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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Coverage Advisory Committee

May 24, 2005

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

Panelists

Vice Chairperson
Barbara J. McNeil, M.D., Ph.D.

Voting Members
Harry B. Burke, M.D., Ph.D.
Mark Fendrick, M.D.
Alexander H. Krist, M.D.
Stephen L. Ondra, M.D.
Mary Starmann-Harrison, B.S.N., M.H.S.A.
Jonathan P. Weiner, Ph.D.

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

Consumer Representative
Charles J. Queenan, III

Panelists (Continued)

Guest Expert Panelists
James Weinstein, M.D.
Sean D. Sullivan, Ph.D.
Richard G. Fessler, M.D., Ph.D.
Daniel K. Resnick, Ph.D.
David F. Kallmes. M.D.
Jeffrey G. Jarvik, M.D., M.P.H.

Executive Secretary
Kimberly Long

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PANEL PROCEEDINGS

(The meeting was called to order at 8:06 a.m., Tuesday, May 24, 2005.)

MS. LONG: Good morning and welcome, committee chairperson, members and guests. The committee is here today to discuss the evidence, hear presentations and public comments, and make recommendations regarding the treatment of vertebral body compression fractures.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interests. To determine if any conflict existed, the Agency reviewed all financial interests reported by the committee participants. The Agency has determined that all members may participate in the matters before the committee today. With respect to all other participants, we ask in the interests of fairness that all persons making statements or presentations disclose any current or previous financial involvement in any orthopedic device company. This includes direct

financial investment, consulting fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room. We ask that all presenters please adhere to their time limit. We have a large number of 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. Please proceed to the chair when it is your turn. For the record, voting members present for today's meeting are Harry Burke, Mark Fendrick, Alex Krist, Stephen Ondra, Mary Starmann-Harrison, and Jonathan Weiner. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including non-voting 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.

And one more brief announcement. If anyone is requiring transportation following the meeting, you should sign up at the registration desk during the break.

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

DR. PHURROUGH: Good morning. I am Steve Phurrough, the director of the coverage and analysis group here at CMS and the CMS liaison for this particular meeting. Let me welcome you. A particular welcome to the panel and our appreciation for their taking time from their busy schedules to assist us in these deliberations. This is one, the beginning of a series of public meetings we expect to have over the next two to three years about issues surrounding spinal surgery. Spinal surgery is very common in our patient population in that they have lots of spinal disease, and we're interested in discussing what the evidence base is for those various procedures, and then perhaps providing guidance to the public on the other kinds of evidence that may be necessary to fully answer some of the questions regarding what is appropriate. We do not currently have a national coverage determination

on spinal surgery, though we may in the future, depending on some of the evidence reviews that we do. So we look forward to a good discussion, thank you again for your participation and willingness to assist us in what we think are important topics for CMS. Barbara.

DR. MCNEIL: Thank you again. I think this will be a very interesting day. We have had lots of material to review over the past week or so and will look forward to hearing additional presentations from the public and the various individuals who have signed up in advance. And I would just echo Kim's comments that we have a really tight schedule so your adherence to the time limits will be very much appreciated. And I would also like to ask you if you can, to be sure that you tell us as much as you think we're going to need during your presentations when it comes to our review of the voting questions. After lunch, the committee will be largely deliberating on its own. While we may ask a question or two of the audience, we expect to get most of the information from you from your morning session, from your morning presentations. So try to anticipate our needs.

So with that, I would like to ask Dr. Feinglass to present the voting questions. Actually, while we're setting up, why don't we have the panel introduce themselves and whether or not they have any conflict of interest that they would like to discuss. So, we can start with Dr. Weinstein.

DR. WEINSTEIN: Jim Weinstein from Dartmouth. I'm currently editor in chief of Spine. I also serve on various organizational boards for the American Academy of Orthopedic Surgery, the American Board of Orthopedic Surgery. I have recently been put on the board for United Health Care. I have funding from NIH, some CMS funding, and I'm trying to think of the third one, but I don't believe I have any conflicts related to this discussion.

DR. JARVIK: I'm Jerry Jarvik from the University of Washington, I am chief of neuroradiology there. I do not have any conflicts of interest.

DR. KALLMES: I am David Kallmes, from the Mayo Clinic. I do receive funding from NIH and don't have any conflicts.

DR. RESNICK: I am Dan Resnick, from

the University of Wisconsin in their spine section, am ex-chairman of Guidelines. I do have a consulting arrangement with Medtronic that has been disclosed previously.

DR. R.G. FESSLER: Richard Fessler, I'm chief of neurosurgery at the University of Chicago. I developed a vertebroplasty set which is not marketed in the United States so I don't think it's a conflict of interest.

DR. SULLIVAN: I'm John Sullivan, from the University of Washington, where I direct the technology assessment program. I have no conflicts.

MR. QUEENAN: I'm Charlie Queenan, the consumer representative. I am an independent consultant and have no conflicts.

MS. STARMANN-HARRISON: Mary Starmann-Harrison, with SSM Health Care, and I have no conflicts.

DR. ONDRA: Steve Ondra, Northwestern University, and I have no conflicts pertinent to this. I have consulting arrangements with Medtronic and DePuy Spine.

DR. KRIST: I'm Alex Krist, with the department of family medicine at Virginia

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Commonwealth University, and I have no conflicts of interest.
DR. FENDRICK: Mark Fendrick, University of Michigan, no conflicts.
DR. BURKE: Harry Burke, George Washington University, no conflicts.
DR. MCNEIL: Barbara McNeil, Harvard Medical School and Brigham and Women's Hospital, no conflicts.
Okay. Why don't we proceed with the questions.
DR. FEINGLASS: Good morning. Thanks for coming to Baltimore on a slightly rainy day. As Steve mentioned, we are looking at several different things at CMS related to the spine. As you know, back pain is a significant concern for our beneficiaries. There are some important and long-term examinations that need to be done with the spine from our perspective. There is a substantial public health impact, leading to a lot of discomfort, loss of mobility, and serious morbidity.
The back diseases of interest to us at this time are degenerative disk disease, degenerative spine disease, and vertebral

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compression fractures, which we are addressing today. As a quick overview, and you will hear more of this throughout the day, but vertebroplasty and kyphoplasty are both minimally invasive treatments. They insert bone cement into the compressed and fractured vertebrae to provide mechanical stabilization.

Kyphoplasty is a variation of vertebroplasty. It uses an inflatable balloon to expand the compressed vertebral body, it attempts to restore natural vertebral height before injecting the cement-like substance, and attempts to correct spinal deformity.

This is the review of the questions for today. They're divided into questions addressing vertebroplasty and questions addressing hyphoplasty.

Number one: How well does the evidence address the effectiveness of vertebroplasty for patients with compression fracture as compared to conservative care?

How confident are you in the validity of the scientific data on the following outcomes: Short-term morbidity, long-term morbidity, mortality, mobility-functional status, pain

relief, with respect to vertebroplasty for patients with acute and subacute compression fracture or chronic compression fracture? How likely is it that vertebroplasty, in the following circumstances, acute and subacute compression fracture and chronic compression fracture, will positively affect the following outcomes: Short-term morbidity, long-term morbidity, mortality, mobility-functional status, and pain relief, when compared to conservative care? How confident are you that vertebroplasty will produce a clinically important net health benefit for patients with a compression fracture as compared to conservative care for patients with acute or subacute compression fracture or chronic compression fracture? Based on the literature presented, how likely is it that the results of vertebroplasty in the treatment of relief of pain and improvement in ability to function for patients with a compression fracture can be generalized to the Medicare population, or providers in community practice? These are the questions addressing

kyphoplasty. How well does the evidence address the effectiveness of kyphoplasty for patients with compression fracture as compared to conservative care?

How confident are you in the validity of the scientific data on the following outcomes: Short-term morbidity, long-term morbidity, mortality, mobility-functional status, pain relief, with respect to kyphoplasty for patients with acute and subacute compression fracture or chronic compression fracture?

How likely is it that kyphoplasty, in acute and subacute compression fracture or chronic compression fracture, will positively affect the following outcomes when compared to conservative care: Short-term morbidity, long-term morbidity, mortality, mobility-functional status, pain relief?

How confident are you that kyphoplasty will produce a clinically important net health benefit for patients with a compression fracture as compared to conservative care for patients with acute/subacute compression fracture or chronic compression fracture?

And the final question. Based on the

literature presented, how likely is it that the results of kyphoplasty in the treatment of relief of pain and improvement in ability to function for patients with a compression fracture can be generalized to the Medicare population or providers in community practice?
Thank you.
DR. MCNEIL: Thank you, Dr. Feinglass.
Dr. Mark.
DR. MARK: Thank you for inviting me.
I see in the schedule that what I'm doing is presenting the results of our TA, and I'll explain what that TA is. TA stands for technology assessment, and at the Blue Cross Blue Shield Association we periodically review procedures, diagnostic tests, surgical procedures, and we try to do an objective review of the literature and apply certain criteria to the selection of studies for quality, and evaluate and synthesize the data from these studies and see if they meet our criteria. Our reports for Blue Cross Blue Shield Association are reviewed by an independent panel and then these reports are forwarded to the Blue Cross plans for them to make a coverage decision.
So in our review, we try to set a

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minimum quality standard for selecting articles and then we try to establish a format for extracting all the data from those studies so that it's in a way that could be easily visualized, look at subgroup outcomes if possible or necessary, and then for Blue Cross Blue Shield Association, we have a specific set of criteria that we apply to see if the procedure is effective or not.

For this particular, for the topics of vertebroplasty and kyphoplasty, we used these selection procedures for studies. We looked for full-length English language studies, although there will be a few exceptions that I will mention below. We wanted to select studies that had a clinical indication for osteoporosis or malignancy, and that they fully reported a consecutive or near consecutive series of patients, the studies identified a current procedure, and that they studied relevant outcomes of pain, functional status or quality of life. We did not select studies that had purely anatomic outcomes, and we will see that in several of the studies some researchers report changes in the anatomic shape of the spine, but we did not look

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at that directly as an outcome. As a slice to attempt to get better quality studies, we wanted studies that looked at both pre and post-procedure assessments of these outcomes. Some studies will only report retrospectively after the procedure, asking the patient, how do you feel after the procedure, and we felt this was not as rigorous a method for assessing outcomes. And just to cull the literature for a reasonable quantity of studies, we set a minimal sample size of 20 patients for osteoporosis, and because they were used less frequently for patients with malignant processes in their back, a slightly smaller sample size. And this wasn't a rigorously determined, statistically driven sample size, it was meant to be practical and to be overly generous in including studies. If we were looking for something more statistically rigorous, we would have upped the sample size, but this leaves a sufficient number to examine. In our exceptions for published literature, we had several reviewers and they directed us to comparative trials, either randomized clinical trials or nonrandomized

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comparative studies, and where these were available, we accepted what information was available in abstract form or from foreign literature. So, we were particularly interested in trying to find those studies which actually compared vertebroplasty or kyphoplasty to other procedures.

And what we didn't include would be a lot of the biomechanics, biomechanical type studies. Vertebroplasty and kyphoplasty are used for other diseases, angioma of the spine is a common indication and that was not in our review this time.

Non-health-related outcomes, we did not look at case reports, although our full technology assessment does have a review of complications that are known about and discussed.

And there are some other important questions that are sometimes in the review of our technology assessments, but given our time and space, we didn't cover those as comprehensively. For example, for these procedures, an important question that the evidence is probably not in on, is there a risk of future fracture after you have had the procedure, does vertebroplasty make it

more likely to have a subsequent fracture elsewhere, and that's a complicated question. My feeling is that the literature is probably incomplete on that question, but we did not address that in a fully comprehensive way in this review.

