIL: Thank you, Dr. Marotta. Kim.

MS. KUEBLER: Has there been any, have you looked at any phenotypic reactions or different ethnic backgrounds?

DR. MAROTTA: All of our studies include general populations, but we haven't seen any in terms of race or sex. We also haven't seen any issues in terms of smoking or steroids, nonsteroidal antiinflammatory drugs. It seems that although all of those drugs and the smoking adversely affect bone formation in autograft patients or control patients, with the BMP-2 patients, they were able to overcome some of those

effects, and so in terms of actual scientific

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evidence, I don't think we've analyzed that.
DR. KIRKPATRICK: There were two things that came in in Dr. Marotta's presentation that I just want to make sure I'm understanding correctly. One was that IRB oversight was needed for off-label use on HDEs; it's my understanding that all use of HDE requires IRB oversight.
DR. MAROTTA: Right.
DR. KIRKPATRICK: The second one is that you indicated that the FDA trial looking at the INFUSE in the spine anterior was equivalent. My understanding was that was a non-inferiority trial and from what my experts tell me, and the panel I hope can confirm or correct me, that a non-inferiority trial is very different from an equivalency trial, which is very different from a superiority trial. And so, I just want to make sure that the panel understood the nuances of that. That's much more important to you than me, but that became very critical in FDA panel deliberations on that device; is that not correct?
DR. MAROTTA: Certainly. In terms of the HDE, you have to have IRB approval to bring the HDE product into your hospital to use it within the exemption. There is a phrase or a

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caveat in the law that says under emergency situations you can use an HDE product off label but you have to go back to the IRB and follow the IRB emergency procedures. IRBs have emergency provisions for using essentially unapproved devices and in an off-label situation, an HDE product off label is actually considered unapproved, so you have to use those IRB emergency procedures. If you don't use those, you can't use the HDE off label.
In terms of the spine study, the spine study was set up, I believe it was set up as an equivalency study, but at the end when they came

up with the numbers of patients and were running statistics, there was no difference between the two groups, and if we had only taken 20 more patients in that study of 279 patients, if we had 299 patients, we would actually have been able to show that at least on bridged radiographic fusion in the BMP group was 95 percent fusion and the autograft was 88 percent fusion at two years, and we would have actually had a P value which would have shown superiority.
DR. MCNEIL: But you don't have those data, right?

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DR. MAROTTA: We do have that data, and in fact what we did was we did a metaanalysis where we combined that study, that LTK study with data from a laparoscopic study where we, instead of having an open procedure where you open up the entire cavity and put the LTK in. They weren't the same study, but it was a metaanalysis of combined studies, which often is done when you can't go back and do another 500-patient randomized controlled trial.
DR. MCNEIL: Just to be absolutely clear, I just want to be sure everybody is on the same page here, the randomized trial had 270 patients, is that what you said?
DR. MAROTTA: 279 patients.
DR. MCNEIL: And had you had another 20 patients, blah, blah, blah, but for the 279 --
DR. MAROTTA: For the 279 all we could show was equivalence, and that's all that we can state in our FDA indications is equivalence, that BMT-2 is equivalent to autograft.
DR. MCNEIL: Leslie.
MS. FRIED: This is a general question but I have to ask it. If we're talking about the Medicare population, many of who have

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comorbidities and certainly the under 65 have a disabling condition. So my question is, for many

of these studies or other studies I have been involved in looking at, elderly people with comorbid conditions are often excluded because they have high blood pressure, they have a heart problem, whatever. So my question is, I looked through all this exclusionary criteria as it relates to whether there was nonunion or union, et cetera, and so my question is, were people excluded from participating in the studies? And you're there so you get to answer, but other people can pop up. Were people excluded because they had high blood pressure or because they had diabetes, or because -- clearly they were allowed to smoke, but other disabling conditions which would affect the use of the studies for the purpose we're here today?

DR. MAROTTA: In the BMP-2 trials, the ones that I'm aware of, and I'm not aware of another company studying it, but in our BMP-2 trials we did not exclude them for smoking or if they had steroid use. We also didn't exclude them if they had spinal litigation, which actually, you know, people who are suing someone for back

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problems tend to heal at a much slower rate, I'm not quite sure why.

(Laughter.)

DR. MAROTTA: But no, we didn't exclude diabetes, we didn't exclude obese patients, we didn't exclude Medicare age patients, we essentially took all comers so long as they weren't pregnant, they didn't have cancer and they didn't have an infection, so we essentially took all comers in those studies.

DR. MCNEIL: Any other comments about Leslie's questions and the design of other studies? What I would like to do is have the responses to that question now and then move on to the public comments.

DR. DICKSON: In terms of the OP-1 study, the only exclusion was infection, so we took all medical conditions.

DR. WHITMAN: For the ultrasound there were no comorbidities like that.
DR. MCNEIL: One question I'm trying to remember, somebody presented -- oh, Mark, did you want to follow up?
DR. FENDRICK: Just one last question. This morning is not typical in that no one is

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coming up to speak as a proponent of the tried and true intervention which you all trained on, which is the autogenous bone grafting, and I would like to ask maybe one person from the TA perspective. When you get a lay of the land about where things are now in terms of how to fuse, and if these innovative interventions are relative to what might be compared to autogenous bone grafting, and I would like to start with our real doctor, at least he's self-described, but Dr. Whitman first. But also for anyone else, is there a role? I mean, the way we hear these presentations is we shouldn't be doing this anymore, and I presume there are probably a few orthopedic surgeons out there who are a little more conservative who would probably wait and see for more data on some of these interventions, and I imagine all of you have done this intervention fairly recently, and the impression I get is we're not going to be seeing any of these bone graft procedures done if you guys get your way.
DR. WHITMAN: First, I need to clarify. I don't think I described myself as a real doctor, just a simple doctor.
(Laughter.)

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DR. WHITMAN: The point I was trying to make is I see a different patient, I don't see a patient who has been to five or six surgeries. I don't see a patient who has been walking around with a nonunion or not walking around with a nonunion for two years. So I have an entirely different patient population.

To answer your question, do I do a lot of iliac crest bone grafts, no, I don't. Because I can do a joint replacement, I can do any other surgery, and the procedure that my patients complain about most without question is the iliac crest graft.

DR. DICKSON: I do tons of iliac crest bone grafts, so I still think it's the tried and true method, and so I do tons of them, and while we're in the process of looking -- I don't know if I'm a simple or a complicated doctor, but I'm unemployed.

(Laughter.)

DR. DICKSON: But the idea is, I still think it's the treatment of the nonunions, and I make a big distinction between delayed union and nonunion. To me a nonunion will not heal with any of the modalities that are without surgery, and so

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that is my distinction, so I don't treat them with ultrasound, electrical stim. The patients that I treat with some electrical stim are those patients that have the medical comorbidities, may be going towards union. If they've had a definite four-month period where I see no radiographic progression and I see no clinical progression, to me, that's a nonunion, I have to see four months of no progression and then I don't think anything special is going to happen later on, so those people need surgery.

DR. MCNEIL: Okay. Three very, very quick comments.

DR. DAVIS: I will just say that no one has ever described me as simple, so that's very simple. But five years ago, as a CBT code analysis, I did on average between 350 to 400 cases a year and took about 125 autologous iliac crest grafts. In the last year and a half, with the combination of the variety of these products, I did seven and eight in the last two years. And it's because many of the patients that I see, spine and general orthopedics, have had multiple

procedures, including the use of a number of these alternative products that I basically will cycle

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them through. And I will tell the patients that the gold standard is autologous iliac crest graft, but they still complain, so the number has gone down dramatically.
DR. MCNEIL: Final comment, please.
SPEAKER: In established nonunions like we talked about, if they go into surgery, are not confident to not do an autograft, and they always get autograft plus some other stuff.
DR. MCNEIL: So there is a question about variations in practice, and I think we just got the answer.
Let's see, we have three members of the public, I believe, who would like to talk, and they each have two minutes. So, Dr. Janet Conway, please, and if Dr. Ann Steforak could follow, and Richard Pierce after that, if they could all be ready, that would be great.
DR. CONWAY: Good morning. Thank you for allowing me to speak to you today. My name is Dr. Janet Conway, I'm at the Ruben Institute at Sinai Hospital in Baltimore, and our center is a large referral center for nonunions. I see a large population of Medicare patients, secondary to the fact that I also do a lot of total knee

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replacements, and they go on to wind up requiring knee fusion. A lot of these patients are utterly debilitated and in order to allow the knee fusions to heal, I use a number of these other modalities. I think my algorithm for treating these patients is very simple as far as, do these patients need extra stimulation for the biology? As far as knee fusion, these patients are very, the bones have been traumatized, they're elderly, and I think they need all the help they can get when I am trying to stimulate the biology of that, and so that's the role where I use the

osteobiologics.
Also, in cases where I see previous infections, I'm not going to use an internal bone stimulator, I'm going to use an external bone stimulator. So that's another thing I consider. You know, if you are going to devise an algorithm, I have an algorithm, maybe I should consider putting it out in the literature, but I think that's how I use all these osteobiologics, stimulation and ultrasound, and iliac crest bone graft, but a lot of my patients are unable to tolerate the surgical time, so all these modalities are very important, and also, my

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patient's bone healing is very important. I did bring extra copies of a letter from one of my patients who was very grateful that she was allowed to use the ultrasound bone stimulator because she went on to heal. She went on to heal her nonunion. So again, I think there is a role for all these things and I do use them in my best judgment in the cases that come up, and, you know, I appreciate you taking the time to consider these things.
DR. MCNEIL: Thank you very much, Dr. Conway. And by the way, please indicate whether you have any conflicts.
DR. CONWAY: None.
DR. STEFORAK: Good afternoon. As a little bit of a change of pace, just supplemental information to ECRI's technology assessment, this is something new that wasn't presented earlier, and you're not voting on this but for future reference. My name is Ann Steforak and I'm (inaudible). We do have some FDA approvals for insertional (inaudible) but we're also doing IDEs that you're probably not aware of.
On delayed nonunions, we're trying shock wave treatments. The results thus far, 50

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subjects were approved, 29 subjects were treated,

and at three months, 14 of the 27 patients have found to be healed. At six-month follow-up, 15 out of the 20 subjects that have been followed have been found healed. And also at 12 months, 14 of the 15 subjects have been found healed. So no adverse effects based on investigator assessment, on patient assessment and also on radiographic evidence. Again, no adverse complications, and the great thing about this agreement is it's a single treatment, not a daily treatment, pretty much single, you may do a second. Also too, as I said, minimal complications and it was found to be effective, so more to follow and you will hear more about this in the future. I appreciate the time.

DR. MCNEIL: And that was not a randomized study?

DR. STEFORAK: No, it's an IDE safety and effect study that's FDA-approved.

DR. MCNEIL: Mr. Pierce, is that right?

MR. PIERCE: The comments I was going to make I think have already been covered by the panelists.

DR. MCNEIL: Thank you all very, very

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much. I think this has been a great morning. We're going to cut lunch a little bit short because I think we're going to have quite a bit to discuss and a number of questions potentially for the presenters. So what I would like to do is be back here at 12:30. And Kim has some of the material that you were asking about that Dr. Laurencin has submitted, so if you would like to take a peek at it, it's here. Thank you all. 12:30.

(Luncheon recess.)

DR. MCNEIL: Welcome back. Just to make sure everybody is clear on the schedule, we now have a period of time with questions to the presenters, then the panel will have some open deliberations, and at some point during that period we will take a very short break, because it

could be a long afternoon. I think we started having a number of very good questions to the presenters, and what I would like to do now is continue that and ask the panel whether they have any additional questions that they would like to ask. Keep in mind in doing this that we have some very specific questions that we have to answer at the end of the

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day, so it would be useful to make sure that we ask anything that would help us answer these questions. I will put two on the board right now, and we can decide whether they're good questions or bad questions.

But the two questions are, is a bone a bone, and the second question, is an orthobiological device an orthobiological device? So just because our -- is a bone a bone, is a deal a deal, is a bone a bone, and is an orthobiological device an orthobiological device? Right now the questions are framed in those generic terms and I just want to make sure that we have information to answer them in that generic way, or do we need to get at it a little bit more specifically. So now, the floor is open to the panel and to the presenters. Just in the interest of time, if you are going to answer a question, as a matter of fact, why don't all the presenters come to the front row now, so we don't have to trip over everyone. Questions?

DR. AKLOG: I guess this is sort of a generic question maybe focused on the doctors who were talking about the orthobiologics. I notice in most of the material that we received that

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healing is really described as a binary, either you have healed or you haven't healed. So I'm just going to throw out the question and wonder whether, especially in perhaps elderly patients, whether there's a quality to healing. Are late fractures an issue in some of these, is there any

evidence that any of these devices or the biologics give you a stronger, the strength of the healing is greater? I notice there was one slide where that was directed at an animal in an animal study where the tensile strength seemed to be greater in one group or the other, but if you could address that.

DR. DICKSON: The very simple answer is no. Bone is a great device in terms of how it heals without scar tissue. There are occasional late fractures but for the most part when the bone heals, it's just as good as before the fracture.

DR. MCNEIL: Thank you.

DR. BURCHIEL: This is more a question to the panel and also possibly Dr. Aaron, and perhaps a third question to add to Dr. McNeil's questions. Is electrical external stimulation all the same? I think Dr. Aaron mentioned something about that, but I think we're going to be forced

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to differentiate between these technologies.

DR. MCNEIL: Okay.

DR. AARON: Do you want me to respond?

DR. BURCHIEL: Sure.

DR. AARON: Actually, I would actually even take a broader view and look at physical stimulation in general. We had an academy symposium about a year and a half ago where we looked at physical stimulation from a variety of points of view, vibrational and electrical, and obviously each one is going to be different in terms of the cell reception of the stimulation. On the other hand, many physical forces, heat, for example, and vibration, are known to accelerate a variety of biological events, and could all stimulate healing by similar but probably ultimately, on a molecular level, different mechanisms. But I think from the clinical perspective, I tend to lump them together, because they produce similar clinical effects, although there is asymmetry too.

DR. BURCHIEL: And I think just the way

the question is being framed, ultrasound is held out separately, but I think at least pulse, EMS and capacitance coupled external devices could

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represent a subset of the electrical stimulation.
DR. MCNEIL: Bob and then Leslie.
DR. MCDONOUGH: That is an interesting question because I'm also thinking that electrical and ultrasound are different, but it's difficult for me to sort of distinguish them in terms of their potential uses. And one of the questions that I have for any of the panelists or any of the electrical stimulation people, have there been any formal compliance studies that actually gets at the ultimate effectiveness of the device as opposed to efficacy in a clinical setting and independent of compliance.
DR. MCNEIL: So you would like to ask that about both ultrasound and the electrical stimuli, is that correct?
DR. MCDONOUGH: Yes.
DR. AARON: I'm not sure I know what you mean by formal compliance, but I know in a variety of clinical trials and in one large study that has actually been published, we did look at the time of utilization of electrical devices, and there is some dose effect as a function of the time during the day that the device is used, and also the duration as measured in days or weeks.

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DR. MCNEIL: Were you asking, could I just clarify, because I thought you might be asking what percent of the patients actually did the 20 minutes a day.
DR. MCDONOUGH: That's for example, right.
DR. MCNEIL: Did you get an answer to that?
DR. MCDONOUGH: For electrical stimulation, how many people actually would use it over time as opposed to using it as a door stop.

DR. AARON: I think in general, the longer the time of utilization during the day and the longer the duration of the days per week the person has to adhere to the treatment, the lower the compliance, and I think we saw that in one particular study. But I personally don't have numbers I can give you to say what the percentage was who complied with ideal usage.
DR. MCNEIL: Can I make a comment here? In some sense I understand the question, but that number is really wrapped up in the results, isn't it?
DR. KIRKPATRICK: I wouldn't say it's wrapped up in the results. The problem is, the

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results are going to give a percentage to union rate. If you've got 100 percent of your patients using it 100 percent of the recommended time, then that's a reliable percent union rate. If you have 25 percent of the people using it appropriately and 75 percent using it nonappropriately, it may actually be more effective than the data reveals. And so, I think it was a perfectly relevant question and I'm sorry that he doesn't have the answer for us.
DR. MCNEIL: So it's particularly relevant to the extent that this particular population doesn't mirror the population at large that would be using this device and these devices outside the study?
DR. MCDONOUGH: Exactly. When people are in a clinical trial, they seem to do a lot more in terms of compliance than in actual community practice.
DR. AARON: If anything, it would bias the results against the technology, the device in a suboptimal way, so I agree with your comments about that.
DR. LAURENCIN: I may have mentioned this before, but the fact that ultrasound devices

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require only 20 minutes a day is a great positive, and this is speaking from just an observational posture, but also just from the clinical experience in terms of patients utilizing different types of devices, if they only have to use it only 20 minutes or for a short period of time, they are going to be more compliant.
DR. MCNEIL: Do you have hard data on that?
DR. LAURENCIN: In terms of whether they are using it 20 minutes a day, again, they're using it for such a short period of time, I'm not sure it has been studied.
DR. MCNEIL: I think he was asking for a hard number, 38 percent or 72 percent, or some percentage.
DR. MCDONOUGH: That's what I was asking.
DR. LAURENCIN: I'm not sure, but I also think that what Dr. Aaron said bears that out in terms of what the efficacy is, but I think the short period of time does help.
DR. MCNEIL: So, did you get your questions answered?
DR. MCDONOUGH: I think that's the best

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answer I'm going to get.
DR. MCNEIL: Mark and then Kim. I'm sorry. Leslie, Mark and then Kim.
DR. WHITMAN: I would just like to say one other thing. And granted, these studies are not the same, but I think you can extrapolate it. In our control trials we did for fresh fracture, the appropriate usage for the ultrasound device was greater than 90 percent with the 20-minute-a-day usage. Now, I think you can extrapolate that where that population would use it appropriately 90 percent of the time, or 90 percent of the patients. I think it's very likely that will happen regardless of what population you're using. Anecdotally from a simple guy, I have not had one patient that I had using ultrasound prematurely

stop, even before this.
DR. MCNEIL: Thank you. Leslie, Mark and Kim. Do I have everybody.
MS. FRIED: Throughout the presentations and even some of the other comments, there was talk about a gold standard, how autograft is the gold standard. Yet throughout my notes, I look at them and my question is, is it really a gold standard for an older disabled

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population? There were comments about how the iliac crest may lack sufficient bone for the use as a donor bone, how there is increased bleeding, and obviously increased hospitalization, et cetera. So I would like to hear comments about whether it's really the gold standard for this population and is that what we should be comparing it against.
DR. LAURENCIN: I think that the concept of gold standard varies with certain people. If gold standard is what was done in the old days, I guess it is the gold standard. But if we look at what will give us efficacy, especially in the Medicare population, I think there are new standards that are coming to the fore.
If we look at these fractures and these fracture nonunions, the problem for us is that quality of life is poor, disability, cost to the system is high. And so if you replace that with an operative procedure, iliac crest incision, which as at least the orthopedic surgeons know, the one complaint that we get after doing a complex operation on an extremity after six months, the major complaint we have is what did you do to my hip, it was fine before my operation.

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And also the fact that poor bone quality is often found in the elderly in these areas. So we have to, it's an old standard, still used standard, but I think that we have new standards that have yet come to the fore, so I wouldn't say it's actually

going to be our standard for the next 10 to 20 years. We have to have new standards, and I think that these modalities present that.
DR. MCNEIL: Could I just follow that up? We're here today, we're not here in 10 years, so we have to make a judgment about the devices before us today relative to a gold standard today. So I think what was being asked is, and I think Harry asked it first thing this morning, what is it that we're comparing against, just to be absolutely clear in like a one-phrase answer?
DR. LAURENCIN: I think that you're comparing in terms of these treatments, you're comparing them on one hand to no treatment and what happens, and so if you have an established nonunion and you don't do anything with it, the percent rate of healing of that established nonunion is zero percent.
DR. MCNEIL: Is that the gold standard?
DR. LAURENCIN: It's not the gold

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standard, but I'm just saying --
DR. BURKE: What are we comparing it with?
DR. MCNEIL: My question is, what is the gold standard?
DR. WHITMAN: Of what, treatment?
DR. BURKE: Let me just back up for a second. So we have no graft, just fixation, whatever you want to do, then we have just a graft, and then we have graft plus adjuvant, and then we have adjuvant alone, right? So those are the possibilities we've got, but they seem to be very mixed up and I don't know the rate of healing nonunions with no graft, not sure what the rate is with just graft, with graft plus adjuvant, or adjuvant alone, so I'm looking for some kind of metric.
DR. LAURENCIN: That's a good question. The metric is in terms of an established nonunion and not a delayed ununion, in which one study showed that three out of 25 healed. But as a

delayed union, I know as an orthopedic surgeon there is a possibility it's going to heal, that we don't call it a nonunion, but delayed union. And also, we know if we look at established nonunions

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at say 22 to 23 months, no correction, just as I think it was very nicely said earlier, no correction and no sign of correction for three or four months, that percent with nothing in there is zero percent healing down the line.
DR. BURKE: Do you have any literature to support that?
DR. LAURENCIN: Absolutely.
DR. BURKE: I would love to see that.
DR. LAURENCIN: If you look at any of those nonunion studies, the studies are themselves, in other words, 22 months of nonunion.
DR. BURKE: What about three months?
DR. LAURENCIN: Three months, I wouldn't categorize that as a nonunion.
DR. BURKE: So it's a timing thing, right? You know, three months, 24 months, and we've got to pick a timing thing here too. Otherwise, we're going to have -- so, can we pick three months? That seems to be what people are using today.
DR. LAURENCIN: People aren't using three months, and I think if you listened to --
DR. BURKE: Okay, three months after expected healing.

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DR. LAURENCIN: Right.
DR. BURKE: But when does the clock start ticking, that's what I want to know.
DR. LAURENCIN: In terms of?
DR. BURKE: In terms of a nonunion that you believe is going to need some intervention. Is it from time of fracture?
DR. LAURENCIN: It's time from fracture, but clearly there are some areas, I think as was explained earlier, there is no

precise definition of the time. However, there are some clear areas where I think most orthopedic surgeons are in agreement. Over one year, clearly.

DR. BURKE: I will give you the extremes, but I don't think people are looking at the extremes. I think we could clarify what the time is, and I wonder if the FDA had discussion on this as well, but I was told it was like three months of nonunion would be what people have --

DR. LAURENCIN: Sir, I want to make sure we differentiate, three months of nonunion or to time after fracture?

DR. BURKE: Well, that's my question. I need a little clarification.

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DR. BOYAN: I would say the definition of whether a surgeon is able to state that he or she thinks it's going to be a persistent nonunion and the freedom to start some interventional therapy at that point for treatment of nonunion that occurs at that time, I want to take two seconds as a scientist, I'm going to take my right as a guest panelist and make a few comments about what really is happening inside a nonunion, and I hope it would make the delayed persistent chronic situation go away.

There are studies, and certainly some of them were done by me, so fair disclosure, that says what happens with cells is they migrate into a nonunion, and people keep saying nonhealing. There is healing in a nonunion, but it heals with tissue, just not bone tissue, so what kind of tissue is in there is scar tissue. And as it gets into, as the cells migrate into that site to fill up whatever the space is before you go on to have a nonunion, these are cells that have the capacity to move, and they differentiate into something once they're there depending on what kind of information that they get.

And some of those cells are stem cells.

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In the first week after an acute fracture or after an acute defect is created by a surgeon, for any reason, the cells explode into potential stem cells that would have the capacity to become whatever they need to be, cartilage, bone, blood vessels, fat, whatever they need to be. After time goes on and by about three months after the time that the injury happens, most of those cells have already met a determined fate, and the number of cells that are left to become anything that's going to save that site are so few in number that in a site that's going to go on to become a nonunion, it's filled up with cells that are fibroblasts that are creating scar, and that are fibrocondyle sites. Most of the fibroblasts that make scars, these are not cells that are going to go on and miraculously heal with bone that site. So this happens right at three months. And if we want to have an intervention that is going to make the patient heal with bone, then the longer we wait after three months, the fewer and fewer of those responding cells are going to be present. So the FDA listened to the panel that was much like this one, talked to them, and finally the panel recommended to the FDA and I

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think that finally the guidance came out that suggested that three months was an opening time frame to start treatment. And I guess as I'm sitting here listening to us argue about this, I would say let's not argue about it, because the biology, and I get a kick out of hearing surgeons talk about the biology, but the biology --

(Laughter.)

DR. BOYAN: But the biology of the cells that are there in that site after three months have less and less capacity, and in older people there are even fewer of those cells. There is documented evidence that shows that older people have fewer potential stem cells to begin with and they will then therefore have fewer of

them in those sites.
DR. MCNEIL: Thank you very much. That was really an important comment. What I would like to do is, I want to make sure, we have a limited amount of time to speak to our presenters, so I would like to ask Dr. Jones whether he has a relevant comment to make to the preceding question, or an irrelevant one, I guess.
DR. JONES: I was up here just to address Dr. Burke's comment about comparing to --

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DR. MCNEIL: Yes, that's relevant.
DR. JONES: And it's a general question, like saying well, what do you use to treat cancer, when it depends on what type of cancer.
DR. BURKE: That's why I asked.
DR. JONES: The reality is that for a biologic stimulus, it was at one point the only thing we had, but now there are some options, including ultrasound, the orthobiologics, if we want to lump them together, that are efficacious. But for a patient with bone loss, ultrasound, electrical stimulation, no matter how often or how much you put it on there, it is not going to make up a bone defect, and we're really only comparing it to autologous bone graft. That's all there is, so a really critical distinction is whether there is bone loss or not.
And as far as three months, what I think we heard in some of those things today, can a surgeon look at an x-ray and see no progression at three months and accurately predict which patients are never going to go on to heal, and the answer to that is yes. There are plenty of patients who at three months you say listen, I

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don't think you're going to heal, I think you're going to need an operation, and they say Doctor, can I wait? You say sure, but the times you're wrong are one percent. At three months either

it's happening, you can see it on x-ray, or it's not, and you have to do something.
DR. BURKE: So there has been a study to show that?
DR. JONES: If you look at -- what you don't get is people who are determined to heal and then elect to have another surgery, so you will have treatment failures in the success group, so --
DR. BURKE: You don't pick the ones who are going to fail, the ones who aren't, and just do an iliac crest and see which ones don't heal well and which ones do, you wouldn't know your accuracy.
DR. BOYAN: I think that would be ethically a nonstarter.
DR. BURKE: So my point is, you really don't know how accurate you are?
DR. JONES: Well, no, because there's part of the control base that says I don't want to have surgery right now, or that have wounds or

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whatever.
DR. BURKE: That's bias.
DR. JONES: Maybe selection bias.
DR. MCNEIL: Dr. Burke, can we just keep to the questions?
DR. BURKE: Right, but I'm just trying to understand what it is we're supposed to be doing here. You know, we're being asked to say whether there is efficacy here and I'm just not clear what efficacy means, given the heterogeneity of the studies referenced today.
DR. MCNEIL: That's what we have to discuss.
DR. BURKE: Right, exactly.
DR. MCNEIL: So for the moment I have Marc, and then Kim.
DR. BERGER: I just want to turn for a moment to the harm side of the equation, and you know, we haven't heard a lot of discussion today about what are the potential risks or harms that

accompany any of these therapies. We are all making a presumption, I assume that the noninvasive therapies have much less harm associated with it, whether it's the ultrasound or the electrical stimulation that's external, but

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I'm curious to know if that's really the case and have people make a comment about the fact, how many people get harm associated with it? I mean, are there any harms associated with it, and how often do they occur?
DR. MCNEIL: Who would love to answer that question?
DR. WHITMAN: I can answer that one for ultrasound. There have been no harmful related events to treatment, and in comparison to placebo, which is an ultrasound head that is basically disconnected, there is no difference.
DR. AARON: I think the same is true for the noninvasive electrical stimulation. The EDI keeps a quite extensive registry, now probably 20 or 30,000 people who have been treated. Some (inaudible) translation possibilities for a variety of EMI, both environmental and therapeutic, and found (inaudible).
DR. CARMACK: The only one that may have an answer that I know, or feel very strongly about, is the orthobiologics, because these are being designed to turn themselves on, be aggressive, and it has been reported that there has been no malignant transformations, but that is

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one concern I have as a clinician in the long run.
DR. MCNEIL: Kim.
DR. KOVAL: I forgot my question already.
DR. AKLOG: I have a question to ask. If we look at the technology assessment, they were very rigorous about including only data that's relevant to the specific questions, but as we go through the talks, there has been a lot of data

that we are being asked to extrapolate from with regard to acute fractures, other sites, and so forth. And I guess ultimately the burden is really on you guys to convince us that it's reasonable for us to consider that other data and extrapolate from that data. Do we have biologic reasons, clinical reasons or any other reasons to justify doing the extrapolating and incorporating that other data?