Now, one of the challenges in trying to view this literature is that there is a variety, even though we had a criteria for outcome measures, there is many ways to measure outcomes, and even within one method, there are many variations, and it's probably a course or a day's lecture to try to study each of the properties of the measurement scales. So, I can't do that so let me just summarize what we have.

There are various methods of measuring pain on a visual analog scale, and a visual analog scale is just like a picture of a thermometer, and the patient rates how bad their pain is. So it's usually classically on a one to ten scale, but in many of these studies, the visual analog scale was a series of questions, so not just one question, but a series of questions asking about back pain, at rest, doing various activities, daily living things, so the visual analog scale is many

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different things, not just one thing in these studies.
There are studies of function and there are studies of function specific to back pain, and probably the best known one is the Oswestry Disability Index, which is a series of ten questions and five choices for each question, and it's most commonly expressed as a zero to 100 scale. People with bad back pain tend to be between 50 and 60 and classically, people have thought that a difference of five to 15 is a clinically significant change in this score. According to some documents in the FDA in terms of evaluating procedures, they like to see a 15-point difference in that scale as a clinically important change.
Again these scales, even if they were developed for back pain, may not have been investigated in depth for this particular subgroup of patients, so that a scale for that particular measurement may be insensitive to the degree of pain. So scales have ceiling effects where you hurt so bad that the scale doesn't differentiate that, or where you have floor effects where people are trying to differentiate a level of pain that

the scale's insensitive to. So it's a very difficult art to kind of tease out what's going on from what we pick up from the patients concerning pain.
There is some quality of life types of outcomes that some of these studies use. One study uses a questionnaire specific to osteoporosis. Again, they try to tie these questions of your back problems and how are you living both physically and socially and mentally.
A very common form of outcome measure is the SF-36 or Short Form 36, 36 questions meant to evaluate your health in two overall domains, physical health and mental health, with four domains within each one, and the physical health domain within the SF-36 includes a pain component, but that's two questions about pain.
And then other studies seem to have adopted some other types of scales which again, the properties of are difficult to assess in relation to this specific procedure. It's very complicated, I don't know if we can -- we'll just kind of have to take what the studies tell us and have the experts inform us as to the properties and abilities of those scales to tell us

meaningful information. So this is just an introduction, it's a very complex field, and I'm far from an expert on each of these individual scales.

So in terms of the nature of the question, what are the effects of vertebroplasty for osteoporosis-associated fractures, these are people with fragile bone that's collapsed versus those that have a malignant process which has made the bone fragile. And what we found mostly is case series studies, that's the predominant form of study out there, and later on I'll review the comparative studies that we found.

But of those studies that met our criteria, we found 11 case series studies with a total of over 900 patients. Varying sample size. And what we see is that there is a variable work-up and imaging evaluation for these studies, and I think the experts will be able to inform us on what the type of work-up is and what type of patients can be included and excluded, but it varies between studies, and so, they could inform us as to what the consensus is and whether different people would agree about who is a candidate for the procedure.

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My report has varied and detailed tables, and I'm trying to get out the major issues, and there is some more detail in the written report, but I will try to present it in an efficient fashion.

But they vary in terms of the average symptom duration, so an important question for Medicare is the chronicity of the fracture. And so, since there were many studies that did not report the duration of both the fracture and the result of any kind of straightforward evaluation all the time, some of the studies included patients with only short-term duration, and one study with a long symptom duration. And then they also varied in the respect that they followed up the patients for their improvement, and you can see there is quite a range in how far out after the procedure the patients were followed.

So, this is my attempt to take our very detailed tables and give you the broad brush stroke of the results based on the outcome of a one to ten visual analog scale or, to the best of our ability, to normalize whatever scale the investigator used to a one to ten scale. So if they used another visual analog scale that didn't

used the maximum score ten, then we kind of scaled the others proportionately and hopefully that makes the studies comparable.

But the studies that varied in their techniques for evaluating the pain, some were a multi-question, some is a one-question, and there might be variations, there are probably variations even in showing the patient a single scale or asking them a single question.

But we can see among the case series studies that at baseline, the VAS scores at this range with ten being the maximum, anywhere from 6.9 up to the nine-point-something. Some of these patients, you can imagine the question being, is this the worst pain you ever felt? And several of the studies only evaluated, four of the studies here only evaluated the patients right after the procedure, but we can see that there was relief down to 1.9 to 3.7, and I didn't put a statistical significance because within the context of these studies and their reasonable sample sizes, the changes of this magnitude are all statistically significant, so you can assume that almost everything I'm pointing out to you here is statistically significant. So several studies

just evaluate the procedure right after and then they don't keep track of the patients after that. And then three studies which evaluated the patients from one month to six months, and again, you can see that there is still a decrease from baseline. And there were some studies that evaluated at a year and further out. Again, these are single case series studies with no control arm in the study.

What's not noted here is that some of these studies have some losses to follow up, so they aren't able to fully, they don't have their full number of patients at the end of the study, that's in my detailed report. Half of the studies, or about half the studies probably had fairly thorough follow-up. I think the studies that really lost track of half of their patients, they were not included in our report.

These are the studies that looked at other outcome measures and as I said, it's hard to know the exact properties of these measurements and even if they are well known for other patients, they may not be well known for these specific type patients, so we just kind of have to accept the scale for what it tells us and kind of

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have a gestalt about what the magnitude of the difference is. But we can see some studies used some ordinal scale for mobility and some ordinal scale for pain medications. The Oswestry score in this particular study, they scaled it from one to five versus one to a hundred, so this is the more common ways that the Oswestry scale, everyone went from 70-something percent down to 16, so a big difference, and then some studies using measures of quality of life on the ordinal scales.

These studies had various methods of showing their complication rates, and the most common being cement leak, so these are the rates of anatomic cement leak as noted on either CT scan or plain x-ray according to the method of the author. And we can see that cement leaks are common, but less common are symptoms associated with those leaks, and then commonly these studies will have a notation about specific patients that had a more severe neurologic type problem. And then some studies showed in a rather nonsystematic fashion the frequency of new fractures at a certain time after the procedure.

We did the same type of review for malignancy-associated fractures for vertebroplasty

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and I will just go over those quickly. Again, a smaller number of studies, three case series studying a total of 70 patients. If we look at the visual analog scale, the results in termination of pain from baseline compared to follow-up and the magnitudes of the change seemed to be similar to that for the osteoporosis patients.

Now we found one published nonrandomized comparative trial comparing vertebroplasty to conservative treatment, and so this study I will review in a little more detail. These patients all had evidence of acute fractures so they had not had a whole lot of time to see if they would get better, and they were all evaluated and they either agreed to have the vertebroplasty or they agreed that they wanted to have conservative treatment. And the results of the study, to quickly sum up, in the vertebroplasty group, their pain level at baseline was 19 and then within a day of the procedure it went to nine and then to five and then to four for long-term follow-up. But the control group, they of course had no pain relief after one day, but within six weeks the difference between the vertebroplasty

and the control groups were no longer significant. The Barthel index, which is a measure of function, showed similar findings, some pain relief within one day, but within six weeks and at six and 12 months, there was no difference between the two procedures.

Dr. Kallmes had a pilot trial, a sham controlled study, and I don't have slides of these. They were two randomized trials that have only been reported in the abstract form, so I don't have slides of those. But these are not published because we -- I will report them because they report randomized controlled evidence, but we only have minimal reporting of these findings.

So, Dr. Dohm did a study of 31 patients and among those patients, they were randomized to either immediate or delayed vertebroplasty, and among the patients who had the vertebroplasty first, they did have some pain relief from an average value of 9.4 to 3.3 after the procedure. And the medical therapy procedures did not have any relief after six weeks of conservative treatment but after their vertebroplasty they did have some improvement.

And then Dr. Kallmes did a small pilot

study, I hope I'm quoting the results of that pilot study correctly. This was a very small study with about five patients who had a sham-controlled procedure, and he might be able to describe the nature of the sham better. But among patients who were initially treated with the sham procedure, they had minimal relief after treatment, they crossed over to vertebroplasty, but then the results after vertebroplasty were similar. Both patients who initially underwent vertebroplasty and had minimal relief in symptoms, and crossed over to receive the sham procedure, and one of these patients reported complete relief after the sham procedure.

DR. MCNEIL: Dr. Mark, we're going to have to ask you to move along. You have two minutes.

DR. MARK: Okay, let me move quickly.

So, the results of this sham-controlled procedure raise issues about regression of the mean, placebo effect, the natural history of patients with this condition, and we found mostly the literature consisted of case series studies and there is a lack of randomized clinical trials in this field. So, the Blue Cross Blue Shield panel made a

decision on reviewing this evidence that it did not meet our particular criteria as an effective procedure based on the type of evidence that exists for this procedure so far.

I will try to spend, just quickly, the results are very similar for kyphoplasty patients in terms of the degree of pain relief that is achieved or that we see in the case series studies, so this is a quick view of the baseline versus the postoperative outcome for patients who receive kyphoplasty. And we see that there were seven case series studies, again, similar baseline pain scores, and a decrease in the VAS, visual analog scales, to one to two to three to four, whatever time period they were evaluated at. So again, mostly case series for kyphoplasty.

Several of these studies measured some functional scales and most of these differences, again, scales are complicated, don't try to absorb it, but there were statistically significant improvements in these domains of quality of life and function.

Cement leaks are much rarer, or the proportion that has cement leaks seems to be lower than for vertebroplasty. Malignancy, again,

similar findings.
We did find two nonrandomized comparative studies for kyphoplasty, one just published this month and the other only available in a foreign language publication for which we have I believe a reasonable translation, although I'm not sure. The difference in these observational studies was that in the Kasperk study, there were improvements in pain, whereas the control group does not change their pain scores. This is the most --
DR. MCNEIL: Dr. Mark, can you wrap up?
DR. MARK: Okay. And again, there were statistically significant improvements in the kyphoplasty group. The other German language publication shows similar findings, again, the contrast with the other observational studies in showing that the control group remained at the same pain level and the kyphoplasty group had improvement.
So, in sum, we have mostly case series that are the predominant evidence, we have a relatively small number of nonrandomized comparative studies, and some randomized controlled trials in abstract form only, and only

one sham-controlled but very small pilot study.
Thank you.
DR. MCNEIL: Thank you very much,
Dr. Mark. Dr. Lieberman.
DR. LIEBERMAN: Good morning. I would
like to thank the MCAC panel for inviting me to
present this morning. It's an honor to be here in
front of a distinguished and esteemed audience. I
would like to share with you some of the work that
we have been doing at the Cleveland Clinic and my
thoughts on vertebral augmentation as it relates
to vertebroplasty and kyphoplasty.
Just so that I'm complying with the
disclosure mechanism, I do have consulting
arrangements with each one of these listed
companies and I have received grant and research
support from each one of these companies.
I have had the privilege over the last
eight years of working with a spectacular team.
We have had a number of fellows, residents,
clinical staff and interesting individuals who
have worked with us on this project of vertebral
augmentation. As a summary, we have now had 12
peer reviewed publications in the literature, four
peer reviewed publications that are currently in

print, two that are in review, six letters and editorial comments, and 14 book chapters. I am absolutely indebted to these individuals for working above and beyond to try to do the science right.

You're going to hear an awful lot today about vertebral compression fractures. There's a lot that we do know, there's a lot we don't know, and the way I like to look at it is that the glass is three-quarters full or one-quarter empty, and I'd hate to pour out the three-quarters full glass because it's only one-quarter empty. Right now we know that two-thirds of these compression fractures are undetected and eventually become pain-free, one-third become chronic.