DR. JONES: To me, I think if you take either a tibial nonunion or a severe open tibial fracture with a lot of soft tissue injury, that's sort of a worst case scenario for fracture healing. It's like growing grass underneath a magnolia tree, it's not going to happen unless something really important changes things. And

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the other side of that is if you can get something to happen in that scenario, it works other places and for other reasons. So if you can get something that hasn't done anything for 42 months over six operations to heal, then that's a real thing, and if you can get a grade three tibial fracture to heal without an infection, without another operation, that is a real thing.

DR. AKLOG: But a lot of the data was for acute fracture, and how can we incorporate the acute fracture data into the effectiveness of the nonunion data?

DR. JONES: Well, one way to look at those is that half of those, or almost half of those more severe open tibia fractures go on to nonunions just from day one. Half of them are not going to heal no matter how long you wait without doing something else. So you can either bone graft them earlier, there's a great study by Polick, et al., that said okay, we're going to take every single open tibia fracture as soon as the wound heals, and bone graft it. And can you get healing, sure, 80 percent of the time. But half of them probably didn't need a bone graft, so is there something better, yeah, probably so.

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DR. PHURROUGH: Could I just add, Barbara has told us that there is a heck of a lot of difference in the number of cells present with a nonunion that she knows is going to be a nonunion at time of injury versus a nonunion three months later. So it does appear difficult to extrapolate the applications of these technologies when applied to a milieu that has a lot of stem cells that may extrapolate, versus a milieu that doesn't have a lot of stem cells that may turn up.

DR. JONES: What she's talking about is acute post-fracture where you see there's a fracture hematoma, there's a normal hemotaxis, and in the study Barbara was talking about was an open tibia fracture with a wound that gets washed out, there is no hematoma, there is a bone strip that's dead, it looks like ivory, there is no cell, no biology, no biology, it's just a hole, and in some cases there is not even bone, so there is no biology there, and that's the reason they don't heal.

DR. BURKE: So the argument shifts.

DR. JONES: Right, but in close proximity.

DR. MCNEIL: Do these relate to this

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particular question?

DR. LAURENCIN: Oh yes.

DR. MCNEIL: Okay, please.

DR. LAURENCIN: Well, just a couple of points. One is, I think the nonunion data stands by itself. The reason why I think we mentioned the data for fresh fractures is, number one, I think it's the only device that has the indication for fresh fractures. And number two is that when we present the mechanism of healing that takes place in looking across the cascade of healing, one obvious question is if you work in all these different areas in terms of healing, one would expect that a fresh fracture would accelerate the

healing of fresh fractures, and that's what occurs, it actually, it does enhance the natural healing process, it actually enhances and accelerates healing the fractures, which has been shown through a number of studies.
DR. AKLOG: But you have to acknowledge that they both could be true, you could have accelerated healing of acute fractures but it might not affect the quiescent nonunion, and you're asking us to make that leap.
DR. LAURENCIN: No, I'm not asking

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anything. I prefaced my remarks by saying that nonunion stands on its own, that's the first preface. So put that there. The second part of it is that epiologically, if one says well, what's the mechanism, the mechanism works on all these different areas of fracture healing. The next question would be, well, if it works in the different areas of fracture healing, one would then expect it may have an effect on acute fractures, and does it have effect on fresh fractures, and it does. So it brings the story around in terms of the mechanism because the mechanism is there and we're saying it perhaps actually would work.
DR. AKLOG: We're not asking you whether the data on nonunions would make you expect it to work in acute fractures, we're saying the opposite, which is that we were presented with a lot of data that was added on top of the TA report on acute fractures and asked to accept that as further support for its effect on these studies and in other areas as well.
DR. LAURENCIN: I think the evidence presented for ultrasound that was in support of nonunion, it does support the mechanism, because

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the mechanism involved in all these different steps, and if one accepts, does it have effect on fresh fractures, but I don't --

DR. MCNEIL: Okay. I don't know at this point that we need to go into the mechanism very much. I think we've got enough to do.
DR. DICKSON: I'm still offended by her comment.
(Laughter.)
DR. DICKSON: I do think there's a little bit of confusion and I want to address that issue. I think one of the problems with when you're defining the nonunions, there are three different types of nonunions, and I think, Dr. Burke, that is somewhat of a problem. Because if you have a hypertrophic nonunion, you know, nine months later, and you just put a plate on it, do absolutely nothing biologically, and it will heal. I'm convinced that the standard is autologous bone grafting, and that is your standard that you need to work on right now for an absolute nonunion. The quasi comes in in how you define it. Now the FDA used to define it at nine months and that's how we administered treatment, and it was absolutely miserable. To me, the definition,

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and this is a definition that I used several years ago when I published on this, was that you had to have a certain period of time. Every fracture is different in terms of the bone, and the tibia, we talked a lot about that. But at two months to three months, the tibia should be healed. Now if it's still progressing toward union, even if you're five months or six months out, you can't have a nonunion yet, you have to call it a delayed union, as long as there is some clinical or radiographic progression. Once that stops and you use a certain amount of time, I chose four months in my paper, and that's important information when you're reading all these studies.
In terms of the ability to take acute data and roll it into nonunion, I don't think you can do that. I think that you have to look at the nonunion data. It would be great, and maybe some of the industries are throwing darts at my back

right now, but you need to look at the nonunion data, that's the question today. We're not talking about acute fractures. And I think that the nonunion data is what it is, and we can argue what it is, but I don't know how much correlation there is between that.

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PANELIST: Can you talk about closed versus open fractures?

DR. DICKSON: There is no question that the higher the injury, I mean, I think there are acute fractures, but whether an injury has closed or opened is a big difference, because an open injury has much more damage to the blood supply and therefore, it's more difficult to heal. And as Alan and Mike said, they had a 46 percent nonunion in a very high level of injury, and these were not doing any bone grafting initially, it was just fixing the fracture.

DR. MCNEIL: John, did you have something?

DR. KIRKPATRICK: Yes. Just to help with an understanding of all this, it sounds like, if I remember the question, it's correlating the basic science knowledge with the use of these different treatment modalities. Am I correct that that's the basic question, right? One of the things that happens in a nonunion when you operate on it, so we're doing operative management of it, is we're basically almost getting back to an acute fracture, because we are actually cutting out the soft tissue there and trying to reimpose the bone,

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and if there's a segmental defect, we're going to graft it to replace that space. If it's a nonunion, we're going to graft around it to get added biology to it, and nowadays we're probably going to add INFUSE or the OP-1.

DR. DICKSON: That's not true, you don't cut around the nonunion.

DR. KIRKPATRICK: You don't debride

your nonunions?
DR. DICKSON: Not -- it's a --
DR. KIRKPATRICK: I can tell you from slides that have been presented today that if you don't take it out, you're not going to correct your deformity and you're not going to get a result.
DR. MCNEIL: I would love not to have an argument.
DR. KIRKPATRICK: From the biologic standpoint, you are rejuvenating the fracture site if you do resectors in arthrosis, okay? And that starts over the biological change that Barbara was talking about. That does not at all apply to the PEMF, to the shock waves, or to the ultrasound, because we're not doing that radical of a thing. Now they may have evidence to show that that

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happens on a micro level, but I haven't seen enough of that to really rely on it. So conceptually, if we're talking about the operative management of a fracture that is truly a nonunion, many times many surgeons will debride the nonunion and create basically a fresh site, and then add biologic stimulus to it.
DR. AKLOG: Just to summarize, do you think it is reasonable to extrapolate to some degree for the surgical adjuncts?
DR. KIRKPATRICK: For the surgical adjuncts, I think the extrapolation is a reasonable jump, but not a hundred percent accurate jump.
DR. DICKSON: I guess my point is when you start with the basics and then try to add on to it by debriding a nonunion, as you say, in a crooked bone, yes, you have to straighten it out, and that turns into a fresh fracture. But if you're going to take out a nonunion site, you're going to basically devascularize it. So as opposed -- I think one of the mistakes made in orthopedic nonunion surgery is they devascularize it by taking it all out, when that's actually

vascularized tissue that can aid in healing, and

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you don't need to delete it.
DR. MCNEIL: Thank you, that's great.
So, I think what I've decided is, it's a little controversial about how you get your nonunion fracture fixed. So what I would like to do is go to Sean, Ken and Mark, and I'd like to ask if there are any other questions, because at this point I'm going to wrap up the questions for the presenters, so I would like these questions to be brief, if possible, I would like the responses to be brief, and at that point we will have an open discussion among the panel members, and there may be another question to the audience as well, but I am really worried that if the group doesn't get a chance to really talk among itself and really raise the issues, we're not going to have a productive discussion and that's going to lead to judgments that may not be as good as we would like at the end of the day. So Sean, please?
DR. SULLIVAN: Well, I learned a lot about bones so far today and I think I'm ready to take the orthopedic exams. The focus on a lot of these discussions has been on bones, and we're talking about human beings. And so my question to the panel members or to the speakers is, to what

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extent do you have from the literature any data on outcomes that are important to patients, function, ability to get back to work, quality of life? I have heard a lot of anecdotes and opinions, but where are the data? Can you help?
DR. JONES: I think we can start with one that there's not a lot of data. If you look at the BMP-2 allograft, we did some patient subjective outcome, instrumentation, and what we saw was the patients had a great deal of perceived disability, and that improved in both groups, there wasn't any significant difference between the groups.

I think what is most important to look at is in the New England Journal, Fosse, et al., published a big series of patients with severe lower extremity injuries, I forgot, open tibia fractures, and a huge portion went on to secondary operations, many of them went on to nonunions. That group is incredibly disabled, and one of the evaluative measures was return to work, and I can't remember whether it's statistically significant, but these patients had a devastating injury. And they just published the five-to-seven-year data, and five to seven years

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later they were just as badly disabled. So this is an incredibly disabling injury. If you wait, let it go on for two or three years, no matter what you do, they don't get back in society, they don't go back to work, and it is truly a life-changing event for most people.

DR. SULLIVAN: Just to follow up, I believe it is a life-changing event and I'd bet if you look at the SF-36 profile, you would find a tremendous burden in these patients with these fractures. I'm wondering, are there any patient-reported outcome data to differentiate any of these products from what would be considered standard or gold standard care.

DR. JONES: No, not that I know of.

DR. SCHOELLES: No.

DR. MCNEIL: All right. Kim, do you remember your question?

DR. KOVAL: I have a comment to the panel and will wait.

DR. MCNEIL: And Mark, which Mark? It was a Mark. Mark Fendrick, did you have a question?

DR. FENDRICK: (Inaudible.)

DR. MCNEIL: Okay, it's duly noted.

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DR. BURKE: Can we ask Dr. Schoelles for her comments?

DR. MCNEIL: Yes, we certainly can.
DR. SCHOELLES: Comment on?
DR. BURKE: On anything presented by our speakers today.
DR. SCHOELLES: Perhaps something more specific.
DR. FENDRICK: We heard from at least one, I think two presenters, that there were longitudinal history studies of nonunion fractures, which I presume would have been very early on in your TA. I'm guessing they're published in a foreign language or in places where you couldn't find them, and I'm not going to ask Dr. Laurencin now, but if there are longitudinal studies that show that nonunions never heal, really in a rigorously designed longitudinal study, even without a control, that would be very useful. But you didn't find that specifically, did you?
DR. SCHOELLES: Perhaps we are at fault, but I don't believe so. In the registry data, there were some studies cited and I looked at those sources and they quoted orthopedists who

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believed that nonunions would not heal.
DR. BURKE: But you didn't find any such things?
DR. SCHOELLES: Not in humans, one in aging rats.
DR. BOYAN: And you missed the one in aging dogs.
(Laughter.)
DR. MCNEIL: I don't think we're going to consider aging rats and dogs as part of our deliberations, is that okay with you? Is this in response to a question?
DR. LAURENCIN: Oh, yeah, it's certainly in response. If you look at the registry data that took place in one of these studies and also look at the Morrow study, the other studies in ultrasound, patients were, what I meant in terms of longitudinally looking at

nonunions, patients were brought in who had nonunions and they had to have at least four-and-a-half months in which they have had no other surgical intervention and no progression during that period of time. And so these patients were, they were self-controlled, all these patients we're talking about, so we winded up with

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a mean time of 21 months, four or five months with nothing, no progression during that period of time. So you know, I think that information, then, that information on these patients really probably speaks to the fact that these nonunions are long-standing and will not go on to union.
DR. MCNEIL: Thank you very much. Are we ready for discussions? We are ready for open panel discussions. Actually, we have a ton of stuff that we can deliberate on.
MS. FRIED: Can I clarify and just ask a question of Steve? There was comment that back in April of 2005, there was already, was it an MCAC decision or was it a CMS decision regarding ultrasound and nonunion fractures? And I'm wondering, I tried to download it, but the database was down a good part of the week. Can you tell me about that?
DR. PHURROUGH: We have an older ultrasound decision that said we would only cover ultrasound post surgery, lots of reasoning behind that, but then we were asked to relook at that particular data to determine if we had made the right call, and should ultrasound be covered without requiring surgery first. And we relooked

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at data and changed the decision to say ultrasound could be covered without having prior surgery. That was the extent of what occurred.
MS. FRIED: And it's for nonunion fractures?
DR. PHURROUGH: Yes.
MS. FRIED: And what was it based on?

DR. PHURROUGH: That was based on a relook at the same evidence essentially.
DR. MCNEIL: Well, yes?
DR. BOYAN: I actually have a question, or two questions. One has been bothering me a little bit and it may be one you can answer. We're really talking about two different things here. One set of treatments are used, require surgical intervention, and one set of treatments do not, and it seems to me that we're mixing apples and oranges in terms of our thinking. If we're asking patients to go through a surgical procedure, the morbidity that's associated with that surgical procedure to me is significant enough, and I'm wondering why we've got it mixed. There are advantages to both treatment modalities and maybe we shouldn't lump them all together. I think what's confusing the crowd down

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here as I was listening to it, they are trying to separate this out, and there are ways of treating what is either an, in answer to the question about this long-term thing, is there data or are there data to say that nonunions do not heal? The long-term consequence of a long bone is a pseudarthrosis, and there are plenty of published papers that show that, so that if left untreated by anybody, eventually these things go on. So if we say okay, we agree that treatment is good and we have two kinds of treatments, one that requires surgical intervention and one that doesn't, then maybe we need to separate our thinking into those two categories and see the positives and negatives of both in addressing these questions.
DR. MCNEIL: How would you like to modify, if you just look at the second question, or the first question, how would you like to modify that?
DR. BURKE: Is this related to open and closed fractures as well?
DR. BOYAN: Well, I guess the way I was

perceiving it with all this augmentation is that if the surgeon says this is going to be a

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nonunion, it looks like it's going to be a nonunion, and has the ability to prescribe a nonsurgical intervention at that point, and then if that fails, says okay, that didn't work, now I'm going to do a surgical intervention, to me it makes, surgical intervention, either just the biologics, just the graft, whatever the mixture is that we all talked about, plus or minus whatever add-ons they might be adding on. That seems to be a more logical progression in the treatment decision-making than saying okay, it looks like it's going to be a nonunion, let's go graft it right now, and especially in the older patients for whom we all know, they have fatty marrow, they have a whole lot of reasons why a surgical intervention might be a second decision rather than a first decision.

DR. BURKE: Would you define surgical intervention, is that a graft you're talking about?

DR. BOYAN: It could be anything where the patient has to undergo anesthesia.

DR. BURKE: Well, those are kind of different things, right, so one would be to fix the fracture and the other is where you're going

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to do a graft.

DR. BOYAN: I would say that if we were going to place the patient in a stiff cast, that would be a nonsurgical intervention. If we're going to put the patient under anesthesia and do something, that is a surgical intervention. If we're going to then also actually have to do surgery that includes grafting, that would still be a surgical intervention.

DR. BURKE: But my point is if you have an open fracture, you have to go in there and fix the fracture.

DR. BOYAN: I'm past the first fix.
DR. BURKE: So you're past the first surgery, so whether they get the first surgery or not, that's not material?
DR. BOYAN: That's right, it's when the surgeon decides that this is going to be a nonunion.
DR. BURKE: Okay.
DR. AKLOG: But I have been trying to make the same distinction as well as far as the noninvasive treatment versus the surgical treatments, but we're not commenting on the surgery itself. It seems that the modalities

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they're looking at are all adjunctive to surgery, so it's really not the decision, correct me if I'm wrong, as to whether a patient needs surgery or not, but well, if he clearly does need surgery, should we add one of these modalities to it. So I mean, that seems reasonable and I just wanted to make sure.
DR. MCNEIL: Alex.
DR. OMMAYA: Yes, a question for Steve, just a clarification on question number five, which mentions, how confident are you that improved net health outcomes will hold for the nonunion treatments when surgery is not first performed, could you explain that in reference to the ultrasound coverage decision and this conversation right now about surgery, what surgery do you mean?
DR. PHURROUGH: In putting these questions together and looking at treatments of nonunion, we were focusing on a nonunion that is defined by time as well as to no sign of healing, versus a clinical decision at the time of injury that this would be a nonunion. I think we need to set those patients aside and only look at those who based on time who have a nonunion.

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And considering as a gold standard, as

we have been trying to establish, that these nonunions would have in fact had in most cases some kind of surgical intervention, whether rodding, plating or whatever. So, the initial questions were in our mind prefaced on a surgical procedure being involved. And then question five is saying, would this work without first having had a surgical procedure? Obviously it's a little bit difficult to do that in something that requires a surgical procedure to be implanted. So that was our original intention. Now if we have gotten those questions wrong, and there may be a better way to word it, but in general, our thinking is that the standard was that you've got to intervene with these patients surgically.

DR. BERGER: I'll try to kick off the discussion with a couple of observations. First of all, much of the evidence that has been presented today is confounding evidence, it's not of the highest quality that I'm used to seeing, and I usually don't look at devices, I usually look at drugs, and the level of evidence here is just appallingly low compared to the kinds of levels of evidence that we look at for drugs.

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Secondly, it's not clear to me, and it was well discussed in the technology assessment before us, how we can completely disentangle with any great degree of assurance what happens when an intervention is made, since there are multiple things that could be used at any one time. So that when they go back in to do something, they're doing other things, whether it's restabilizing or doing something else.

I also am still troubled, and I believe that there are nonunion fractures and I believe that at the end here, at the far end there are nonunion fractures that will never heal and everybody will know that. But I also get the impression that many patients are called nonunion when in fact they are probably delayed union. And I understand there is a judgment call here and

this is the art of science, there is some art involved here, and I also understand that there is a real patient there that may not want to wait for the delayed healing to take place X months later, and therefore to remove suffering and to get them to a better end is not a wrong decision, but that does confound the questions we have in front of us. Because I get the impression that a lot of

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patients that are randomized under these studies might be, if we could have perfect knowledge, you would say they were delayed healing as opposed to nonunion. So having said all that, you know, it makes it really difficult.

And I guess the other point to make is, I have no way to know what is the relative effectiveness of these different treatments. And I will separate those as the noninvasive from the invasive. So I can't tell where you're opening up, but you're putting in an autologous graft or you're putting in one of these biologics, or you're putting in demineralized bone matrix. I get the certain confidence that in the right hands, everybody agrees that any or all of these are helpful, but I can't tell how good those are relative to each other. I see some suggestive data but by no means definitive data that would let me know with any certainty that any one of those invasive things is any better than any other.

Similarly, the noninvasive procedures, whether using electrical stimulation or ultrasound, I have no way of knowing whether one or the other of those is any better than the

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other.

And that's why, the question I asked earlier was about harms, because if I can't tell which is better, then I'm going to go, well, if I think I need to do something and I believe they may do some good, I'm going to use the least

harmful one first. That would be the way I would approach it if I were still a practicing physician, but I'm a recovering physician. But I find it, to me it's just a little surprising how the kinds of things I would like to know in order to make intelligent decisions about, if there was a patient in front of me, about what I was going to do next and which procedure should I use, I don't have a lot of help here despite all of the data that was presented, so that's my contribution to this discussion.

DR. MCNEIL: So, Ken, did you have a comment?

DR. KOVAL: From listening to all this, I'm just trying to find out if there's efficacy, that there is evidence-based medicine that these devices work. And everyone, particularly the non-orthopedists, has said that the level one evidence is not there, and we've heard again and

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again it's not there, and putting blame on the manufacturers who are making these products that level one evidence is not there. And having gone through this process, I can tell you that one of -- I'm not sure the onus has been on them, but it's been approved for -- the FDA approved it and I have asked some of the companies, can you do a prospective randomized controlled study to show that this product works, and they say well, we've been using it for five years now, why do we need to do a prospective randomized study, we've been using it for five years. And the ones that have the best evidence are the ones that had to go through the FDA process, and those are the ones that got the evidence base.

And then when Dr. Laurencin showed his results, that they did a patient controlled as opposed to a randomized controlled trial for EXOGEN, and so I said, well, why wasn't it a better study? Well, it was because the company did the least they had to do to get it by the FDA. Why didn't a company who is a for-profit company,

have to do the highest level when they did what they had to do to get it approved? And the reason why the drug companies, the reason why the cancer

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trial is so good is because the NIH is giving hundreds of millions of dollars worth of trial support to the drug companies sponsoring themselves. So we have to keep that in mind, that the evidence is not there, but it is partially our own government's fault.
DR. MCNEIL: Did you have an answer to that? I have Kim, I have Harry, and Bob. Okay.
DR. BURKE: Magnets, I love magnets. I think magnets do a great job in nonhealing fractures, so I'm going to go out and I'm going to collect some patients, and if the patients don't really do too well, I'm going to kind of skip them, okay? I'm just going to stick with the patients I like and I'm going to pick patients who are really going to heal their nonhealing fractures really nicely. I'm going to put my magnets on them. You know what, I could present this evidence to you today, and you would love it. So the other side of the coin, I don't do any harm with my magnets, so great, so we should move forward with my magnets because there is some evidence, it's kind of encouraging, and I don't know do any harm. Well, that's the other side to that picture. And as to your point,

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standards of evidence have changed over time. Yeah, years ago we had pretty low standards of evidence and we allowed a lot of things to be done and used that we don't anymore today because they really weren't very effective.
DR. PHURROUGH: Can I speak for the government?
DR. MCNEIL: Sure, you can speak for the government.
DR. PHURROUGH: Just a comment. One of the difficulties is that there are various

branches of government, and the branches of government respond to other branches of government that sort of dictate how you do what it is that you're supposed to do. FDA has rulings that it follows, some of which are mandated by law, some of which have evolved over the years. In some cases that's a higher order of evolution, in some cases it's not. And we have different rules. And I think that sort of the place we're in right now is that FDA has standards in which they have approved in the past certain technologies, and as an aside to Dr. Berger, we on the other side of the room who are another agency of the government who are going to have to pay for

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these devices now have concerns that those things that meet certain standards of one branch of the government may not in fact meet the standards that we're concerned about and that is not, are they okay to use on patients, which has been in the past an FDA standard, somewhat higher now I think in many cases, but are they okay to use, to our concern of being, do they work, do they make people better.

So I think that's the sort of tension that we're in now, and I recognize it's a difficulty for those of you in many cases who have been basing decisions both on the industry side of where we're going to put our money and on the academic side of how we're going to support that, to sort of now, you've got two people you've got to play it against, not just those who say you can sell it, but those of us who say whether we're going to buy it or not.

So yeah, there is a problem, but that problem is, I think we're in the right place, where we're going to be careful about the kinds of things that we're going to buy and we're going to ask for good information to make those decisions. And if we don't have good information, we'll do

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the best we can with the information that we have. And because we do the best we can with information we have doesn't mean that we're comfortable with that information, we just have to make those decisions with what we have.

DR. MCNEIL: Well, I think you're also changing the bar.

DR. PHURROUGH: We hope.

DR. MCNEIL: Let's see. I have John, Lishan and Barbara.

DR. KIRKPATRICK: First as a general comment, which may echo exactly what Ken said, and that is that while our colleagues on the panel are cynical of open-spaced medicine in your experience or your practice, orthopedic surgery in general has not been able to attain that same level of evidence-based medicine. Much of it I believe is because of the nature of our patients being so diversified, compared to, for example, somebody who has a single anterior descending artery occlusion where you do a fairly straightforward cardiac study on them. We don't tend to get a large number of patients with the same identical pathology.

In addition to that, we don't have a

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lot of experience among our surgeons in doing evidence-based medicine, so when you combine the two, I think that explains the limited knowledge that we have as far as true evidence-based measures.

We also have a very difficult time getting validated outcome measures, for example, for a tibia fracture. Our professional organization did a tremendous investment into a particular type of looking at outcomes measures and when it all came in, none of it could be appropriately validated to give us good measures for specific entities, and that's the MODEMS program, if anybody is familiar with that.

But I also think we also need to understand the concept of what an orthopedic

surgeon is dealing with in a patient with a nonunion or a delayed union as it may be. The patient is going to come in to us at three months, he has been out of work for those three months, he has a relatively unsophisticated occupation that requires him to be on his feet and he can't get there. We see maybe a little bit of calcification, so it's probably not enough that we will operate on him now, but we want to do

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something to help speed that along, so we might add one of these external devices. He comes back at four months and we see abundant callus. No, I can't tell you a hundred percent that the device made the difference, but to that patient it did, and if the psyche makes a big difference, which is a huge part of well-being for a patient, that may have made the difference and turned the tide to get that guy back to work.
On the other hand, if it's six months out and we've already tried that, then the patient was reluctant to have surgery, now understands okay, we have done everything possible to avoid surgery, now I'll have the bone grafting or the osteobiologic. Then we go through the choices of, well, do you want to have one off the shelf or do we take your own bone graft?
My personal experience is, I've had two bone grafts, one in posterior spine that limited me for about five years, the anterior one only limited me for about 12 months. But nonetheless, they were limiting, and the one that was done when I was in my surgical career did slow me down. So it is a huge problem for the patient individually.
And so, when we get to that nonunion

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that gets optimum management, we also like to be able to add an external device to make sure we've done everything we possibly can. If this building were on fire and they sent one fire truck, I don't think anyone in this room would be comfortable.

If they sent two or three, we might be a little bit more comfortable in making our evacuation and those with offices here would be comfortable with it being safe.

Now these are anecdotal evidence things, okay, and we are being asked to make a judgment based upon the evidence before us. And I'm just trying to ask our panel members to understand that in the orthopedic field and in the clinical practice realm, sometimes we don't have pure perfect data to judge and move on from.

DR. AKLOG: This is probably along the same line and I do agree with everything John just said, but I do think as one of the couple of token surgeons, this is a problem that exists in all surgical specialties, and this came up in a previous meeting that I was at. I think we clearly acknowledge that there is a rising bar with regard to what evidence we need for interpreting the effectiveness of data, but -- and

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also that all surgical specialties get behind in the adopting of good medicine, and I agree with that.

But it's also important that we acknowledge and sympathize and empathize with the challenges of collecting good data in all surgical subspecialties. There are some of the hurdles, whether it's complete randomization, blinding, so forth, this is a really difficult thing to accomplish. As someone who has done clinical trials in surgery, who has tried to recruit patients, and also served on the Society of Thoracic Surgeons workforce for evidence-based medicine, we're trying to do this and it's not easy to do. So the question is, this data will always be questioned, it will always be fuzzy, we will always have to incorporate imperfect clinical data, clinical judgment, clinical expertise. This is not to say that you can't, you know, require better data, but just again, it's a lot more difficult than when you have 10,000 patients who

receive drug A versus drug B. The burden in my opinion, as long as we've satisfied the burden with regard to safety and are really quite confident that there really

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are no safety issues, the bar has to be somewhat different with regard to effective, and not on the ground, but it has to be somewhat different when determining efficacy with surgical products, especially if the clinical confidence like it appears to be in this case is extremely high over a relatively long period of time with a large number of patients. So I empathize, I think there was a subtle implication through some of the comments that it was for lack of effort, either on the company's part or on the orthopedic academic community, a lack of effort to obtain this data, and I don't think that's really a hundred percent fair, because I've been on the same side as well, but I do emphasize to some degree.