Why? We don't know, is it because of true pseudoarthrosis, because of altered biomechanics, because of osteomalacia, or some other unknown reason. But I can put forward to the panel that once that vertebral body collapses down, not a single one of those vertebral bodies ever regains its normal height, nor does the spine regain its normal sagittal alignment, unless of course we intervene.

Today in orthopedics, we would never

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even dream of leaving Granny in bed with a broken hip, we know the problems associated with that. We would never dream of leaving a wrist or an ankle fracture in a malunited, in a physiologically or biomechanically compromised situation. Well, why in the spine up to now have we been content to leave these vertebral bodies in a biomechanically and physiologically compromised position? Because we haven't had good treatments up to now. Surgical repair has been invasive and these patients are vulnerable; they have multiple comorbidities and surgery was a major undertaking with very poor outcomes.

I would like to spend a few minutes just talking about the biomechanics of the spine. Load transfer through the vertebral bodies is a very complex phenomenon. If you've got a normal vertebral body, the normal vertebral body on the left-hand side of the screen, if you load it, what you see is up to 80 percent of that load is transmitted through the center of that vertebral body, whereas but 20 percent of that load is transmitted through the compact cancellous shell surrounding the body. On the other hand, if you've got an osteoporotic bone and you load that

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bone, far less of that force can transmit through the bone and what happens is you transfer that force through that shell anteriorly and surrounding it to get down to that next vertebral body. So we see a force transmission issue through that vertebral body.

So the spine then becomes like the leaning tower of Pisa. If you've got a crack in the bone but you've got physiologically normal bone, that bone will heal. The crack may settle a little bit, but will not collapse down any further. If on the other hand you've gone an osteoporotic or an osteolytic process, the spine continues to collapse. The resulting bone edge is exaggerated and what you see is forced concentration at that index level. Well, the physiologic process doesn't get any better, but the leaning tower of Pisa keeps leaning, and what we now see is force transmission to the vertebral body or the bone below, to that vulnerable anterior cortex where because that center of the vertebral body above is deficient, you have more force concentration, so kyphosis begets further kyphosis.

Dr. Mark Kayanja is one of my fellows

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and is now on staff at the Cleveland Clinic. He just successfully defended his Ph.D. thesis, a culmination of four years of work looking at all of this information. And what we've done is look at the strain distribution above and below, look at prophylactically augmented vertebral bodies, look at the strain distribution after a fracture, look at the biomechanical effect of varying different numbers and different levels of cement augmentation, and he has created a very elegant model for looking at all of this, and he's come up with significant conclusions that really do mirror what we see clinically, and we were able to look at that in the lab and verify the effects of what we are doing with respect to our intervention. He found that the strain is concentrated at the apex of the curve, the forced concentration. The superior adjacent vertebra is at higher risk of subsequent fracture, which is exactly what we see clinically. Cement augmentation normalizes the load transmission through that vertebral body, so if you put a block of cement in the middle, you infiltrate that vertebral body, you are no longer transmitting the force through the cortex, you're normalizing the

load transfer. Increasing the centrum load transfer from augmentation reduces the stiffness. Now, there is a lot of confusion in the literature about these terms, stiffness and strength. The stiffness is a function of the surrounding bone so as you continue to load it beyond physiologic loads, that bone is still going to compress, but that cement block is going to transmit the force. And then while we increase the number of levels, the segmental stiffness and strength is maintained. That just proves that we are protecting the spine in the upright position. So all of these conclusions are now the basis of three papers, two of which are already in print, one is in press, and a multitude of papers that are currently being prepared or in review. So we've got this spectrum of vertebral augmentation from vertebroplasty to kyphoplasty, and we're looking at stabilization, reduction or formal reconstruction, and these treatment methods should not be considered mutually exclusive. These are tools in our toolbox that we should pull out of the toolbox and use at the most appropriate time in the treatment of these osteoporotic and osteolytic compression fractures.

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I would like to share with you now some of the work that we've been doing clinically at the Cleveland Clinic. I have now had the privilege of treating over 500 patients from April '99 to the present. Again, I'm indebted to my clinical staff for helping collect these data and being religious in the follow-up, driving the patients home and bringing them in for x-rays, and all sorts of things like that. We did a prospective cohort study, we planned things ahead of time, we used given objective validated outcome scores and did all the statistical analysis. Two of our papers have already been quoted; we've got a third paper which is now in review with Osteoporosis International.

What I'm going to show you is the work we've done analyzing 329 of these patients, of which about 70 percent were osteoporotic patients, 25 percent were myeloma patients, and we had a number of other malignancies. We have performed 917 kyphoplasties in these patients. If you look at the spectrum of vertebral bodies that I've treated, it goes all the way up and down the spine, but again as we know clinically, it's at the thoracolumbar junction that is the vulnerable

area. Our mean follow-up is about 55 weeks. The duration of symptoms in this group was anywhere from one week to five years. 93 percent of these patients underwent general anesthesia, seven percent underwent local anesthetic, and the average hospital stay in this group was 1.1 days. Now this is probably the most important slide. This is our whole group, N=329. We had full information on 72 percent but the analysis was done with an intent to treat. This is the SF-36, these are the combined scores on the SF-36 and the Oswestry disability. The white bars represent age-matched controls, so 70-year-old North Americans with no comorbidities. And you can see statistically significant improvement in bodily pain, in mental health, in the raw emotional score, the physical function score, the social functioning and vitality, as well as improvements in their Oswestry disability score. So I have no doubt that we are intervening and we are changing the natural history. We are showing that these patients are better, and you're going to hear a lot more about the natural history of compression fractures and the function of our patients as they get going.

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We broke it down. We have done this analysis a dozen ways.

So now we took minimum 12-month follow-up, 94 patients, again, complete information on these 94 patients in an intent to treat analysis, statistically significant improvement across bodily pain, physical function, role function, social functioning and vitality in that group.

We did one with a minimum 24-month follow-up, 48 patients. Again using an intent to treat analysis, looking at these, there is a statistically significant improvement in bodily pain, physical function, social function and vitality.

We move on to just the osteoporosis now, so we pulled out only the osteoporosis patients. 73 percent follow-up, similar trend, approaching age-matched control with statistically significant improvements pre and post-op.

We looked at our myeloma patients. 80 patients, 76 percent follow-up, very similar trends. We are making a difference in their pain, in their function, in their vitality in this compromised patient group.

And then here is the tumor group, and this would be one area that we're a little deficient. We only have 21 patients and a lot of these were palliative procedures. We don't have as good of follow-up, only 66 percent, and you can really only see three areas, physical function, social function and vitality, where we made or showed a statistically significant improvement. But overall, we have documented that these patients do well after this intervention.

The next issue is the vertebral height restoration. In one of our initial papers we showed that on average we were able to restore about 47 percent of the height lost. That was early on, that was before I really understood a lot of the subtleties of vertebral compression fractures.

We have now got a study that is still ongoing, although the initial results have been published in abstract form, 23 patients, single level osteoporotic vertebral compression fractures, new patients coming in, one level. We look at their pre-op x-rays, we compare them to the prone position x-rays after we inflate the balloon, after we deposit the cement, and then

post-op standing x-rays. And you can see that there is a significant improvement from post-op standing at 11 millimeters. There is a positional effect. When we put these patients on the table we do get a hyperlordotic moment, we do get some passive correction. When we place (inaudible) another four millimeters correction. When we deposit the cement, we are able to maintain it. They stand up on average with the measures that we get, 11 millimeters of height improvement.

The complications, and some of my papers were reported in the first talk, we had far less than ten percent cement extravasation, most of these through little fissures in the end plate or through the sidewall, and we've developed techniques to try to minimize that. In this group of patients we have had absolutely no neurologic complications. We've had no acute infections, but I do now have three patients that presented with latent infections, two of which were neurocompromised tumor patients, one of which was a very debilitated elderly woman. All of these presented more than six months out after the procedure.

The issue of subsequent remote and

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adjacent level fractures, that's a big issue and intuitively one would think if you're going to put a block of cement in the spine, you're going to change or alter the biomechanics, you're going to generate other fractures. Well, we set out to look at exactly what our incidence was. We looked at 115 patients and saw that in that 115 patients, 26 of them had 33 fractures, but we quickly realized this was a mixed bag. If we took out the primary osteoporotic patients, we saw that they only had an 11.25 percent rate of remote or adjacent level subsequent fracture. If you looked at the osteoporotics due to steroids, we saw that they had a 45 percent rate, two separate animals. So we've got to go back to that natural history; Lindsay reported a natural history of about 19 percent after your first compression fracture. So if we look at our osteoporotic group, we are about half of the natural history, with biomechanics, restoring the alignment of these patients. I still don't know why in our patients with secondary osteoporosis the rate is so high. I suspect it's because it's a younger population that is more active, you fix their one fracture and they go out and feel they can shovel

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snow again without taking care of the rest of their bone problems.

So we can go through the literature, and this literature is going to be harped on over and over again, but I just wanted to point out a couple things. Dr. Ledlie's paper, the visual analog score went from 8.6 to 1.4; height restoration, 66 percent to 85 percent.

In Dr. Phillips' paper he had visual analog scores rating pain relief from any type kyphotic correction of 14 percent, remote or adjacent level fracturing, nine percent, very consistent results.

This is a paper that was alluded to earlier by Majd, which has just recently been published in Spine Journal. 360 kyphoplasties on 222 patients. Mean height restoration, 50 percent, a 12 percent adjacent or remote level fracture, and median pain relief in about 90 percent of these patients. Again, large series, independent series, very consistent results.

This is the paper that we alluded to earlier, Komp's paper looking at 19 kyphoplasties versus 17 patients that were treated nonoperatively. The results, you can see the

kyphoplasty results out to 24 weeks. The visual analog scores improved considerably and considerably in the nonoperative group, the visual analog scores deteriorated. Oswestry Disability improved considerably, in the nonoperative group, deteriorated considerably. So they conclude that kyphoplasty is superior to nonoperative treatment for these vertebral compression fractures.

Here is a typical example. This was an 82-year-old male who presented to me in September of 2000 after cutting down trees in his back yard and moving around, he had typical back pain. You can see the 12-millimeter loss of height, kyphosis of 23 degrees, and you can now see after the vertebral augmentation, it restored the height to 29 millimeters, with kyphosis of 8 degrees. Now by no means is this perfect, but this is certainly better than when he started out.

If we go to the vertebroplasty literature, there are a lot of good papers out there that show, again, that vertebral augmentation does make a difference.

Here's a paper by Evans reporting on 488 patients. Duration of pain was two weeks to a year. They analyzed this with a telephone

interview at seven months and the pain score which was 8.9 before had improved to about 3.4. This is Grados's paper, and the reason I put this up is to show the difference, again, biomechanically in the spine. They reported a 52 percent remote and adjacent level fracture rate and I believe that that's because of the biomechanics and the realignment issues which would not be addressed with this technique. Here is Amar's paper looking at ambulation. Again, 51 percent of their patients improved. Quality of life, 74 percent improved. Here is Hiwatashi's paper looking at positional height restoration average of 2.2 millimeters, but when you look at 39 of their patients, it was greater than 3 millimeters, but there are difficulties in these measurements. And here's McKiernan et al's paper looking at their height restoration, and the important thing here is they report an 8.4 millimeter height restoration from positioning with a kyphosis restoration of about 10 degrees. So in good hands, qualified hands, you can get very, very good results with these vertebral augmentation techniques.