DR. MCNEIL: I'd like to interject one thing here and then go to Barbara. I'd just like to call your attention to the questions that we're answering, just so that we're all on the same page. So the questions will say how confident are you in the data, they don't say how confident are you in the evidence, they don't say how confident are you in the evidence conditional upon the ability of a particular field to do a good study. Just so we all keep in mind the question that

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we're answering, and I totally understand the points that you've made but the question is quite specific, it is not conditional upon the ability of a given specialty or group of doctors to do a particular kind of study.

So let's move on. I have Barbara, I have Kim, I have Bob, Deborah and Leslie. Anybody else? Oh, and Mark, okay. Barbara.

DR. BOYAN: I would like to take us back too, because I think that we're getting away

from the fact that there was a tremendous amount of data that was presented to us very quickly. There certainly, with some of the modalities that we saw presented here, for instance the electrical stimulation devices, there were many studies that were done at a time in our scientific world when using retrospective studies was permitted, when using literature controls was permitted, but they were done in the state of the art at that time and they insured effectiveness and safety, so that these products have been on the market for, some of them as long as 25 years, and they have had tremendous success in the eyes of the people who use them. Many case studies have been presented at peer reviewed scientific meetings and even to

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the point where the academy and NIH cosponsored a workshop that was I think two years ago, Roy Aaron actually cochaired that workshop at which the scientific evidence was presented. And it was felt by the people that attended that workshop, about a third clinicians, a third engineers and a third basic scientists, that they felt at the end of the meeting that they were satisfied it was safe as the art was at that time, and identified future areas for research. So at least in the orthopedic community, this is not a black box technology, this is definitely a scientifically based effective technology, and I don't want that to go unstated in any way, shape or form, and that's without any one specific particular modality being identified.

DR. MCNEIL: I think we've heard that.

DR. BOYAN: Okay. The next thing I want to say is about the biologics. There is an equally large amount of research that has been done on demineralized bone matrix. We focused on the BMPs here but we really didn't talk about another osteoinductive material and I think that came out, I hope too, and I don't want that to be, that there should be an understanding that that

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too is based in science and that too has clinical studies that have been done, and certainly from 1965 to now, which is however many years, I think 40 years.

So these are technologies that are well understood in the orthopedic world and are used daily. Autologous bone graft, as agreed, is the surgical control of choice and I don't think anybody would argue with that. So I think there is some stuff we can all say is, the quality of the data is excellent.

DR. MCNEIL: Could I just interrupt?

DR. BOYAN: Yeah.

DR. MCNEIL: That is a conclusion, it may very well be correct, and that is one of the questions we will be voting on, so you will have a --

DR. BOYAN: I was just voicing my opinion.

DR. MCNEIL: So I think for now, let's not answer the questions. I think we've all seen the data and it's our opportunity to discuss the results of the data with each other. I'd just as soon keep the answers to the questions at the time we answer the questions, if that's okay.

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DR. BOYAN: That's fine. I guess what I would like to say in summary is I thought we saw a lot of data, I think in the stuff we saw there was a lot of information, but I don't think it was exhaustive, it maybe didn't present the entirety of the information in the field that's available.

DR. MCNEIL: Would it be fair to ask the ECRI, is Karen still here?

DR. SCHOELLES: Yeah, but I'm going to defer to Dave Schneider.

DR. SCHNEIDER: Dave Schneider. I wrote the systematic review.

DR. MCNEIL: Could you come to the microphone and identify yourself? I just wanted to make sure you had a chance to rebuke the

assertion that the literature review may be incomplete.
DR. SNIDER: I'm Dave Schneider, senior research analyst at ECRI. I wrote the systematic review portion of the report. I can assure you, we found all the data with regard to demineralized bone marrow use in nonunions. There are probably others, and you made statements about fractures, fresh fractures, but that was not part of our report, that's a completely separate issue.

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DR. MCNEIL: Thank you. So, let's see. Kim.
DR. BURCHIEL: My question really gets to the work product and maybe if we don't run out of time, maybe we can get to that right away. But admitting that we've seen the data and we're going to make a decision based on what we heard, and it sounds like a pretty complete assessment, do we want to talk about whether we want to fractionate these questions a bit more, because I do submit that we do fractionate some of these questions in order to give reasonable answers.
DR. MCNEIL: That's a good point. Let's put that as something we have to come to terms with very shortly. So what I would like to do is go to Bob, Deborah, Leslie and Mark, and then if there are no further questions, start answering the question that Kim just asked. So, Bob.
DR. MCDONOUGH: I guess I have more of a question on the questions too. I'm having some difficulty understanding the questions and sort of the distinctions that we're trying to get at, for example question two versus question three, question two and the validity of the scientific

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evidence, and also, some comment on the reason I think there are probably good reasons for making distinctions about validity of scientific evidence by, on the basis of the available evidence

regarding each of the individual end points.
DR. MCNEIL: Why don't we hold that, then, and wrap that up in the same discussion with Kim's, would that be okay with you?
DR. MCDONOUGH: That's fine.
DR. MCNEIL: Okay, so Deborah.
DR. SHATIN: Just a couple of comments and questions concerning the data that we've seen today. We've heard and seen from the technology assessment report that the definition of nonunion can be questionable, and what it boils down to as we've heard today is that physician judgment is critical. And it seems that various technologies are in our arsenal to treat patients, so I think it's important to recognize the role of clinical judgment here.
And related to that also, in terms of the nonunion, the disability in terms of the elderly patients is critical to think about, along with the time that goes on in terms of atrophy, things like that, I think that compounds it and I

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think we need to keep that in mind.
And finally, in terms of the questions, we're not really, the way they're stated, we're not comparing each therapy to the other therapy, it's what is the evidence for these specific four types of therapy.
DR. MCNEIL: Yes, I think we will separate out the questions, but that is exactly how they read now, Deborah, you're right. Leslie.
MS. FRIED: I've got a very similar comment but I want to state it. I remember reading in one of these -- I actually read these studies, and there was a comment in one of them and I wrote it down because it really struck me, and the comment was whether the treatment accelerates the time for healing and union such that it would be a great benefit to the patient by decreasing disability and functional loss and other factors. And for me as I was reading the evidence, that was really what came to mind, and

when I read about 60 or 70 percent heal rate and saw that the control was less, to me, that was a really good thing, because it meant at least for those people that had that treatment, that was very important. So it may not be the gold

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standard, but for older people who not being able to walk means they are only home-bound, maybe getting home health care services, whatever, but it really impacts their day-to-day life because they lose a lot of independence.

So, I do have a question and it's really for some of the providers, and I don't know if any of you are private practitioners, but I was interested in the standards of care at this point based on what Barbara was saying, or at other times to some degree, maybe not so much. So my question is, are these the standard of care and are other insurers currently reimbursing? Because if Medicare came out and didn't cover it, then you would have a situation where people over 65 may not be getting access to care that the rest of our populations are.

DR. MCNEIL: We certainly have Aetna here. Do you know, Bob?

DR. MCDONOUGH: Yes, we do cover these.

MS. FRIED: All of the technologies?

DR. MCDONOUGH: Yes.

DR. MCNEIL: Harry, do you have a direct response?

DR. BURKE: No, I can wait.

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SPEAKER: Well, may I have a quick response? If there is believable data that 70 percent are healing or 70 percent are not, that's important. The question is, is that data something you have a high confidence in, and the fact is the design of these studies does not give you a high confidence. These studies are maybe supportive of it, and depending on how strict you want to be in terms of the evidence you apply to

it, some people may say you have a low confidence in it or a moderate confidence in it, but no one would say they have a high confidence in this data.

DR. MCNEIL: So I have Mark, is that your question? Oh, it's the other Mark.

DR. FENDRICK: As some of you know, I sometimes tend not to be sympathetic, but I will say that MCAC from the inaugural formation of this committee has been struggling with the difference between drugs and devices and procedures, and from the beginning there are several white papers. And we understand, since Dr. Burke has started the conversation, we know that there are huge differences between pill A and pill B, and devices and procedures depend on the time of day, whether

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you played golf that day well, the day before or not, whether your kids are happy or sick, or whether it's warm weather or not. We acknowledge all those things and think it's very important that we say that as we're trying to, I thought there might have been some push back there for the level of evidence for an orthopedic procedure or any sort of procedure has to be the same as what's currently going on in the FDA, as Steve mentioned. But also, we're not mandating and suggesting that randomized controlled double-blinded trials be done for everything. It is remarkable for me to hear, as I've seen over the past decade, surgeons particularly being defensive, and I don't want to make excuses for not having the skills as providers, the training of the fellows, all these things. But if you wanted to do studies at every one of the institutions, there are very willing people who will sit down with you and help you get there. You may say that the funding may or may not be available, but those are issues whether you're going to the Feds or not.

But I will tell you that we have learned, as Dr. Sullivan and others, we've learned

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from volume reduction surgery, we've learned from CABG, we've learned from arthroscopic procedures, we've learned every time we've gone through this, we have been able to do, not randomized trials in every case, but trials that have controls. If the effect size is so great of the anecdotes that we heard from the real doctor or from the example from Alabama, the trials could be small, the trials could be controlled by their own patients, and they would be very inexpensive in my opinion, particularly if we believe, as I do, that nonunions do not heal, that the true definition of a nonunion is -- I would accept a study of having someone see you for three more months and then get whatever treatment you want, and they go back to work saying that they are, have a higher quality of life. And if there was P value, sir, after your conclusory statement that your patients are happier compared to what they did if you did nothing, I think most of us on the methodologic side would be very happy and would not require this study that in many of your minds is a thousand-patient three-year study costing $500 million. I certainly do not think this is the case.

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The last thing, very quickly, is that if you go back to the questions we will be voting on, to give you some positives, we are asked questions about validity of data but then we are asked questions about this trichotomy of the likelihood that all the end results that you tell us would actually be played out if the study would be done.

And then the last point, as Dr. Berger mentioned, it's all about confidence here. I think some of us have different opinions, but I don't think there's a right or wrong about where we all sit on whether it's anecdotal or the case series or the case controlled or randomized

controlled trial matters, it's a matter of confidence, and we as panelists may differ on the exact same data. No excuses anymore, I think the trials can be done, and they don't always have to be at the highest level.

DR. MCNEIL: Thank you very much, Mark. I would like to make this suggestion. Harry and John had their hands raised speak, and then if there is another quick question, we'll take it. Otherwise, I would suggest that we take a five-minute break and then come back and wrestle

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with the questions, what exactly it is that we're answering. If we come to terms with that, then I'm sure that might generate some more internal discussion. So I would like to focus on the end product very soon so we can focus on the subject matter. So Harry, do you have a quick one, and then John.

DR. BURKE: I was struck by the paucity of the evidence and by the technology assessment, and the fervor of the people actually doing it. It actually seems like something like a dichotomy. Also, I'm usually at Mark's side, but he's being very nice today. I do like to have randomized prospective clinical trials and, you know, you don't have to have a placebo group but you really do have to have something. Also, I'm not sure this whole area is well thought through. In other words, this whole idea of who's at risk, it's not clear to me that you know. Secondly, what are the indications for treatment, it's not clear that we know that. What are the appropriate treatments for a particular subgroup of patients, smokers, not smokers, whatever, it's not clear to me that we know that. And the outcomes, it's not clear to me that we

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even know what outcomes we're talking about. So I think this is a terribly difficult area to judge, because there is so little good information to

help us.
DR. MCNEIL: Thank you, Harry. So John, and then Sean, and then a break.
DR. KIRKPATRICK: I just wanted to answer that Blue Cross Blue Shield of Alabama, which covers about 85 percent of the lives down there that are covered, does reimburse it for the population that we see at my center, which is the University of Alabama. The University of Alabama also has included it in a charity program in conjunction with the company; in other words, they will cover the care that we're doing to prescribe it and the company basically provides the device for free for a number of the patients that are meeting appropriate charity criteria. So apparently there's enough data there to make the company take some risks as well as for our foundation to take some risks.
MS. FRIED: Is that for all the technologies?
DR. KIRKPATRICK: No, that's just for the external devices, and I can't comment on Blue

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Cross Blue Shield nationally, that's only Alabama.
DR. SULLIVAN: Barbara, I had just two quick technical questions about the questions we're about to address when we get back from break.
DR. MCNEIL: Do you want to ask them now?
DR. SULLIVAN: Yeah, I do, and hopefully you have an answer, or someone does, maybe Steve or whoever. For some of the questions where I may want to answer there is no evidence, there's no place that say no evidence. For example, question number three which asks, how likely is it the following treatments for nonunion fractures, blah, blah, blah, will affect the outcomes, and there's morbidity and then the four different -- what I'm saying is that not likely is different than no evidence, so what do we do there? Sorry, Steve.

DR. PHURROUGH: This is a bit of a problem with the way the questions run; generally we expect there to be some evidence. The questions are, one, is there any evidence; two, how good is the evidence; three, is there an effect of the evidence. So if you answer no on

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one, then there's no answer to the rest of the questions.
DR. SULLIVAN: So we shouldn't vote then?
DR. PHURROUGH: That is not a route that this panel has ever chosen to take, but you could, absolutely.
DR. SULLIVAN: At the last meeting I had the same issue and I kind of fudged it. So the second question, the use of the term net health outcomes, when I think of net health outcomes I think of the difference between one thing and another, some comparative effectiveness. Am I thinking of that the way you intended it?
DR. PHURROUGH: We always used the risk/benefit ratio, do the benefits of the particular technology outweigh the risks of a particular service that's being provided.
DR. SULLIVAN: Thanks for that.
DR. MCNEIL: Deborah?
DR. SHATIN: I have a question related to the data for other panel members who would like to answer, which is for the technology assessment report, almost each of the therapy results were,

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you know, 80 percent healed after a period of time, but the, it included also stabilization techniques, stating it as if that were a negative aspect of the study. So the question is, should we assume that the therapy could automatically require whatever stabilization technique might be suggested by the surgeon?
DR. MCNEIL: Let's hold that until we

address the question, because that would clarify the nature of the question, what is the comparator, really, or what is the base of the technology itself, either way. Okay. Ten minutes.
(Recess.)
DR. MCNEIL: I guess we're all here. What I would like to do now is clarify the nature of the questions that we are answering, and so far I have heard several perturbations that we might consider. One relates to a refinement of the nature of the devices or the biologics. Another relates to which bones are involved. Another relates to which patients are involved. Is there something else?
DR. AKLOG: One other one would be the type of nonunion. It seems like there's a general

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agreement that the hypertrophics are not really, that none of these treatments would be capable, so would it be reasonable to qualify all of these to say atrophic nonunions, or is that obvious?
DR. MCNEIL: To me, nothing is obvious at this point.
DR. KIRKPATRICK: I think going to the different types of nonunions would confound many of our votes, because I think they were all grouped together.
DR. AKLOG: But compared to hypertrophics, is that a problem?
DR. KIRKPATRICK: I think what I'm telling you is that we are being asked to analyze the data that we were presented and that we have in our packet to review, and I don't think we can separate out those three categories of nonunions.
DR. MCNEIL: Fair enough?
DR. KIRKPATRICK: Did you mention separating the different biologics?
DR. MCNEIL: I did.
DR. KIRKPATRICK: Okay, thanks.
DR. MCNEIL: Let's start with the technologies. Right now, the technologies are as

you see them in questions one through the end.