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So what are the indications? Well, just like anything in spine surgery, patient selection is absolutely critical. These procedures are indicated for patients with progressive painful osteoporotic or osteolytic vertebral wedge compression fractures secondary to osteoporosis primary, secondary osteoporosis, multiple myeloma, or lytic metastases. If you were listening closely you would have heard me say progressive first, and I think you can feel my bias towards biomechanics of the spine and spine deformity as opposed to pain. Granted, a lot of the pain will settle down. What are the contraindications? Well, as with any procedures, there are contraindications to the anesthetic; pregnancy; bleeding disorders; pain that's unrelated to the vertebral compression fracture, and we certainly do see that; various different fracture configurations; or it's technically not feasible. If you've got a complex fracture or fractured pedicles or facets. The issue of solid tumor still hasn't been resolved and you have to evacuate the solid tumors first. Allergies to the device or procedures, and patients less than 40

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years of age. I'm still troubled by the current trend of taking patients under 40 and being subject to this kind of treatment. Here is an example of a 40-year-old construction worker who fell off a scaffold. He walked into the emergency room with this burst fracture configuration, was seen by the physicians and told you need this operation. He went and had this operation and in the recovery room it was noted that he was neurologically compromised. CT scan noted that and he was immediately rushed back to the operating room for a decompression. What I would like to pay attention to and unfortunately (inaudible) anterior of that vertebral body, look at the quality of that bone. Here he is six months later after the decompression. That bone in front is completely melted away. That was normal healthy bone and I suspect what has happened is that we have created an environment of osteonecrosis. This gentleman has not been done any service by our profession.

So, why have there been no randomized controlled trials addressing vertebroplasty and kyphoplasty? Well, I have personally been

involved in five attempts and to sum it up, it's lack of collaboration. We haven't been able to get the various factions together to decide how to do the study or even participate in the study. There have been studies with design issues and IRB issues. One study that I was potentially involved with demanded a sham procedure, and my IRB would not let me do a sham procedure. There have been various funding issues. Some of us have tried to garner funding from various national and federal agencies and we have been told because this isn't (inaudible) or because there aren't other things or other conflicts, we do not get funded. But the last and probably the most important is the recruitment issue. We're dealing with an elderly population who don't have the time or the patience to come back for all these follow-ups and to fill out all this paper work.

So, what are the fundamental differences? I don't think there are significant differences in terms of the pain relief outcomes, but in terms of the biomechanics, the techniques, the skill sets required, these are two different procedures which are associated with different skill sets and different work. There are issues

of indications, issues of timing, the biomechanics, the number of levels, the void filler, and the physiology of the spine. I think that the risks are minimal in both these procedures, but we have to remember that the consequences may be substantial.
And with that, I would like to thank you very much.
DR. MCNEIL: Thank you very much, Dr. Lieberman. Why don't we have the panel for the next five minutes or so pose questions to Dr. Lieberman and/or Dr. Mark, and these would be questions for clarification. Are there any questions?
DR. JARVIK: I have one small comment and then one clarification I would like to ask for. You referred to the series of patients that you collected as a cohort and in general I think a cohort requires a control group, and I don't think you had a control group in this series of patients that you collected and reported on. It's a small point but I think an important point.
Just as a clarification, you mentioned that you analyzed this with intent to treat. What do you mean by that? That's usually, I think,

reserved for randomized trials.
DR. MARK: I am not a statistician. We do have statisticians at the Cleveland Clinic and as well as Johns Hopkins who have collaborated with this. I don't know the exact definition of a cohort. My interpretation of a cohort is a group of patients. This group of patients were prospectively defined and followed consistently, so that represents the cohort.
With respect to the control, these patients acted as their own control because we had a pre-op, pre-intervention baseline on each one of these patients. The analysis of intent to treat was done according to what the statisticians explained to me. As we did not have complete data on these patients, they were considered failures in that, and the statisticians have various methods to address the deficiencies in the data by various averages and what have you, so it was as if they did not do well within that cohort.
DR. MCNEIL: Yes, Dr. Weinstein.
DR. WEINSTEIN: Thanks for your presentations, a lot of work in a very hard area to do. Likewise, I think that intent to treat is probably a misuse there. I think intent to treat

means that you had some people that were intended to have nonoperative treatment or referred for some other treatment and they got that, versus those who were intended to have the intervention and got that. You can do an intent to treat analysis in an observational cohort but you need some comparative group. Did you have some patients who refused the procedure potentially who you followed? And second of all, what was the average age of your patients?

DR. LIEBERMAN: We didn't have a nonoperative group that we consistently followed. And again, I left that definition up to the statisticians to develop, who again, were independent and not involved in any of the collection of the data, and that was their description to me of how to present this information.

The average age of the entire group was 73 years of age, I believe, I can't remember that slide, I can pull it up and get you the exact number, but that was the whole entire group. In the myeloma group the average age was a little bit younger than that but the osteoporosis group was found out to about 77.

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DR. WEINSTEIN: And in patients who refused treatment, did you follow those?
DR. LIEBERMAN: I still follow them in my clinic. I must say, I don't recall very many patients that refused treatment. We do have a very large practice and it's standard that all patients are followed in combination with our own operative spine physicians and our osteoporosis specialists and myself, but we haven't been documenting their outcomes.
DR. MCNEIL: Dr. Ondra.
DR. ONDRA: Dr. Lieberman, you emphasized spinal alignment and biomechanics. There's also a lot of discussion both in your talk and the literature regarding people with height restoration to a more limited degree, local (inaudible) correction. Is there any data that discusses the actual sagittal realignment, the question of the levels adjacent to, regional as well as global sagittal alignment.
DR. LIEBERMAN: Yes, there is data but the data is not significant at this point. The error of measurement in three-foot scoli films was just too difficult. We tried to monitor that, we took hundreds of x-rays trying to find the T2

vertebral body versus the T12, and the quality of the x-rays and the angle of them just made it too difficult. We are now looking at using one of the quantitative deck scanners to look at overall alignment with that, but the problem is the patients are lying down to get that study so that doesn't help us at all either, it does help us with other fractures. It's a difficult area and we're looking for other ideas and if you guys have any suggestions as to how you think I can do this, I'm wide open, but it really is a tough thing.

DR. MCNEIL: Dr. Resnick.

DR. RESNICK: I would like to have some input from you guys as to what the differences were between the Diamond study and the Komp study, and I haven't had a chance to read the Komp study since it just came out, but it seems that the Diamond study seems to have a comparison looking at vertebroplasty and they didn't really notice much of a long-term effect. It was really more of a short-term effect because a control group which refused treatment got better after about six weeks or three months, whereas in the Komp study it didn't get better. Do you have any insight as to what the differences between those two control

groups are?
DR. LIEBERMAN: I don't know, either investigation studies or those two papers --
DR. MCNEIL: Dr. Mark, do you have a comment on that?
DR. MARK: Yeah. Let me try to remember some of the details. Now both of those studies, the difference between the Komp, the Komp study was a kyphoplasty study, an observational study to my recollections, and I might have to dig into the papers a little bit, but those patients had acute fractures. The Diamond study was a study of vertebroplasty, they also had acute fractures, and here's where the workup is kind of critical.
The Komp study had some issue and again, this is a translation from the German about active fractures, mobile fractures and some kind of imaging study that was done, so they may have a slightly different subgroup of acute fractures. And again, that is my memory, kind of gleaning what the differences between these two groups of acute patients, but there seemed to be some additional criteria in that German Komp study.
DR. MCNEIL: So this, I guess going

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back to I guess Dr. Jarvik's point, would talk to the issue of a control group, if we're not entirely clear how the subsets differ from one population to another.

DR. MARK: Yeah, I think one study uses slightly different criteria, and some of the studies focus on issues which you're an expert on about mobile fractures, and I imagine that means something that you can see move on a different dynamic mobility and imaging, and other studies seem to not address that as a criteria.

DR. MCNEIL: Dr. Fessler.

DR. R.G. FESSLER: I have a question for Dr. Mark. I'm confused about your conclusion and maybe you can clarify it for me. It seems to me that you reviewed prospective data but not randomized controlled data for several thousand patients, and then on the basis of one study made the conclusion that we're not able to assess the technology, primarily because those other studies are not controlled or randomized and the small study was. That seems to deny the sniff test, you know, the obvious benefits this has to the patients in the six months they're enduring severe pain, and if you look at the six-month or one-year

data, their pain seems to be normalized. It seems to me you're making a conclusion that we can't assess the technology after reviewing thousands of patients that it seems so effective on.

DR. MARK: I think our conclusion was based, not that the randomized controlled trials are definitive evidence of no benefit, but that the deficiencies of some case series studies, and again, sometimes they can be believed. But these patients, there is no control group and each patient is their own in-flight control in a case series study. But again, due to the selection criteria, the natural history of patients who have gone through the selection process may not be as well defined. But I think the issue is, do these case series kind of give us reliable evidence of efficacy without control groups? Yes, these patients did get better, but is that definitive evidence of efficacy in the group?

DR. MCNEIL: I'll just say a word here. I think what the Blue Cross groups do is pay special attention to the U.S. Preventive Services Task Force on Quality of Evidence, as well as to the Cochrane collaboration's criteria on quality of evidence. When both of those sets of criteria

are looked at, the randomized clinical trials obviously come out on top and case series, cohort studies where a definable controlled group can be easily identified fall down a little bit, and I think that's what Dr. Mark is saying.

I think we're probably going to have to move on, but I would just like to ask, as I took one quick look at the Cleveland Clinic experience, you say you had a very large osteoporotic clinic. Can you tell me how many acute fractures or how many patients who may be eligible for this procedure you would see there in a year?

DR. LIEBERMAN: I don't know the quantity of patients that come to our clinic, but we have 13 regional satellite hospitals, we've got six osteoporosis specialists and five nonoperative spine specialists, and they all see that volume of patients. I can tell you in the surgical group, we are doing probably close to 250 vertebral augmentations a year, and then we have our anesthesia group and our radiology group who are also doing vertebral augmentation, they probably add another 50, so we're talking about 300 patients a year that come through the Cleveland Clinic that get vertebral augmentation, but I

don't know the total population.
DR. MCNEIL: So, the question I was getting at, what fraction of that is the total and how do we know the characteristics of that related to the operation group?
DR. LIEBERMAN: I don't know the total. I know the symptomatic ones do get sent, there is a triage mechanism in place right now.
DR. MARK: There is one other study that we reviewed, a Kasper observational trial that actually looked at all the patients that they evaluated to enter the trial, that met their original entry criteria and eventually went on to be either eligible for the procedure or the observational arm, and they estimated with patients with fractures and pain and some disability, about 50 percent of those patients were deemed anatomically and through other kinds of indications to be eligible for either the observational trial or their intervention arm.
DR. MCNEIL: Great, thank you for that clarification. Why don't we move on to Alabama. Moving south, Dr. Saag and Dr. Bian, are you both speaking, or dividing it, or how is that working?
DR. SAAG: Thank you very much. Good

morning. It's a pleasure to be here. I am a rheumatologist and outcomes researcher, and also an osteoporosis specialist. I spend part of my time seeing patients with real-life fractures. It's a pleasure for me also to acknowledge the support that we received through the Agency for Health Care Policy and Research, the group that supports our Center for Education and Research on Therapeutics. We're one of seven centers funded by AHCPR to look at the safety and effectiveness of drugs, devices and biologics.

What I'm going to do is follow in the theme of the other speakers and comment briefly about the natural history of osteoporosis as it pertains to the vertebrae, talk a little bit more about some of the evidence and our interpretation of this, and particularly highlight where we see a major gap in the evidence, and then use that as a segue to talk about a study that we're doing right now in collaboration with Blue Cross and Blue Shield and with the FDA looking at vertebroplasty.

So I think to back our discussion up just a little bit and highlight the public health implications of vertebral compression fractures, we've heard already about some of the significant

consequences, the fact that many of these fractures are silent and do not present clinically as very important, and hesitation in terms of doing studies that appropriately identify and follow these people longitudinally. We've heard about height loss, and there are other consequences of vertebral compression fractures that listed here, which are indeed significant. The effects on daily living activities are truly important but it has also become realized that not only do we need to worry about morbidity of vertebral compression fractures, but there is also a higher risk of all-cause mortality, bearing in mind that oftentimes this is a harbinger for other comorbidities and a predictor of other disease states. This is some data that highlights the likelihood of developing a subsequent vertebral compression fracture based on results of the control arms of a number of randomized clinical trials looking at a variety of different osteoporotic therapies and also cohort analyses. And you can see that not only does vertebral compression fracture denote a much higher risk of having a subsequent event, a figure of 19 percent

or 20 percent was used earlier as the likelihood of fracture in the next year, but there's also a higher likelihood of having fractures at other sites, particularly in the hip, where we know there is a very substantial morbidity and higher mortality.

Well, this data is perhaps somewhat surprising. This is work by John Kanis and colleagues looking at a group of patients in Sweden, and showing that although we normally think about hip fractures as having the highest attributable mortality, it was actually vertebral compression fractures that seemed to look a little bit worse in following people longitudinally over time.

And lest we forget, there are other therapeutic approaches to osteoporosis, and that surgical approaches, while potentially effective in restoring height and relieving pain acutely, have some issues that we have been discussing today and will discuss further. There are a variety of medical therapies that have been tested in a variety of large randomized clinical trials and this is just a non-head-to-head comparison of the variety of therapeutic agents ranging from

Raloxifene to Teripartide, showing the level of relative risk reduction that can be achieved among women that have had at least one fracture, and this is looking at the development of the secondary event. And you can see a range in relative risk reduction ranging from 30 to 65 percent across studies that are really not comparable. We're looking at different inclusion criteria, even different definitions of how vertebral compression fractures are defined within these populations. And we get the sense that with some limitations on study design that there are a variety of therapeutic options that seem to be effective in attenuating the risk of subsequent fractures.

When we begin to hear today extensively about vertebroplasty and kyphoplasty, and we have seen some pictures already of what the procedure looks like, it's interesting that it has not been available for that long in the United States, and it is a procedure that has been around longer internationally.

This just provides a brief synopsis of kind of where we think we are with the literature at this point in time. It's also interesting to

note that this was an off-label use of bone cement until very recently when the FDA approved the use of KyphX for this indication. And we have seen data already from our first two speakers highlighting the short-term to moderate-term pain relief from the restoration of vertebral height that has been fairly consistently identified with both vertebroplasty and kyphoplasty. What we've also heard very loud and clear is that there is little evidence on long-term effectiveness and safety. It's also been highlighted in a recent editorial, there's been roughly 200 studies in this area, and we heard from our earlier speakers that there are only two RCTs that have been presented in abstract form. So mostly, we're focusing on observational data, we're looking at small observational studies that are occasionally comparative, but generally case series without comparison groups.

We've also heard today about the potential complications and adverse outcomes, the short-term ones being bone cement leakage, a potential during the actual procedure, rib fracture, and then the potential procedurally associated issues of other forms of embolic

applications.
Where our interest is focused and what
I will be discussing and Dr. Bian will be
highlighting in terms of the study that's
underway, are the long-term complications. What
about the increase risk of adjacent fractures or
secondary fractures after this procedure, as Dr.
Lieberman began to address as well. And then also
unknown is the subsequent risk of polymethyl
methacrylate toxicity, particularly in this body
location.
So, I wanted to just highlight a couple
of studies, and this is the Diamond study that has
already been mentioned. I won't spend much time
on this since it's been covered in some detail,
but what I think is very intriguing about this
study was the consistency with other earlier
studies without comparative groups of the
short-term improvement in symptomatic relief with
pain being reduced substantially within 24 hours.
However, as was highlighted at six weeks and then
again at six and 12 months, it was very similar
pain control.
As we look at the data, and Dr. McNeil
began to highlight this very issue, we see that

there are different grades of evidence, and most of what we're dealing with in this field to date, again because of the challenges in doing RCTs of surgical therapies, the difficulties in this procedure being relatively new, are mostly evidence in the III and IV and V class and not so much even well-designed cohort studies or RCTs that address this either with sham control or some other form of control.

And I want to just conclude my section of this before turning it over to Dr. Bian, just focusing on an issue that I think is a very relevant clinical question, that being the development of subsequent fractures after the procedure. And we have already heard about the first paper highlighting the relatively low risk, about 12.4 percent of new symptomatic fractures, which seems to be at least historically concordant, or maybe even less than what would be seen with the natural history of vertebral compression fractures. A study, though, looking at kyphoplasty, which was published in the Journal of Spine, showed a higher risk, a 26 percent risk of subsequent fractures, with the majority in both of these studies being fractures at adjacent

levels, and I believe the next speaker will comment on some of the biomechanical considerations that might predispose.

So what could these be? Well, vertebrae treated with polymethyl methacrylate are stiffer than fractured vertebrae, and in some of the biomechanical studies that have been done, the increased stiffness and load was transferred to the adjacent vertebrae and resulted in unfavorable biomechanics, and that's been shown also in some modeling studies where there was an elevated load to the adjacent levels.

I want to turn the program briefly over to Dr. John Bian, a health services researcher who is part of our Centers for Education and Research on Therapeutics, and John will highlight a study that is underway and really points out a couple of things, both where there is a lack of evidence and also what the methodological challenges are in doing research in this area. John.

DR. BIAN: Thank you so much. I'm glad to be here, even though I broke my arm in the car while coming here. This is an ongoing project; its aim is to investigate outcomes related to vertebroplasty. I would like to emphasize, this

is a collaborative effort of UAB, the FDA and our local Blue Cross Blue Shield of Alabama, and it has been an honor to be working with them. Although I am unable to present the results of our project because our study is still at the very preliminary stage, but we believe our project will provide, at least emphasize, highlight some of the gaps and limitations in study design used to assess outcome associated with vertebroplasty.

We have a couple objectives in our study. The primary objective is to assess risk for recurrence of vertebral compression fractures (VCF) for a period up to 24 months following a vertebroplasty. Secondary objectives include, one, to determine characteristics of patients receiving the procedure as well as the providers who perform the procedure, and to examine the association of procedural characteristics with short-term outcomes. Please keep in mind, the rest of the discussion will be centered around the primary objective.

Based on our careful literature review, we have hypothesized that people who have vertebroplasty are associated with a higher risk

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of recurrent fracture. This study will be a retrospective cohort study which uses a nonequivalent control group with a pre and post assessment. It is analysis of administrative data as well as medical record reviews.

We are going to use two major data sources. The first is the administrative data on Blue Cross Blue Shield, which covers approximately a 3 million population, most of them under the age of 65. The information we got from them, including the administrative claims files, which consists of inpatient-outpatient submitted claims, as well as pharmacy claims data. We also retrieved information on patient demographics and provider specialty. Because of the nature, the asymptomatic nature of VCF as well as the sensitivity and specificity, we were not able to always use the claims data to identify the procedure, so we also used a targeted medical review, which included the filings of the claim for the patients and we also looked at the records both prior to and at the time of vertebroplasty. The information we retrieved pertained to spinal treatment levels, surgical approaches, techniques, material used, as well as the perioperative

adverse events.
Because the panel has repeatedly asked questions about control comparison groups, I want to spend a little more time on this particular slide. We think it's very important to answer the question whether the vertebroplasty may lead to a potential bad outcome. It's very, we define two groups, we call it exposed group or the treatment group, and the unexposed group or comparison group. It's relatively straightforward to define treatment group, including the VCF patient who actually underwent vertebroplasty.
The challenge is how to construct a comparison group. There is no one way to do that, there are a number of ways to do it, and we spent a lot of time in putting together a relatively reasonable appropriate comparison group. So we have, we're looking for several potential candidates. One we call a concurrent, which we focus on VCF patients who did not receive vertebroplasty during the same time we defined the treatment group patient. Now there is limitation because really we do not know, even though we have observed information on the difference in characteristics of two groups, but still they are

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likely to have some unobserved characteristics that we would not be able to control. So we constructed another, a second potential comparison group which would look at the period before the window used to define the treatment group patient, focus on that window, again the patients in that antecedent group who did not receive a vertebroplasty.

We also looked at some other possibilities. For instance, we focused on the patient who had a severe osteoporotic fracture, who was in hospitalization, so we can look at subgroups in each of the two unexposed groups to see how they compare to the treatment group patient. I will be glad to answer more questions on this slide after I finish this talk.

Once we identified a study cohort, we defined the index event which signaled the prospective and retrospective follow-up of the patients. The index event for the treatment group was the first vertebroplasty, whereas the index event for the comparison group was the first VCF diagnosis.

There are a number of variables of interest. The key variable is outcome variable,

which is the VCF post-index event. There are other ways to measure outcomes. We can look at the frequency of recurrent VCF post-index events. We can also look at the time to a recurrent VCF post-index event. We could also potentially look at the rate of frequency on VCF at adjacent treatment level, so there are a couple options to look at. The key variable is self-explanatory compared to treatment versus comparison. There are other companion covariates which may include patient demographics, severity of osteoporosis, comorbidities, provider characteristics such as specialties, as well as the number of treatment levels.

Our statistical approach is relatively straightforward. We used matching to reduce the number of comparison patients because of the consideration of (inaudible). Once we determined who to study, we also used a multivariable case mix just based on observed characteristics, and I have discussed that in the previous slides.

Compared to what's in the literature, our study has a number of advantages. The key strength using the claims data analysis with the comparison group is that it can provide timely

information on effectiveness and the safety of vertebroplasty. And we use a comparison group which allows to us to control the baseline differences. Equally important, we focus on -- most other studies focus on pain relief and improvements in functional status. Our focus is on the recurrent VCFs, which have been speculated potentially as an adverse outcome of vertebroplasty.

Our study has some inherent limitations. By design, this study is subject to unobserved confounders. We also have concern about diagnostic detection bias, in other words, those patients who receive the vertebroplasty are more likely to have radiologic fallout because the nature of VCF, these patients are more likely to have a higher rate of recurrence of VCF. Our sample size is also an issue, but we are also looking at extending our time frame to include more patients or subjects in our study. The last one is the generalizability issues, because our data is from the state of Alabama and most are under the age of 65, but we are exploring the possibility of taking our study to a Medicare screening.

In summary, there is a large body of published evidence that seemingly supports the short-term pain relief associated with vertebroplasty. There is especially a risk of fracture, particularly at adjacent levels, so there is a need for controlled studies, RCTs addressing patient outcome, and good patient follow-up is the gold standard to more definitely address the effectiveness and safety questions associated with vertebroplasty. In conclusion, there is little consensus on what are the contraindications for vertebroplasty based on a very limited number of high quality scientific studies.

DR. MCNEIL: Thank you very much, Dr. Bian. I think what we'll do at this point is, since you proposed kind of an experimental approach for the analysis of this, and we will ask the panelists if they have any questions of you with regard to your approach. Yes, Dr. Fessler.

DR. RESNICK: Am I correct that there are no functional outcome measures here and the results simply represent a cohort with recurrence outcomes only?

DR. BIAN: That's correct.

DR. SAAG: There is no way to measure functional outcomes in an observational data study, but you can look at other forms of morbidity or mortality.

DR. MCNEIL: So you're basically using administrative data?

DR. SAAG: Well, administrative data with medical record review. Given the limited data that is available through a medical record review, our focus is on the radiographic picture.

DR. MCNEIL: Why don't we start with Dr. Weinstein, and spend a couple of minutes on this.

DR. WEINSTEIN: How many questions can we ask?

DR. MCNEIL: You can ask 1.2.

(Laughter.)