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Ultrasound strikes me as being ultrasound; is that correct?
DR. BURKE: We like that, good start.
DR. MCNEIL: Internal electrical stimulation, do we like electrical stimulation, is that okay?
(Panel agreeing.)
DR. MCNEIL: How about external electrical stimulation, is that okay?
SPEAKER: I think we should fractionate that into pulse DMF and capacitance coupling, because we had really two separate lines of critique or reading for those.
DR. MCNEIL: Well, they were certainly discussed separately. Do we agree on that?
DR. BURKE: Are these being rewritten?
DR. MCNEIL: We're going to do something, it will be afterwards, but we're working on some kind of visual aid.
DR. AKLOG: Can we go back to internal for a second? Does that include adjunct to surgery? For the internal, are all those by open procedure or do these include a puncture?
DR. KIRKPATRICK: It's generally not a puncture, I would be open to the manufacturer

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representative commenting, but it's generally not just a puncture, we do the surgery and implant the coils into the nonunion area.
DR. AKLOG: So it's an open procedure?
DR. KIRKPATRICK: Right.
DR. MCNEIL: Okay. So far we have ultrasound, internal, and have fractionated the external into the capacity and the pulse. Now the orthobiologics strike me as coming in three different ways; is that right? Is it more than three? So it's the DBM, the BMP-2 and the BMP-7, also known as OP-1. Is that correct?
DR. KIRKPATRICK: I don't want you to

separate it, but making our ability to vote different things different ways. I only saw good data or adequate data on one demineralized bone matrix, which I believe was the Grafton product. There wasn't a lot of information on the countless other DBMs that are out there.
DR. MCNEIL: So what is your recommendation?
DR. KIRKPATRICK: So if you want to just comment on that one DBM, I don't think we can comment on others, or we'd have to downgrade the whole group.

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DR. MCNEIL: I see. So you want us to just do the Grafton DBM?
DR. KIRKPATRICK: I think if you separated out Grafton, it would be a little bit more reasonable, because there's about 20 on the market, there was data for three that I remember seeing, so including it with a group is very complicated, because some DBMs are processed differently, some of them have been alleged to leave some of their purification products in a mildly toxic formation, things like that. There's some that state that the amount of different bone morphogenic proteins in those DBMs varies based upon the different suppliers. And there's also differences in where the grafts, the donors come from, so it's a very complex issue to group all DBMs as one thing.
DR. MCNEIL: Lishan.
DR. AKLOG: If they're that specific for one manufacturer-specific category, is that true for the others, and the other ultrasound, you know, we've been talking about ultrasound that comes from one company, and if we're getting specific as to one category, is it reasonable to do it for just that one category as opposed to

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others?
DR. SHATIN: Also, if we have specific

categories, what does it mean for the other companies in terms of what we're doing here?
DR. MCNEIL: I'm sorry, I didn't hear what you just said.
DR. SHATIN: So what does it mean if we're saying here just for that one particular product, what is it saying for that particular therapy?
DR. KIRKPATRICK: I guess what I'm saying is if you ask me to give you a vote of the data regarding Grafton, my answer might be one thing. If you ask me about all DBS, my answer is going to be very much lower, because if I look at the numerator, it's huge with DBMs, whereas with Grafton, I have a reasonable understanding.
DR. AKLOG: Is that true for the other modalities such as ultrasound?
DR. KIRKPATRICK: I don't know of another ultrasound manufacturer. I would assume that they would be measured by the production of the effective pulse, which is not being measured in DBS, in other words, we don't know what the actual individual effect of DBS is, we know that

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one company has a reasonable clinical trial with it, but we don't know that the others have the same active element in their DBS.
DR. MCNEIL: So I have Kim, Karen and Harry, and I want to be sure we're all on point on this. Yes, Karen.
DR. SCHOELLES: I just want to say that in the TA it's not the Grafton product that we found the study on, we found the allomatrix injectable, the injectable putty. We did not find studies for nonunion for the Grafton product. We understood that studies presented were for bone voids and that it was a gap filler, which according to our orthopedic consultants are not the same.
DR. MCNEIL: Let me make sure I understand this. I don't understand it, actually.
(Inaudible colloquy.)

DR. MCNEIL: Are you thinking of something else?
DR. KIRKPATRICK: Basically, the data I'm familiar with on Grafton was from segmental defect bone, and I understand her making the difference and I do need to keep that in mind. We don't really have good data on any of them as I

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understand it for a nonunion bone.
DR. SCHOELLES: Except the allomatrix putty.
DR. MCNEIL: I thought we did have data on that, but the judgment is about the decentness of it. So when we're fractionating the orthobiologics, we're going to do the putty as one, is that correct?
SPEAKER: I would suggest we don't do it by company, because that's a very dangerous and slippery slope.
DR. MCNEIL: Okay. What would you propose?
SPEAKER: I'm not sure the data is that good for anything, but if we start doing it company by company, we're going to be here for weeks.
DR. MCNEIL: So how would you do it then?
SPEAKER: Just leave it. With all due respect, I would leave it just as DBM. We have to take the data as we find it.
DR. BOYAN: I actually support that. I'm willing to hear from the orthopod side of the table, but I think it's going to be very

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complicated to try to understand all of this and in fact we haven't clarified the kind of injection that Dr. Dickson said, where we leave some nonunion tissue there and add some DBM product, versus leaving the hole void by doing a resection of the nonunion and in effect using it as a bone void filler, so I think we should just leave it as

a generic.
DR. MCNEIL: Is there a consensus for that? I don't mean to cut you off but we have just so much to do, once we've made a decision, I'd like to just move on it. Is there a consensus on DBM as a generic? All right. So just before I take the other individuals, I just want to make sure. We didn't finish on BMP-2 and 7. Do we have comments on that or do we agree that those are separate? Alex.
DR. OMMAYA: I would support BMP-2 and BMP-7.
SPEAKER: I would say for the orthobiologics, if you look at the tech assessment, there are only four assessments in there, so if we try to break it up into three categories or two categories, it's going to be very difficult. I would recommend that we keep it

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as one category.
DR. MCNEIL: But they're biologically very different is what I'm hearing.
DR. OMMAYA: That may be true, there is no evidence to make a decision between the groups.
SPEAKER: We're grading the evidence and if there's only four studies encompassing all of them, no matter how you divide it up, the evidence is poor.
DR. SCHOELLES: And we don't have an included study of BMP-2 given our inclusion criteria. The tech assessment does not include a study of BMP-2.
DR. BURCHIEL: Could I comment on that, because I think that's the danger, if we have one where there is a reasonable study, not fabulous but reasonable, we will damage everything by the lowest level of evidence. That's my concern.
DR. SCHOELLES: I assume the committee is free to make their decision based on unpublished evidence or evidence presented in papers at meetings, but I'm just saying in the technology assessment given our inclusion

criteria.
DR. MCNEIL: Well, Steve just said it's

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our call in terms of what data we include. We heard a presentation of BMP-2.
(Inaudible colloquy.)
DR. BURKE: We could separate it out and recognize that in some of the subcategories there is no evidence, and some others do have evidence.
DR. MCNEIL: That would be the danger.
DR. AKLOG: Why don't we keep them as distinct categories of therapy as opposed to proprietary products?
DR. MCNEIL: What I've got, then, is DBM is one, BMP-7 is two, and BMP-2 is three. Is that correct, is that the spirit of this? Okay. So now what we've done for the first four is redefined for all of the questions the technology, so I'm going to repeat them. We've got ultrasound, we have internal electrical stimulation, we have capacity external stimulation, we have pulse electrical stimulation, we have DBM, we have BMP-7, and we have BMP-2. Are we okay with that? So that takes care of the technologies.
We agreed that the type of nonunion, everything is as it was presented, so we're not

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going to try to deal with that.
We then raised the issue about is a bone a bone, and we have the question at the end, number 7, which is 7.A. Most of the data that was presented involved tibial fractures, although there was certainly some other long bones presented, but so the question is, do we, what is our inference in answering the questions when we say nonunion fractures?
DR. FENDRICK: Can I ask a question, and I want to turn to the end of the table again. I believe Dr. Jones when he says that the tibia

issue is probably the most difficult, which is unusual for this panel, because sometimes investigators will choose the easiest way to show that a therapy works. But if our orthopedic colleagues agree, or could at least comment to me briefly if they agree with the idea that if it works in a tibia nonunion, it's likely to work in other nonunions, a quick answer could be very helpful to me.
DR. KIRKPATRICK: The tibia is the worst case scenario but it doesn't mean it would work in every other bone.
DR. FENDRICK: Would it be reasonable

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to extrapolate what was found in the tibia nonunion to other nonunions in the non-tibia? Since I have no idea, I'm asking the panel at least to give me -- we heard it from the presenters, but I want to get at least some internal validity. I see some nods, so, I'm not saying it's definitive, but is it reasonable?
DR. BOYAN: I think it's reasonable. You have to start somewhere.
DR. KOVAN: I don't know. I mean, my understanding is that some things work better in the tibia than the humerus, so I don't know that I agree with that statement.
DR. MCNEIL: Okay, so we don't know. So let me ask the question again. How should Steve and his group interpret our answer about nonunion fractures? Because I could imagine that just the way we were talking about difference in technologies, we could get to the lowest level of evidence, we could maybe reduce the value of things by mixing everything together, when in fact the data for tibial fractures may be much more compelling than they are for, say, scaphoid fractures, and we wouldn't want to, I don't think, downgrade all fractures when in fact most of the

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data that we've looked at involved tibial

fractures.
DR. BURKE: We have to be limited by the data that's presented, so since this data focused predominantly on one type of fracture, how can we generalize that to all?
DR. MCNEIL: Let's pause for a minute and just read the question. If you read the question, it says in the treatment of nonunion fractures, so if I were a lawyer interpreting the answer to that, I would say that nonunion fractures could include a fracture of anything. I just want to confirm that that's what we mean to include when we answer that question.
DR. KIRKPATRICK: Barbara, if I may, it might be reasonable to get the answers of the grading of the evidence first and then ask when, if for example there's generalizability to different fracture types. Just guessing, if that is really really low, then there might be some comment about what we think versus what we know that will be of help to CMS.
DR. AKLOG: I don't think it's all that troubling. I think from most of these studies, one or two fractures were dominant, and I think

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what CMS would have heard is that we're weighing it based on the distribution of these fractures, and then we have an out in 7.A to say that for types for which there were no clinical studies, that that argues the generalizability issue.
DR. PHURROUGH: We would be comfortable with your answering the questions based on the data as a whole, which includes all bones, even though it may be heavily weighted toward one bone, with a comment as we have our comments, that says we're uncomfortable that you can extrapolate this beyond tibia.
DR. MCNEIL: So then, the derivative question is, are there any fracture types of any prevalence that are not included in one or the other studies that we looked at that would make Question 7.A moot if we answer it in the way we

just described? I mean, if we answer it in the way we just said, then we're covering everything in the first two questions and there is no such thing as 7.A.
DR. AKLOG: Maybe we could modify it a little bit and say for which there is little.
DR. BERGER: I think one thing, these are long bone fractures that we're talking about,

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and there are spine fractures that are a very common problem and one that is not addressed by the data.
DR. MCNEIL: Okay. So that would be the cause for 7.A. Okay, just to repeat, when we answer 2, we're answering it considering all of the studies that were presented, mostly long bones, but there were a few scaphoids in there, there were no spinal, so that when we come to answer Question 7, we are largely thinking of things like spinal fractures and maybe there are some others that I can't think of offhand. Is that fair? Everybody agree with that? Okay. Okay, that takes care of the bones and devices. What else would anybody like to query in terms of these questions? Lishan.
DR. AKLOG: With regard to, because it comes up several times referring to net benefits, Steve had mentioned that was a risk-to-benefit ratio, and I just want to make sure that we're implying that if the risk is low that benefit could be -- for therapies where the risk was low, we could find that net benefits are relatively low as well.
DR. PHURROUGH: If the numerator is

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low, even if the denominator is extremely low, the net benefit is still low. If you have a low benefit, you can't have a high ratio regardless of what the risk is.
DR. AKLOG: But if it's a moderate benefit with a low risk --

DR. BURKE: If you subtract harms from the benefits, net benefits, that's your max, that's it.
DR. MCNEIL: Now, are we confirming with this, as I'm hearing this, that we're not making any comparison with another standard of care?
DR. BERGER: Well, Question 8 really mixes things up, because it begins to compare and we don't have comparative evidence at all, so it does tend to blur the distinction, I think.
DR. MCNEIL: I'm a little confused about how to answer these questions about net benefit. I understand the definition of net benefit, but what I don't understand is whether we're comparing it against something else as the randomized clinical trials did.
DR. BURKE: As compared to not having the treatment.

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DR. MCNEIL: The reason I'm asking is, we did make a big deal about what the comparative group was this morning, quite a big deal actually, and now we're saying we wasted 20 minutes of time discussing that; is that right?
DR. BURKE: Well, it's either to the gold standard or it's to not having treatment, and I think we just have to pick one.
DR. PHURROUGH: You are comparing adding, for the first item, ultrasound to a treatment group who had been treated identically as if you didn't apply the ultrasound. And our expectation when we put these questions together was that you were comparing this to a gold standard of surgical intervention, and in some cases that surgical intervention was there whether it was rodding, plating, or bone grafting, whatever was appropriate for the patient, and if you add ultrasound to that, is there a net health benefit available from that treatment?
DR. MCNEIL: So we're subtracting out the benefit.

DR. AKLOG: That can't be true for noninvasive therapies, because the noninvasive therapies, the proposal was an alternative to

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surgery.
MS. FRIED: Exactly.
DR. PHURROUGH: That is where you get down to Question 5. Question 5, if you don't have surgery first, so 1 through 4, you're saying you had your surgical treatment and you have applied ultrasound to it post-op, you have applied internal electrical stimulation as part of your surgery, you have applied external capacitance or PEMF post surgery, or you have applied within surgery the orthobiologic.
DR. KIRKPATRICK: You have just changed everything.
DR. PHURROUGH: Those are the way the questions were drafted.
DR. KIRKPATRICK: It that's the way the questions were drafted, it should be for questions 1 through 4, surgery is performed for a nonunion. In addition, do you think the scientific evidence supports ultrasound, internal electric stimulation, external electric or orthobiologics in conjunction with that?
DR. PHURROUGH: Yes.
DR. KIRKPATRICK: That's what you want to ask, okay. Because the whole discussion today

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seemed to be geared around the progression of treatment that I talked about where you might try the ultrasound alone at four months when you have no radiographic data of progression to union.
DR. PHURROUGH: And that is what we were attempting to get to with Question 5.
DR. BURKE: It's almost like Question 5 is unnecessary, and I think it has to do with the heterogeneity of the field and understanding how these therapies work together, that we're just realizing that in questions, in other words, the

questions are bringing out the problems in the field.
DR. AKLOG: I thought there were just noninvasive therapies that were being judged as sole therapies, and the invasive therapies were being judged as adjunct to open surgery. If that's not the case, then I have to sort of rethink here.
DR. MCNEIL: We are assuming that surgery was performed on day one for the acute and then three months later, boom, it's not a union, just to clarify what Steve said, so there's surgery three months later, nonunion, and at that point the issue could be is there another surgery

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on top of what's been performed, or are these performed without any surgery?
DR. KIRKPATRICK: That's what we're clarifying. Many times in the treatment of a fracture, you don't do surgery at the beginning. So what we need to say in my opinion, and Steve agrees with this, we have an established nonunion, quote-unquote, three to six months, whatever you want to call it, for Questions 1 through 4, okay? On Question 1, for example, if you do internal electric stimulation or you do an orthobiologic, you're doing surgery. If you're doing ultrasound or external, you may or may not be doing surgery. The data that's presented showed mostly nonsurgical for external and ultrasound at that time point. And we could also ask the question, would it help if you had surgery in addition to that, but you know, that's what's making the water muddy, so I think we need to go back and say we have an established nonunion, and your treatment is one through four.
DR. BOYAN: To define it a little bit further, the surgeon has determined that there is going to be a nonunion or that there is a nonunion, or in his or her best judgment, this is

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going to heal.
DR. BERGER: So after we tried to do a union, you found you have to operate, okay?
DR. KIRKPATRICK: No, you have to intervene.
DR. BERGER: I'm just talking about the last spot, talking about biologics. The surgeon decides I'm going to operate, okay, and so what really the question we want to answer is, if I operate and if I go in there and put a new peg in, put an internal fixation in, I can put an external fixation in, I can do a whole bunch of things, and I can use an orthobiologic. And what we're interested in knowing in that case is, what was the incremental value of the orthobiologic separate from your having gone in and done the surgery. Because what we don't have, we don't have a comparison group that's going to do the surgery but doesn't put in the orthobiologic, but that's what we're trying to impute based on the studies where they compared it to the autologous or whatever they compared it to. But the question for this question is not whether it compares to autologous, it's whether it compares to if you did the surgery and you just didn't put the

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orthobiologic in.
DR. MCNEIL: So could we answer, just to be clear, we have a nonunion and that point we either operate or non-operate, and at the end of that period, there is a chance or decision node at which we can do one of several things. So if you operate -- oh, Mark has it.
DR. FENDRICK: It was said earlier. The decision to operate or not should be made very clear about how we note on each of the technologies. But I have to disagree with Dr. Berger that sometimes the decision to operate, they may only use the orthobiologic, and one design might be the noninvasive versus the double whammy, so unfortunately, it's not as clear as you say.

DR. BERGER: That's right, but in most cases they don't go in and do one thing.
DR. MCNEIL: So Mark, why don't you describe your decision tree then?
DR. FENDRICK: This is a decision between the surgeon and the patient whether they're going to be invasive or not. If they are not going to the OR then you make a decision among what I would call these adjunct noninvasive

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therapies, the external electrical stimulation as well as ultrasound. The OR would be grafting, biologics, or which I would like to say, you fix them with nothing else, and then there is the internal electrical intervention. And then of course on top of that, as we heard from the real doctor who left, you might actually after surgery add ultrasound or external electrical stim, so I suggest we should look at the combinations.
DR. MCNEIL: Well, we don't write these questions. We don't have to keep them, the stems exactly as they are. We, for example, could make the second -- let's skip the first question for a minute. We could make the second question, how confident are you in the validity of the scientific evidence for the biophysical enhancement in nonunion treatment with surgery as the primary modality, as augmented by autologous graft, biologic A, B or C, or internal electrical stimulation.
DR. KIRKPATRICK: Again, Barbara, we're getting off what was presented. You can't comment on what ultrasound did after surgery, so I think you just leave it the way it is, modifying the understanding of what Steve said.

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DR. MCNEIL: I didn't have ultrasound in there, did I?
DR. KIRKPATRICK: Okay. I thought you were just repeating Question 2.
DR. MCNEIL: No, I wasn't. Let me

reread the McNeil potential question. How confident are you in the validity of the scientific evidence for biophysical enhancement in nonunion treatment, treated primarily in nonunion greater that three months, treated with surgery followed by or in conjunction with a graft, an autologous graft, a biologic of type A, B or C, or internal electrical stimulation.
DR. KIRKPATRICK: I would submit it would be unfair to ask about autologous grafting because that evidence wasn't presented.
DR. MCNEIL: Okay, so get rid of it.
DR. KIRKPATRICK: That's okay.
DR. AKLOG: Wouldn't it be okay if we just left it alone and acknowledged that for the invasive therapies, they are by definition adjuncts to surgical therapies?
DR. KIRKPATRICK: I agree with that.
DR. BURKE: Why don't we just for surgical therapies, just recognize the surgery

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that preceded that therapy for the question, but for nonsurgical therapies, recognize that surgery did not precede.
(Inaudible colloquy.)
DR. KIRKPATRICK: Only one study had bone grafting.
DR. FENDRICK: There's only four RCTs in the whole field, and you want to throw one of them out?
DR. KIRKPATRICK: But you're also throwing out a huge volume of non-RCT data on bone grafting effectiveness.
DR. FENDRICK: I'd take one RCT over a thousand observational studies. I think the Friedlaender study really stands out in this whole, and I suggest that we reconsider that.
DR. BURKE: I think that just recognizing which therapies are preceded by surgery and which are not are adequately --
MS. FRIED: Don't leave ultrasound out because it is preceded by surgery in a prospective

series cited in the TA, or it can be.
DR. MCNEIL: Didn't John just say it couldn't? Why did you say it couldn't?
DR. KIRKPATRICK: It's not only used

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after surgery. I agree with those that are saying leave it alone, and understand that the internal electrical stimulation and the osteobiologics are with surgery.
DR. MCNEIL: So does that mean for Question 2, and 1, external electrical stimulation is not applicable?
DR. BURKE: It's applicable but doesn't require surgery.
(Inaudible colloquy.)
DR. BURKE: Because each modality is either associated with surgery or it isn't, and we're just going to recognize the association.
MS. FRIED: Because with the ultrasound and the external, you can have surgery but you don't have to.
DR. BURKE: We can parse that in 2 and move on. At 2 we can talk about whether we want to vote on it for with surgery and without surgery.
DR. AKLOG: In clinical practice, ultrasound and external stimulation is primarily adjunct therapy even though chronologically it may also precede surgery, isn't it?
DR. KIRKPATRICK: In my experience,

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most of the time the external modalities are applied before trying surgical interventions.
DR. BOYAN: Actually, Question 5 addresses that.
DR. MCNEIL: Well, let me ask Steve, is Question 5 relevant if we have made this implicit judgment in Question 2 about whether surgery is -- I mean, if we assume --
DR. PHURROUGH: Let me throw out, one of the difficulties is, we take these

recommendations that you make to help make payment decisions, and so based upon the format you just threw out, we should never pay for ultrasound or external electrical stimulation after surgery, because it's only used before.
DR. BURKE: We recognize that sometimes it's used before surgery and sometimes it's used before surgery, but both of those are separate issues to the relevant questions.
DR. FENDRICK: It's like Question 5 the way it's written. Why would you have internal stimulation or orthobiologic if there was no surgery, if there wasn't any surgery? Question 5 should be, what do you do if you don't go to the OR?

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DR. BURKE: And we're going to answer that by binarizing some of the questions earlier, we're going to answer that.
SPEAKER: I'm still confused. You can't have interval interventions for a question that says there's no surgery.
MR. MCNEIL: So 5 has to get rid of internal stimulation and orthobiologics, by definition.
DR. BURKE: Right. We're going to answer 5 in 1 through 4, and parsing it to with and without surgery.
DR. PHURROUGH: Let me finalize it, these are our questions so let me finalize it. Questions 1 through 4 are asking about these technologies applied during or after surgery, all of them, including ultrasound, including external electrical, applied during -- hang on a minute. Let me finish. Question 5 asks the question only of ultrasound and external electrical applied before surgery. So then we're getting the ultrasound and external before and after surgery. Okay?
DR. FENDRICK: So the noninvasive ones -- I mean, the invasive ones are obvious, because

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they are adjunct to the surgery, you are literally in the OR at the time of surgery.
DR. PHURROUGH: We pay for it the day they go home from surgery.
DR. AKLOG: But what if they do it three months later, is that considered?
DR. PHURROUGH: We pay for that also, but we could parse this into 28 different things. The questions you will answer, 1 through 4, all applications following surgery; 5, only the externals, not following surgery, okay? So I will get rid of the orthobiologics and the internal on Question 5.
DR. MCNEIL: So, let me just regroup here. Where are we on -- do we like the outcomes on the left-hand side of Questions 2 and 3?
DR. KIRKPATRICK: I just want to make sure I understand what Steve's telling me. I need to be thinking, instead of as a surgeon, just analyzing data, because as a surgeon I would normally try nonoperative treatment first, but to make up the questions we're going to cover surgery first and then we're going to talk about nonoperative management.
DR. PHURROUGH: Just because of the

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layout of the questions.
DR. KIRKPATRICK: I just want to make sure I understand.
DR. MCNEIL: If we answered Question 5 first, would you feel better?
DR. KIRKPATRICK: No. I'm just saying, you know that orthopedic surgeons are known as kind of being at the slow end of the intellectual scale, so I just want to make sure I understand what you're telling me I need to do.
DR. BURKE: You will do fine.
DR. MCDONOUGH: So Questions 2 through 4 are talking about adjunctive treatment.
DR. BURKE: Yes.
DR. MCDONOUGH: Okay.

DR. BURKE: Well, 1 is too, 1 through 4 are adjunctive.
DR. MCDONOUGH: Is Question 1 dealing with adjunctive treatment?
DR. MCNEIL: Yeah, 1 through 4 are adjunctive, and then Question 5, we've eliminated the two components to it.
Now, how about off label, which is Question 6? Did we discuss that for the biologics?

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MS. FRIED: We discussed that it wasn't allowed.
DR. KIRKPATRICK: I would suggest that it's actually very closely related to what 7 is asking, different fracture types and that sort of thing, unless you want us to comment on whether something used for a nonunion could be extrapolated for a spine piece, which I hope we're not going there.
DR. MCNEIL: I think that's what the question means, doesn't it? I'm not sure that I love Question 6.
MS. FRIED: I may be mistaken, but I thought it was not allowed off label for the OP-1; wasn't that the presentation, and then the other, we didn't have any information about, right?
DR. MCNEIL: But do we want to be confident about something that's illegal?
DR. BURKE: I'm not very confident.
DR. BERGER: Our answers will tell them that.
DR. PHURROUGH: It's not a legality question.
DR. FENDRICK: I promise this will be my last comment, because I really like the way it

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worked out with surgery, no surgery, but now we don't have a question about the level of evidence for the adjunctive therapies, or we don't have a Question 1. So Steve, would you allow me to make

a motion to add to Question 5 a 5.A that allows us to talk about the evidence?
DR. PHURROUGH: My computer is running out of lines.
DR. FENDRICK: We need a question, though, for what we think the evidence base is for ultrasound and external electrical stimulation before surgery. It does not exist in the current state of the questions.
DR. BURKE: Listen. I believe that more generally, Mark's point is 1 through 4 should also occur for the nonsurgical questions as well as the surgical, and it seems like we're looking at two tracks here, one with surgery and one without surgery. Is that it, Mark?
DR. FENDRICK: I would have to take them out.
DR. BURKE: So it's a whole set of questions, 5 generates 1 through 4 related to 5, right? If we don't have a question related to 5, in other words, without surgery, for ultrasound

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and external electrical stimulation, 2, 3 and 4 would apply as well; do you see what I'm saying?
(Inaudible colloquy.)
DR. MCNEIL: The suggestion was just made that we go back to Question 1, we subdivide external electrical stimulation into capacity and pulse, so that's now two columns.
I think we'll take a break while we get ourselves together, but everybody stay here while we get everything on the table, don't go.
(Recess.)
DR. MCNEIL: Does everyone agree that the other components are fine as listed, morbidity, which includes infection, amputation, permanent loss of limb function; radiographic healing; clinical healing; and radiographic and clinical healing? Yes.
DR. MCDONOUGH: If we make (inaudible) for healing or a nonunion, would that reduce the morbidity of permanent loss of limb function, or

are we talking about adverse effects?
DR. MCNEIL: Morbidity is adverse effects of treatment, is that the question?
DR. MCDONOUGH: So then, it would seem in answering that question with respect to

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morbidity that if something reduces morbidity, then it would be something that, for example, a nonunion if it heals, it would restore limb function and hence, it would reduce morbidity, wouldn't it?
DR. MCNEIL: Correct, so you're saying it's a redundant question?
DR. MCDONOUGH: Yes, unless you don't believe that (inaudible) are clinically related to an improvement of function.
DR. MCNEIL: We may need some discussion on that, so let me repeat the issue, everybody listen if you could. The morbidity now, I think what is being suggested by Bob is, that the issue of clinical healing embeds in it improvement in limb function, so to have loss of limb function would imply no clinical healing, and therefore, we should get rid of permanent loss of limb function as a morbidity.
DR. KIRKPATRICK: Can I comment, and maybe Steve can help me on this. You're just talking about whether there's risks to doing the procedure, and some of those risks were just listed as a possibility. You might get an infection if you operate, if nothing works, you

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might end up with an amputation. Obviously amputation would be a permanent loss of limb function, but another loss of limb function might be a nerve palsy if you affected a nerve when you were doing the surgery. So all those are potential morbidities and I think they're perfectly relevant to the surgical treatments.
DR. PHURROUGH: Right. You don't need to consider these are the morbidities, these are

just examples of morbidities.
DR. MCNEIL: So these are e.g.'s.
Okay. Is there any other -- we're writing down to, let's see, any other clarifications?
DR. BOYAN: I have a concern.
DR. MCNEIL: Sure.
DR. BOYAN: We have a definition of orthobiologic and I think minimally, orthobiologic should have something biologic in it. And a calcium filler is not biologic unless it has in it something biological.
(Inaudible discussion.)
DR. BOYAN: I'm back. We got rid of all those.
DR. MCNEIL: Now, are we adding DMB to Question 8?