DR. WEINSTEIN: First of all, I was interested in the Swedish study because, you know, hip fracture, the mortality rate in the United States is about 30 percent and theirs were less than 20 percent, so I was curious about that population that shows comorbidities in these studies.

The issue of working with this database

with patients that are less than 65 where most of the studies have been done for people averaging in the 70s could be confounding and could lead to a huge problem. Dr. Bian also shared with us your concerns about what the covariates and variables are, and this leaves me with hundreds more questions than answers.

DR. MCNEIL: Okay. Dr. Jarvik? Why don't we just run along and --

DR. JARVIK: I pass.

DR. SAAG: Would you like us to address those questions?

DR. MCNEIL: Quickly, sure. It sounded like he had 500 of them.

DR. SAAG: I will try to remember them all, but if I skip a couple, John will remind me. The data is consistent with what I've seen reported previously with mortality after hip of about 20 percent, and I'm not sure where you're getting the 30 percent.

DR. WEINSTEIN: I think it's about 30 percent in the U.S.

DR. SAAG: So again, I can't comment more specifically about that study. And I think you've highlighted some concerns that we have

about the studies and I think John has nicely illustrated some of the limitations. The purpose of presenting this was not to even really provide answers, but more to highlight some of the questions, and what we tried to do is focus on one particular area where we think this procedure is of most concern long-term. We've seen data and will continue to have discussions today about the short-term effects of the procedure, both in terms of pain relief, the effects on height restoration over maybe the longer term, but the key area that we feel has really been understudied and the concern that exists for many of us in the medical community is how do the results of this procedure compare with the results of medical management two years or five years or ten years later, and that's the point of our study. We recognize that it is a demonstration study and the purpose of it is to develop methodologies that we can use with other larger data sets, recognizing that Blue Cross Blue Shield, as Dr. Bian suggested, has some limited generalizability.

DR. WEINSTEIN: But Alabama has a unique population itself, has a unique setting for health care and may not be as generalizable as

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you're alluding to. And just a simple question, what about the other results on these people?
DR. SAAG: Well, you're right that Alabama is a health care system that doesn't have an electronic medical record, and there might be a problem with that.
DR. MCNEIL: Maybe one more burning question.
DR. R.G. FESSLER: The burning question here is a question of relevance of the questions. Years ago before becoming a physician, I was an experimental psychologist, and we were always under the criticism for spending millions of dollars of the government's money to prove the obvious or the irrelevant, and I wonder if we're not doing the same thing here. As a clinician, I can tell you that if a patient comes in with eight out of ten pain and we can get them up in 20 minutes with two out of ten pain, it doesn't matter if we've got a five percent increased incidence of recurrent fracture two years down the road.
DR. MCNEIL: That is one of the value judgments we will come to at the end of the day. Mark.

DR. FENDRICK: I appreciate that medical therapy is in fact moving along, as well as interventional therapy, but I'd like you to comment on the need for further elucidation of what might happen in the patients who are channeled to vertebroplasty and the high likelihood that they will get other care interventions that may look like it's the vertebroplasty that's doing things but it could be better medical care, being followed, so on. So, you mentioned your potential covariates, and I think a major covariate that is not on your slide is the fact that people might get taken care of better given the fact that there's more aggressive care than because they've gotten the procedure done already.

DR. SAAG: That's a very interesting point, and if your point is a bias because of the hypothesis, I'm not sure it would make a significant difference if indeed one is there, and indeed the bias could be in the opposite direction.

DR. BIAN: We have some information on the pharmacy claims, so we know what kind of drugs they have been on, for how long, and those

probably control some of those biases.
DR. FENDRICK: It will control some but not all.
DR. MCNEIL: Okay, why don't we move on? Thank you very, very much. That's an interesting approach. And we move on before the break to Dr. Belkoff from Hopkins.
DR. BELKOFF: Thanks for inviting me. In the area of disclosure, I think it's fair to assume that I've done research for practically every orthopedic company in the United States that offers support for research. I have served as a consultant for various companies on typically a fee for service, providing information for disputes, things like that, but I'm not a paid consultant or on staff for any of these companies. As I understand it, I have been asked to just kind of peruse the literature and provide some information to the panel as to whether it's worth paying for these procedures, whether vertebroplasty should be reimbursed or whether kyphoplasty should be reimbursed. In the process of preparing for this presentation and for a book that we're working on, I reviewed 449 articles in the peer reviewed literature up to last month and

of those there is not one, you've heard, prospective randomized controlled study with long-term follow-up, okay?
Of that group of studies, there are perhaps five that I recommend reading and the rest of them not. Many of them are my own limitations because my stuff is basic science and biomechanics, so I can't talk about long-term follow-up and pain relief. And it gets frustrating because vertebroplasty has been around for over 20 years and it's obviously well overdue to have a definitive study, prospective, randomized, et cetera, so it gives you little option. If I had a disclosure to make about bias or about conflict of interest, it would be toward clinical outcome studies, and I would like to see one.
To open my talk, I want to give some background on osteoporotic compression fractures, I know you've been sitting here, and the problem with being the cleanup guy is that I have to maybe be repetitive with the previous speakers. When you look at an osteoporotic compression fracture, the biomechanics of it, the standard treatment primary indications are pain relief, and then

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address the issue of performing correction. This is kind of the way I see vertebroplasty. Where you've got an acute or a complex fracture, should you seek treatment? If you seek treatment, should it be conservative or should you go on to have some sort of interventional procedure, i.e., vertebroplasty? If the physician decides to go the route of vertebroplasty, you go to the next step and get some sort of kyphosis reduction to perform the correction, and if so, which method should you choose?

And what I'll do now, since we don't have any good literature really to support any of these decision trees, I will try to move around the edges and tell you what we do know and what we think is going on from, and maybe from all the case studies and so forth that are out there, get a perspective as to what might be going on.

So here's a normal vertebral body cross-section from an engineering point of view, which I am, by the way, I've got a Ph.D. in mechanical engineering. This here has basically the structure including the columns, and these columns bear the load of the axial spine. The

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column, the strength of these columns is a function of the spine, because if you notice, not only do you have less materials there, the materials are, the collagen and mineral content ration has been varied, more brittle, you have fewer, or more atrophied horizontal cross braces, which in fact makes these columns longer, and the buckling strength of a column is inversely proportional to the square of its length. So as your columns increase in length by a factor of two, you decrease the strength by a factor of four. That's why we have osteoporotic compression fractures.

Plus the fact that the modeling process (inaudible) creating concentrations in defective structures, you end up with vertebral body compression fractures. That's the kind of mechanical evidence we're looking at. So what happens with vertebroplasty, what causes the pain relief mechanism?

Well, it could be thermal. People hypothesize a thermal effect. Some of the materials are actually thermal, so they hypothesize they give off heat and the heat actually kills the nerves or cooks the nerves. It

could be that the cement that's used as a copolymer is cytotoxic, possibly so high in concentrations that it causes necrosis of the nerves as well. Or it could be simply a mechanical process that causes the healing. We looked at a fair amount (inaudible) back in '98, did a lot of studies, one of which was looking at measuring temperatures in vertebral bodies, and when we looked at the various bodies of cement and so forth and measured temperatures, and while it's theoretically possible that the heat could cause thermal necrosis, the fact of the matter is that we didn't take into consideration active heat transport due to blood perfusion and so forth, and what not. The fact that the temperatures in the central vertebral body were high enough to cause necrosis is of probably not so great significance anyway, because there would be no blood supply to it. The periphery around the vortex of the vertebral body, the periostomy has the majority of the nerves, and the temperatures were not high enough or were not likely to be high enough to cause necrosis of those nerves and give you pain relief. Similar studies have been done in goat

spines that might support our theories in live goats. The problem there is they happened to use smaller volumes of cement than they would use in humans, so it's kind of hard to make a comparison due to lack of data.

Cytotoxicity, we looked at the apoptotic effect of monomer on breast cancer cells, the apoptotic effect on these cells, MCS-7 cells, was very similar to epithelial cells, and we decided the literature that looked at this was not even finished, but the concentrations of monomer that caused apoptosis were orders of magnitude higher in time, duration and exposure to create apoptosis in breast cells than would be likely to have available in vivo after vertebroplasty. The highest concentrations we measured in vivo were basically .12 milligrams per milliliter, and that was a hip replacement operation and that only was, the exposure time was three minutes. And this would be expelled through the lungs within one circulation, one route of the circulation system of the blood, whereas to kill these cells in cell culture, we had to have five to ten milligrams per milliliter, so an order of magnitude higher, exposed for an hour to create

apoptosis. So it's very unlikely that the free monomer will filter around to cause neurotoxicity. So what is it most likely? It's probably a simple orthopedic situation of stabilizing the fracture, internal fixation, and preventing micromotion or motion of the periostea which aggravates the nerves, that's something that has happened.

Now how much vertebroplasty in general will restore the strength of the specimen, the vertebral body, how much of that restoration occurs kind of depends on the properties of the cement, how much cement you use, and the condition of the body, but it will generally happen if you stabilize the fracture, preventing micromotion. Once again, if you have your son break his arm or break his leg or his forearm, and getting a cast or splint, you're preventing micromotion. You guys are doing it internally with cement instead of putting the cast on the outside of the vertebral body.

Again, how much cement do you need? We've done some studies on a cadaver specimen, it's not a whole lot, about 30 percent will restore stiffness and prevent micromotion, and

that's basically about four to six milliliters of cement. There are reports in the literature anecdotally of course, that suggest that a volume as small as 1.2 milliliters of cement will give pain relief.

Does the cement respond to spine mechanics, kinetics, and put you at risk for future fracture? The data is very inconclusive. From what we have available from a mechanical point of view, it's unlikely that just putting cement in will cause a stress concentration and put you at risk for future fractures. The bottom line is these patients are osteoporotic, they are still osteoporotic after vertebroplasty and they will continue to be osteoporotic, and they are at higher risk for vertebral compression fractures, and that's in my opinion the most likely mechanism and unless we can show otherwise, that's my story.

If I look at formative correction, we did some work for Kyphon, and I think there is probably not much doubt that there is some height restored. We got about 3 millimeters of height restoration, which is consistent with Dr. Lieberman's paper with about 2.9 millimeters, that may change in his subsequent study, but on average

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that was kind of what we got. Whether the height was restored or not, I think is not the real issue, but let's talk about some other possible mechanisms other than height restoration. Some people reported that simple traction, bringing back the traction devices of the middle ages, I saw a cartoon once with that on it. Hyperextension, placing pillows under the patient to put them in hyperextension and try to get some height restoration or some kyphosis reduction, there was one report of that. Vertebroplasty itself was reported as getting a height restoration on the order of 2.5 millimeters which Hiwatashi reported in some journals, I'm not sure if it's significant or not, but it makes for some interesting reading. And then there's Paul Heini, with a thing called lordoplasty, where he basically cemented a medial cannula below the level of the fracture and then essentially pried the spine back into alignment and then did a standard vertebroplasty at the intervening level, and achieved some height correction or deformity correction that way. Again, there is one report

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in the literature about that. So, in summary, I wish I had more to tell you, but the bottom line is we don't even know what patients are really indicated for vertebroplasty, what constitutes an acute compression fracture versus a chronic compression fracture, how long is acute and how long is chronic, when do you transfer over. Which patients respond better to vertebroplasty or kyphoplasty, and which patients don't? All those sorts of things haven't been sorted out. There was that one study that was nonrandomized, although it was prospective, had a very limited number of patients and you can explain yourself. The Australian study that compared to the conservative group and as you know, they found that there was a short-term benefit of pain relief but long-term didn't seem to make a whole lot of difference. That stands to reason from my perspective. Again, my opinion is that once they have stabilized a fracture, provided internal fixation, allowed a stable environment for healing to occur and then as the fracture heals in six to ten weeks, you would not expect a huge difference in those two patient

groups. Now long-term, there might be a difference two or three years down the road, I don't know, because the information is not available.