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DR. BOYAN: Yes, I think so. DBM.
DR. MCNEIL: I'm sorry, DBM. We all should be thinking for a second, and so the first question is, how well does the current scientific evidence support the use of these technologies, and now it's going to read ultrasound with or without surgery, internal stimulation alone, capacity stimulation with or without surgery, pulse stimulation with or without surgery, DBM, BMP-7 and BMP-2. Is everybody on the same page?
Okay, Kim?
So you're going to be holding up these cards, and this is a fairly complicated vote so you're going to be asked to hold them up for a while since there are a lot of us.
I'm going to read each question as we go through this just so we're absolutely clear.
How well does the scientific evidence support well-defined indications for each of the technologies in the treatment of nonunion fractures, recalling that nonunion fractures encompass the database that we've considered today?
So we will vote from one to five on ultrasound without surgery, going from poorly,

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current scientific evidence is poor, to current scientific evidence is very well.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Internal electrical stimulation.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: External capacity without surgery.
(Panelists voted, with staff recording the votes.)
DR. KIRKPATRICK: A clarification. You are going to do PEMF separate, correct?
DR. MCNEIL: I am. The next one is the same thing with surgery, in conjunction with surgery.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Pulse stimulation with surgery. It's with surgery on the table, so why don't we do with surgery first, so it's pulse with surgery.
(Panelists voted, with staff recording the votes.)

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DR. MCNEIL: Now pulse without surgery.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: DBM.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: BMP-7.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: BMP-2.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Now we can roll down the screen to Question Number 2, and we're going to go

through each one of these for the specific outcomes. The outcomes, just to recall, morbidity, infection, amputation, permanent loss of limb function, those are all for examples, radiographic healing, clinical healing, and both. So the first one is ultrasound with surgery specifically with regard to all of those things. Morbidity. So the question is, how confident are you in the validity of the scientific data for the enhancement of nonunion treatments on the

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following outcomes? Ultrasound with surgery.
DR. MCDONOUGH: Are we talking about morbidity for this one?
DR. MCNEIL: You're right, that doesn't make any sense. So the first one, I guess the morbidity question is moot, right?
DR. BURKE: No, the next one.
DR. MCNEIL: I'm sorry, the next one is moot.
DR. KIRKPATRICK: I don't think any of them are moot. The question is, do we think there's valid evidence that demonstrates that the morbidity is a problem.
DR. MCDONOUGH: Can I ask a question? When you say ultrasound, is there a problem with the surgery or with the addition of the ultrasound to the surgery that it increased the morbidity?
DR. MCNEIL: This is a package.
DR. KIRKPATRICK: We're not answering the question of the surgery's morbidity, we're answering the question of the ultrasound morbidity in addition to the surgery.
DR. MCDONOUGH: Whether it's adding to the morbidity.
DR. KIRKPATRICK: Whether there's valid

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evidence that tells us that ultrasound adds to the morbidity.
DR. MCNEIL: This is all prior surgery

pretty much, though.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. Radiographic healing, and we're still with surgery. This set of questions is --
MS. FRIED: Oh, we're going down.
DR. MCNEIL: It's better to look up here at me. Ultrasound with surgery, radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both clinical and radiographic.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. Now we do ultrasound without surgery.
How confident are you in the validity

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of the scientific evidence for ultrasound without surgery with regard to those same things? The first one is morbidity.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Ultrasound without surgery with regard to clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. That question related to the state of the evidence. The next one is electrical internal stimulation. Can we move up the chart, up some more to internal

electrical stimulation.
How confident are you of the validity of the scientific evidence of that with regard to the same things? Morbidity.
(Panelists voted, with staff recording the votes.)

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DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Could you move the screen down, please. External stimulation without surgery -- sorry. External capacity without surgery. Morbidity.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. So now, external

00265

capacity with surgery. Morbidity.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording

the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Okay. If we move up the
screen to line 41, thank you. So, PEMF with
surgery. Morbidity.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording

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the votes.)
DR. MCNEIL: Now, PEMF without surgery.
Morbidity.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: If we can move up the
screen, please? Okay. Now we go to DBM,
morbidity, and realizing that we have all DBMs
lumped in here even though we talked about
primarily one.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)

DR. MCNEIL: Clinical healing.

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(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Moving up to BMP-7, morbidity.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. BMP-2, morbidity.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.

00268

(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. This next one, now addressing the issue, how likely is it -- oh, sorry. We were on both, radiographic and clinical.
(Voting continued.)
DR. MCNEIL: Now to Question 3, so let me repeat everything we just did, except related to the effect on the following outcomes, where the

outcome is positively related to the respective biophysical enhancement. So data, and now outcomes. So, the first one is ultrasound with surgery. Morbidity.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: How about radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording

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the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Moving up a line please to without surgery, so how likely is it that ultrasound without surgery will positively affect morbidity, as indicated above?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. If we could move line 78 up. So, how likely is it that internal electrical stimulation will positively affect morbidity?
(Panelists voted, with staff recording the votes.)

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DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording

the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Moving up to the top,
external capacity without surgery will positively
affect, how likely is it that it will positively
affect morbidity? External capacity without
surgery.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)

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DR. MCNEIL: Moving up to electrical
capacity with surgery, with morbidity, how likely
is it that it will positively affect morbidity?
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Moving on, how likely is
it that pulse stimulation with surgery will
positively affect morbidity?
(Panelists voted, with staff recording

the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)

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DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: PEMF without surgery, same
thing, morbidity.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Okay, moving up. First
orthobiologic, DBM, how likely is it that it will
have a positive effect on morbidity?
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Radiographic healing.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Clinical healing.

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(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording
the votes.)
DR. MCNEIL: Okay. BMP-7, how likely
is it that it will have a positive effect on

morbidity?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing, BMP-7, OP-1.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Okay. BMP-2, how likely is it that it will positively affect morbidity?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Radiographic healing.

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(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Clinical healing.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Both.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: So, the next question we actually didn't discuss, and I'm realizing that we should probably -- well, let me read it to you, Question 4, can you put it on the screen? How confident are you that the following technologies will produce a clinically important net health benefit, and then we list ultrasound, internal, external stimulation, and they should be split just like the others were. So while Steve is doing that, we will vote. So, how confident are you that ultrasound with surgery will produce a clinically important net health outcome?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: How about ultrasound with

no surgery, ultrasound alone?
(Panelists voted, with staff recording

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the votes.)
DR. MCNEIL: Okay, ready? Internal electrical stimulation.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: So capacity with surgery, electrical capacity stimulation with surgery.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Without surgery.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Now the PEMF has to be divided, if anybody is listening to me. Are we ready to go on to PEMF? And just pretend there are two lines under there, and the first one says with surgery.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: PEMF without surgery.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: DBM.
(Panelists voted, with staff recording the votes.)

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DR. MCNEIL: BMP-7.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: BMP-2.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Now we've got a couple easy ones coming up, before we go brain-dead. The next question is Question 6, just as it was. How confident are you that the improved net health outcomes will hold for off-label treatments using orthobiologic devices?

DR. BURKE: Whoa. What about 5?
DR. MCNEIL: 5 we felt we answered already. So how about 6, how confident are you that the improved net health outcomes will hold for off-label treatments of nonunion fractures using orthobiologic devices?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: So the seventh one, we didn't divide this one either, Steve.
DR. PHURROUGH: We didn't discuss 7 much, but as I understood the discussion from the clinicians, that if a bone is completely healed, a

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bone is completely healed, regardless of how it completely healed. So that perhaps the question, rather than for each of the interventions, whether the question should just answer A, B and C across all the way down. Because if you get completely healed regardless of the type of modality that healed you, how likely is that completely healed to affect A, B and C.
DR. MCNEIL: Okay. So A would be for fracture types for which there have been no clinical studies, with the exception of -- what?
DR. KIRKPATRICK: I think we're talking about generalizing between saying a tibia and a clavicle might be relevant for a radius or ulna, but not to the spine.
DR. MCNEIL: I don't have clinical studies for the tibia and ulna.
DR. KIRKPATRICK: We don't have them for ulna as well as we do for the tibia, we don't have them for the radius as well as we do for the tibia.
DR. MCNEIL: No, I understand that, but I thought when we were voting on Questions 2 through 5, we were voting for all of the things, however infrequent they were in that big table,

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and then Question 7.A simply included things that

were not in that table, like spinal fractures. Maybe I misinterpreted.
DR. KIRKPATRICK: As a clinician, I would exclude spine fractures from a majority of all this discussion.
DR. PHURROUGH: And we did not intend to look at spine with this, so I think we're essentially saying how does tibia compare to everything else in general, those with less or little data. In other words, those we have a lot of data on, can we generalize those to where there was very little data?
DR. BOYAN: Before we do that, I want to make sure I didn't vote different than everybody else. On Question 6, specifically we were saying that these methods, that the way that we see these methods, if other orthobiologics that might come along will also be reasonably good, is that what the question was?
DR. BURKE: No. It was off-label use of these orthobiologics.
DR. BOYAN: That's fine. Like for things that are not currently used.
DR. MCNEIL: That was Question 6.

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DR. BOYAN: I voted the way I wanted to vote, okay.
DR. MCNEIL: So with the generalizability to non-tibia, that's 7.A, so the question is: How likely is it that completely healed nonunion fractures, however done, can be generalized to, since most of the data we saw came from the tibia, to the scaphoid just to stylize it, or to the ulna or humerus or whatever?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Now the providers, here we're talking about places beyond the sites where these clinical data came from, realizing we didn't talk about that a lot, but in general they came from high volume places which specialize in the kinds of things that we talked about.

(Panelists voted, with staff recording the votes.)
DR. MCNEIL: And finally, to the Medicare population, we talked a lot about that.
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: So if we're up to it, we have one last question. How likely are we that

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all of the orthobiologics, that's BMP-7, BMP-2 and DBM, are equivalent?
(Panelists voted, with staff recording the votes.)
DR. KIRKPATRICK: May I speak for Steve and ask one more question, and that is just to compare the two BMPs? My answer is totally different when they were with, in the original question which did not include the demineralized bone matrix versus the two BMPs, and I'm wondering if that would be helpful to Steve.
DR. PHURROUGH: I'm not sure what you're asking.
DR. KIRKPATRICK: Osteobiologics now includes demineralized bone matrix preparations, of which there are about 20, and two BMPs. In my mind and in my experience, those are totally different performance criteria that were evaluation, and I'm wondering if it would be helpful to you to look at the original question which was between BMP-7 and BMP-2.
DR. PHURROUGH: So you recommend comparing two and seven versus DBM? Versus two, seven and DBM, all saying they're equivalent.

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DR. MCNEIL: He wants to vote on the original question.
DR. PHURROUGH: Let me hear your interpretation of the question you want.
DR. KIRKPATRICK: What I just voted on was, do I think that demineralized bone matrix

preparations, OP-1 and INFUSE are all equivalent in the treatment of nonunion fractures, and you can see my answer. If you change that to saying just the two BMP products, my answer would be very different, and I think some of the panel would also have that difference.
DR. PHURROUGH: I see. So Question 8 was all of them, and you're saying that Question 9 would be --
DR. KIRKPATRICK: Just the two BMPs. And I think when you guys get into cost analysis, you will find a big difference there too.
DR. MCNEIL: That's --
DR. KIRKPATRICK: I'm not saying we're doing a cost analysis, I'm saying he has to do a cost analysis.
DR. PHURROUGH: He's asking a scientific question. The question is, or he would like the panel to ask, are two and seven

00282

equivalent.
DR. KIRKPATRICK: I think the information that I'm looking at, the BMP-2 and BMP-7 --
DR. PHURROUGH: Let me interrupt. That's a yes or no question.
DR. KIRKPATRICK: Yes.
DR. PHURROUGH: Would the panel like to ask that question?
DR. MCNEIL: Sure.
DR. PHURROUGH: Let's ask that question.
DR. MCNEIL: Got the question, Kim, Michelle? It's the original Question 8, the one on the printed sheet is --
DR. PHURROUGH: No. The one on the sheet says all orthobiologics such as, so number 8 was all of them. So number 9 is, how confident are you that just the recombinant ones are equal?
(Panelists voted, with staff recording the votes.)
DR. MCNEIL: Wow. We finished. I must

say, just standing up there I could see the votes, and when we asked about variability, it was largely there, but it was quite clear that the

00283

spectrum was in the two-three range with some fours and virtually no fives, some fives, but not as many. Right.

So Kim, do you need to adjourn us, are there any further questions or issues that we would love to add on at this hour of the day? If not, then I think the meeting is adjourned.

DR. PHURROUGH: Just quickly, thank you very much. This was helpful to us. I recognize it was a challenge and it's always a challenge to make sure that we ask the right questions and you always tell us in that regard. Our current plan is to take your recommendations, look at our current policies and see if they should change, and see if there is something to stimulate the world to look at these particular technologies in a different light. Thank you very much and we will look forward to the next meeting in November.

(Whereupon, the meeting adjourned at 4:17 p.m.)