If you decide to go to the next step and look at kyphosis or deformity correction, and there's a lot of theoretical benefits to this, if you can show that there is a decrease in premature sentiety, lung capacity, if there is a decrease in depression with patients who have a more normally aligned spine, if there is a decrease in secondary fractures or fibrosis, then those are all, I think, very good reasons to consider a kyphosis reduction procedure. But that has to be shown, and so far that information is not there.

And then once you decide that that is important, that creating an anatomically correct spine or anatomically aligned spine is important, then you decide which procedure do you want to pick from, and which of these is better than others. Is hyperextension with pillows better than kyphoplasty or lordoplasty, what are the benefits of all this, and again, the bottom line is the information is just not there.

So, that's kind of a whirlwind tour of

how I perceive the literature to date.
DR. MCNEIL: Thank you very much, Dr. Belkoff. Is there a question or two for him? I would like to just ask one question. You mentioned that you didn't know when fractures became chronic?
DR. BELKOFF: Correct. I read some study that divided the patients into two groups, one fracture is less than a year, one fracture is more than a year, and I would suggest that a fracture that is a year old is probably comminuted and not acute, but I'm not a physician and I think Dr. Weinstein might better address that question.
DR. MCNEIL: It might be useful for us to get a handle on exactly what chronic is, because we have to make a decision about our judgments on the basis of acute or subacute, versus chronic.
DR. PHURROUGH: We defined it as six months.
DR. R.G. FESSLER: For chronic or for subacute?
DR. MCNEIL: Chronic. Any questions for Dr. Belkoff?
DR. WEINSTEIN: I think the question

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about pain is interesting. We have heard some presentations talking about deformities, sagittal alignment, and these may be important, but pain is important. And you hypothesize that the cement may have some effect on the pain receptors. I think there are a lot of patients that get better and as Dr. Lieberman said, only about a third of these patients actually show up for treatment. So why aren't those patients painful, why are you hypothesizing this?

DR. BELKOFF: I missed the part about showing up.

DR. WEINSTEIN: There are patients that have vertebral fractures that don't have treatment, we know that. Dr. Lieberman suggested, and I think the Swedish study said there are fractures of the vertebrae that don't have mechanical interventions.

DR. BELKOFF: I think there is under recognition of fractures, I think this is similar to sacral fractures, where patients may have pain short term but don't seek attention. They may do guarding, say I felt something in my back, had pain for a few weeks, it went away, I didn't want to seek -- my grandfather was that way, he

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wouldn't go to a doctor to save his life and in fact he didn't, but he would not seek medical attention. And we saw from the Australian study, and you probably see a lot of in your own clinic, those who show up in your clinic who have compression fractures but have no pain associated with those fractures?

DR. WEINSTEIN: I usually don't see someone without pain. Do you have an information about how it affects the pain in a biomechanical study?

DR. BELKOFF: I didn't talk about -- when I said that there's certain models where it's being restored and so forth, these are just the studies, and there is no way I can measure pain, but I'm hypothesizing that restoring stability to the spine is probably a mechanism that causes the pain relief.

DR. WEINSTEIN: I was trying to make it clear for the listeners (inaudible).

DR. BELKOFF: It's very hard to do. That's why I'm so interested to see a clinical trial, for instance, looking at, documenting the amount of cement that was injected and seeing if there's a dose-response relationship, how much

cement do you need? Certainly the less you use, presumably you decrease the risk for subsequent injuries with lower applications. But right now, other than cadavers, and no cadaver needs to have to restore their strength, so I have no idea what that would be clinically in terms of pain relief and long-term outcomes and as you can tell from my demeanor, I'm a little frustrated with the lack of clinical information.

DR. MCNEIL: I think with that, that would be a good time to take a break. So, we actually have a 15-minute break but I would like to say one thing before the break. We have some scheduled public comments that start at 10:15 that go for an hour. We have 15 speakers, that means four minutes each, and I would like to be advocates of Doctors Mathis and McKiernan, the last two speakers. So if the first speakers eat up their time, they're not going to be happy, because they won't have any time, so we're really going to keep the public discussion session moving. Thank you.

(Recess.)

DR. MCNEIL: Thank you all for joining us. I realize I omitted something very important

for our speakers this morning, so I need to ask Doctors Mark, Lieberman, Saag, Bian, each one of them individually if they would come to that microphone and make any statements about conflicts of interest, and that would include consulting fees, stocks, stock options, or any other financial remuneration related to any of the products that would be under discussion for today's meeting, and I will obviously ask prospectively now each of the speakers to do that as well. So Dr. Mark, do you have any conflicts you would like to indicate?

DR. MARK: No.

DR. MCNEIL: Dr. Lieberman, are you here? Okay. Dr. Saag? Not here. Dr. Bian? Not here. Dr. Belkoff.

DR. BELKOFF: I received research funds from Stryker, Almedica, Zimmer, DePuy, I don't know, basically every orthopedic company that does research have assisted me at one point or another. Companies that are start-ups. I get royalties for vertebroplasty work, not from every one that has been made or sold, but there is still a royalty agreement with them. There are various company fee for service, and it's all related to Hopkins,

and I can tell you they are the most draconian when it comes to conflicts of interest, it clears their board, if they weren't happy with the information they had on file, it won't happen. As far as stocks, I think I have a little bit of Zimmer stock somewhere.

DR. MCNEIL: Thanks very much. Did Dr. Saag and Bian come back? We can ask them later then. With that, what I would like to do to make this session move along, I would like the next speaker always to sit in the speaker-ready chair so we can make sure everybody gets their fully allocated period of time. So we'll now hear from Greg Przbylski.

DR. PRZBYLSKI: I know it's a tough one. I'm Greg Przbylski. I'm a professor of neurosurgery at Seton Hall University and director of neurosurgery at the New Jersey Neuroscience Institute at JFK Medical Center in Edison, New Jersey. Today I'm speaking on behalf of the North American Spine Society as board member and co-chair of the counsel on socioeconomic affairs. I do not have any stock or formal financial interest in any orthopedic device company or receive financial support from any orthopedic

device company other than what may be in my retirement mutual funds. My transportation today was paid for by the North American Spine Society. I have served on advisory committees which evaluated these devices as well as the reimbursement committees of the North American Spine Society as well as the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. I have not been contacted by an orthopedic device company prior to this meeting to discuss anything that I'm presenting to you today.

NASS, who I'm speaking on behalf of, is a multidisciplinary nonprofit educational society representing physicians who are interested in spine care. There are more than 4,000 members, including physiatrists, radiologists, orthopedic surgeons and neurosurgeons. Clearly from the presentations this morning, we have heard that with an aging population, many of whom have osteoporosis, that development of vertebral body compression fractures is an important cause of pain and disability in the Medicare population. Many of these patients have transient pain, as has been pointed out, and usually respond

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to a period of time and use of opiates or other medications to resolve their pain. I think an important thing that has been brought out this morning that perhaps ought to be clarified is that nonoperative treatment does help a lot of these patients, and that the question that Dr. McNeil asked earlier, what is that denominator, what is the total population that we're looking at, versus the population that is going to be treated? Speaking on behalf of myself and my colleagues at our institution, I would estimate that fewer than ten percent of patients with vertebral body compression fractures actually undergo a subsequent treatment such as vertebroplasty or kyphoplasty. It is that small subset that really is not addressed in the Diamond study that has already been presented. That was a small study that really looked at a six-week time limit for post-treatment compared to a nonoperative treatment, and I would submit that many of those patients are getting better in that first six weeks. In our personal practice, we are typically not treating those patients until they have gotten into that subacute phase which I would estimate as being somewhere six weeks after they

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sustain the fracture, and if they continue to be symptomatic at that point, that's when we treat them.

For these patients, the North American Spine Society believes that both vertebroplasty and kyphoplasty offer early rapid post-operative pain relief and allow restoration of function, and reduction or elimination of the use of opiate medications or other medications for managing their pain. The results of both treatments we believe are similar and that although the data does suggest, as has been pointed out this morning, a smaller leak rate by kyphoplasty, the data does not support the fact that that is clinically relevant. As we've seen, the outcomes of morbidity and mortality are similar between the two procedures. Both treatments may in some patients restore in part vertebral body height and reduce angulation.

It is also estimated that the physician work with both procedures is similar and has recently been reviewed by relative value update committee, of which I represent the AA and NASS at, and the conclusions of the multidisciplinary relative value update committee was that the

physician work was similar between the two procedures.

The North American Spine Society requested a tracking code for the procedure of kyphoplasty, recognizing the fact that the literature, as we've heard this morning, is somewhat incomplete. We requested a tracking code to give additional time for additional literature to be developed, for additional comparisons to be played, to really determine whether there is a difference between kyphoplasty and vertebroplasty. Naturally, since both procedures are equally effective in the treatment of subacute vertebral body compression fractures that persist despite the duration of nonoperative treatment, we would support a coverage decision for both procedures in the subacute patient and recommend that facility and non-facility payments for both those procedures are based on the least expensive supply costs and that the determination of hospitalization is really based on not the procedure but the comorbidities of the patient to justify hospitalization.

I would like to thank the members of the MCAC for the opportunity to discuss both of

these procedures and share the viewpoints of the North American Spine Society about vertebroplasty and kyphoplasty.
DR. MCNEIL: Thank you very much.
Dr. Jensen.
DR. JENSEN: My name is Lee Jensen. I am the director of interventional radiology at the University of Virginia and have experience with vertebroplasty. I am speaking on behalf of several radiologic societies. I do not own any stock related to these devices. My transportation was paid for by the ASITN. I am currently not on any paying boards. I have been a (inaudible) for Carolax over a year ago, and have also been a consultant to the FDA orthopedics panel in the past.
On behalf of the combined membership of the American Society of Interventional and Therapeutic Radiology, the Society of Interventional Radiology and the Society of Interventional Radiology, I would like to thank the board for allowing us to comment on this exciting topic. It is the position of the society that vertebroplasty is a safe, efficacious and durable procedure in appropriate patients with

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systematic osteoporotic and neoplastic fractures that have failed medical therapy. This procedure if offered only when traditional medical therapy has not provided pain relief or pain is significantly altering the patient's life style. Since 1987, multiple case series and retrospective and prospective nonrandomized studies have shown statistically significant improvement in pain and physical activity, with response rates usually in the 80 to 95 percent range. These results have been confirmed in two prospective studies when compared to a control group, and a prospective randomized controlled study. In the Diamond study of 79 patients, 55 patients treated with vertebroplasty showed statistically significant improvement in pain and mobility compared to the nonrandomized control group of 24 patients.

Please keep in mind that all the vertebroplasty patients had an MR documentation of acute pressure fractures, but only 65 percent of the self-selected controls agreed to MR, making the etiology of pain unclear in 35 percent of this group. In this study 42 patients were hospitalized for pain control; those treated with

conservative therapy remained in the hospital on average six days, or 40 percent longer than the vertebroplasty group.

In a study published this year from Kodiyashi, et al., of 175 patients, 96.4 percent showed statistically significant improvement in pain at 24 hours after vertebroplasty, a pattern of pain relief not seen in natural history. The pain relief was complete in 44 patients. 94 of 115 immobilized patients, or 81.7 percent, were mobile by 24 hours after vertebroplasty.

Retrospective comparisons with a control group of 80 patients treated conservatively showed the average time of ambulation in that group was 24 days, over three weeks longer than the vertebroplasty group. In fact, seven patients never became ambulatory.

In a prospective randomized controlled trial done by Jobe, et al., 40 patients were randomized to vertebroplasty versus conservative therapy. All vertebroplasty patients showed statistically significant improvement in pain and activity levels and decreased medication use. The medical therapy group showed no change in these parameters at six weeks. 16 of the 19 patients

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were allowed to swap after six weeks. After receiving the vertebroplasty, they too showed statistically significant improvement in pain and mobility. Overall outcomes at one year using the SF-36 showed that both treated groups showed significant improvement in most of the subscales, demonstrating the durability of the procedure. The benefits of vertebroplasty far outweigh its risks when compared to conservative therapy and its success rate is consistently high, thus remaining cost effective and producing immediate improvement in patients' quality of life, primarily through the alleviation of pain and rapid return to ambulation, in addition to reducing the need for skilled care, expensive drugs or orthopedic devices which have not undergone randomized controlled prospective trials. A return to ambulation can reduce other adverse outcomes, including mortality in elderly patients confined to bed. Vertebroplasty is an effective and appropriate therapy for the treatment of vertebral compression fractures, and it is the recommendation of the societies that vertebroplasty be a covered service for the medical indications outlined in the published

data. Thank you for your attention.
DR. MCNEIL: Dr. Hirsch. Thank you.
DR. HIRSCH: Thank you. My name is Josh Hirsch, and I am an interventional radiologist at Massachusetts General Hospital, speaking on behalf of the ASITN, who funded my travel. As I was unaware that I would be addressing this auspicious committee today, I have not previously presented the following disclosure, and I apologize for not having provided it. I am a physician advisor to ArthroCare, Cardinal Health, and others in orthopedic technology, and in the past I have received honorarium checks for presentations.
Choosing a topic to present in four minutes is indeed a challenge. As was previously mentioned by Dr. Lieberman, I would like to emphasize that I do believe we are talking about tools in a toolbox. Our practice is (inaudible) unhappily or happily seeing less so than before, and that we routinely perform vertebroplasty and kyphoplasty, and do large volumes of both of these procedures.
Speaking colloquially, if we just review the extensive literature, we will forget

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the human aspect of this procedure, and it's my opinion that we cannot forget this human aspect. The remarkable impact that this has had on patients' lives has forced a change in my practice and the fact that I spend a great deal of my time doing these procedures.

I think there are a couple groups in society that demonstrate the success of this. A, patients who have had a fracture before, in my experience, almost never want to go to conservative therapy, they want to be treated almost immediately. Also, physicians that have been cited in papers that are experts in medical management routinely refer their patients to my practice for treatment with both vertebroplasty and kyphoplasty.

In the pursuit of science, it takes dedication to (inaudible) and Dr. Kallmes of course is the principal investigator of that trial, and both Dr. Kallmes and Dr. Jarvik (inaudible) this to be done. They cited as reasons the extensive literature supporting vertebroplasty and decided to proceed with vertebroplasty only, and the considerations of a sham trial. I think it should be pointed out that

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I was willing to challenge my own ethics to participate in a sham trial because of the crossover possibility. I believe there is extensive data to demonstrate that treating conservatively in patients that are bedridden, et cetera, is the same as no treatment at all. I myself have cited David Kallmes' abstract for the sham trial feasibility, and I think that it was never the purpose of that abstract to serve as a pivot point in discussions regarding the validity of vertebroplasty as a procedure, rather the inability to do the sham trial. I would point out that I think in Boston, it has become near the standard of care to perform one of these treatments for a compression fracture and I think it would be extremely difficult to actually randomize patients into this type of trial, and I think this reflects a national experience.

I guess in closing what I would like to do is invite members of the committee, there are many speakers here today, the human aspect of the story is real, to discuss the clinical impact on patients without thinking about that is really not right, and I invite you to come to my clinic or

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any of the physicians' clinics that are here and see whether or not the implied cohort is a real phenomenon. I thank you.

DR. MCNEIL: Thank you very much, Dr. Hirsch. Dr. McGraw.

DR. MCGRAW: I'm Dr. Kevin McGraw, an interventional radiologist in Columbus, Ohio. I need to disclose that I am a physician advisor for Cardinal Health and also ArthroCare Spine. I am representing today the Society of Interventional Radiology, who paid for my travel. I want to thank you very much for this opportunity to speak to you today about this very important topic. When considering treatment options for compression fractures, you must ask yourself and tell yourself that conservative therapy is not without risks. Patients are often placed on conservative therapy which includes bed rest, immobilization, or narcotic analgesics. During bed rest, virtually every organ is adversely affected, and that is going to be more pronounced in elderly patients. Bone density declines about two percent per week in patients who already suffer from osteoporosis, muscle strength declines about one to three percent per day or 10 to 15

percent per week. Nearly half of all strength is lost within the first three to four weeks of bed rest. Other complexes are also affected by immobilization, leading to contractions, which are more prone to develop in elderly patients. There's a lot of evidence to show that early immobilization after initial stabilization can lead to contracture formation.

Early mobilization also decreases the amount of pressure sores that can develop. There were studies done of pressure sore development in patients 70 years or older. Once a pressure sore or decubitus ulcer does develop, nursing calls increase by as much as 50 percent with a total treatment of one pressure sore being estimated to be 15,000 to $20,000.

In patients placed on bed rest, they have a risk of developing deep venous thrombosis 61 percent of the time. Pulmonary embolism can be sustained in up to 10 percent of the patients with fatal PE seen in 0.5 to 10 percent of patients.

If we subject a patient to six weeks of bed rest, they've lost 12 percent of their bone density, half of their muscle strength, they develop a decubitus ulcer, and they have a 10

percent chance of a PE. In a recent study by Brown, et al., in which almost 500 patients with compression fractures were followed, they received conservative therapy only, they were divided into three groups, low mobility, intermediate mobility and high mobility. It was found that patients with low and intermediate mobility, that these were independent predictors of poor outcomes at discharge, with poor outcomes being defined as a decline in activities of daily living, repeat hospitalization or death.

Since vertebroplasty results in early mobilization, the SIR, ASITN and ASNR believes that vertebroplasty is superior to conservative treatment. To summarize, vertebroplasty increases mobility, increased mobility decreases patient morbidity and mortalities. Thank you very much.

DR. MCNEIL: Thank you. Dr. Richard D. Fessler.

DR. R.D. FESSLER: Good morning. I am Richard D. Fessler, I am an associate professor of neurosurgery, radiology and neurology at Wayne State University School of Medicine in Detroit. I am speaking on behalf of the American Association of Neurological Surgeons and the Congress of

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Neurological Surgeons, who funded my travel here today. I do not have any financial disclosures to make with regard to any orthopedic company.

On behalf of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, I would like to thank you for allowing me to be here today to present our views regarding the use of vertebroplasty and kyphoplasty for the treatment of vertebral body compression fractures. The AANS and CNS consider vertebroplasty and kyphoplasty to be safe, effective and durable treatments for relief of pain due to osteoporotic or malignant compression fractures. When performed in accordance with published protocols, those procedures offer immediate pain relief for those patients who are not improving on conservative treatment. Vertebroplasty and kyphoplasty should be available to Medicare patients when deemed appropriate by their treating physicians.

When a patient does not improve within several weeks, we do not believe that the patient should be required to endure the pain and disability of an additional waiting period when we have procedures that can alleviate such suffering.

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For these patients, acute pain relief, acute quality of life and mobility should not be withheld by the benefit of vertebroplasty or kyphoplasty when indicated. Conservative treatment itself has been shown to pose significant risks. In the elderly population, immobilization, prolonged bed rest and narcotic pain medication has serious health consequences. The risks and benefits of vertebroplasty and kyphoplasty have been thoroughly examined over the last several years, and if these procedures are not available, other medical and surgical alternatives may have greater complications, especially in the elderly population. We believe that vertebroplasty and kyphoplasty should be reimbursed appropriately. Again, thank you for the opportunity to be here today. We have submitted our full opinions to the evaluative questions that the panel will be asking. These questions were carefully considered by a group of experts from the AANS and CNS joint section on spine and peripheral nerves, and reflect the clinical experience that we submit for your consideration. Thank you again.

DR. MCNEIL: Thank you, Dr. Fessler.
Dr. Gold.
DR. GOLD: I'm Deborah Gold, an associate professor of medical sociology at the department of psychology and psychology at Duke. I also serve on the board of directors for the National Osteoporosis Foundation and chair their education committee. For disclosures, I have a consulting relationship with Kyphon, who paid for my travel today.
I hope I'm speaking for all of the people who suffer from vertebral compression fractures in my talk today. It concerns me some that there is a misconception in this room that vertebral compression fractures automatically get better with a nonoperative treatment. That is not at all what the data show. After a vertebral compression fracture, patients show no significant improvement at six months in pain, function or disability. Two years after a fracture, patients still show no improvement in physical function, and they remain physically impaired five years after their last vertebral compression fracture. These last two studies used the SF-36 as their point of departure.

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Nonoperative care doesn't always prevent spinal deformity. We know that people who have a fracture are more likely to have a second fracture. In a study of over 200 patients, over 50 percent had fractures that were evident from the beginning and did not improve. 42 percent had fractures with continued wedging over six to 18 months, and worsening pain. Patients lost height in clinical trials for pharmaceutical agents, even when they were on those drug treatments.

To me, the most important thing for you to understand today is that the impact of vertebral compression fractures goes beyond the spine. When the body configuration changes, the pulmonary function is limited because the thoracic area is restricted. Too, the abdominal area is restricted and there is gastric distress, including loss of appetite due to that abdominal restriction. All kinds of compensatory mechanisms reduce gait velocity, affect balance, and create chronic fatigue. And despite the fact that many physicians have dismissed vertebral compression fractures as not worth paying attention to, there is increased mortality with these fractures, due to both fracture severity and hyperkyphosis.

And here are the people I'm talking for and telling you that these people did not have access to operative care, and you can see that fracture begat fracture, and the physical consequences are obvious.

Here we see that vertebral compression fractures deform, debilitate and disable this woman in nine years, when she went from being a person capable of independent ambulation and then was condemned to a walker.

We also know that in comparison, many people consider the hip fracture worse than vertebral compression fractures and yet when we look at the evidence, we see that the vertebral compression fracture, patients have lower SF-36 scores in several studies, and have excess mortality after vertebral fractures greater than after hip fractures. Here is a visual way of looking at that, age-matched control, hip fracture and spine fracture patients. The relative risk of death in 3.8 years is eight times that of the age-matched control in the vertebral compression fracture group.

The impact of vertebral deformity on quality of life is substantial, and if you look at

the quality of life as measured by the SF-36, the radiographic vertebral fractures, it was comparable to that of patients with COPD or cardiac disease. Patients with three or more radiographic fractures lost of quality of life comparable to patients with stroke or with cancer. Thank you very much.

DR. MCNEIL: Thank you very much, Dr. Gold. Dr. Cher.

DR. CHER: Good morning. My name is Daniel Cher. My financial interest is that I'm a Kyphon employee. I'm also a board certified internist who trained at Yale and Stanford Universities. I have ten years' experience in clinical research and seven years' experience in medical devices.

In the next few minutes you're going to hear about over two dozen studies on kyphoplasty. I would like to address two of these studies that have been referred to, these are concurrently controlled studies.

The first study involved 36 patients with osteoporosis who had a single acute fracture. The mean fracture age was 34 days, and again, this study enrolled patients in whom there was, quote,

functional instability of the vertebral body on functional study radiographs. Of patients who chose treatment, that is, they chose either balloon kyphoplasty or nonsurgical treatment, and at baseline the groups were very well matched. Most of the patients were women, mean age was in the eighth decade, height, weight and concomitant illness were very well matched.

In subjects treated with balloon kyphoplasty, pain as measured on a zero to ten point scale decreased from a mean of 5.4 to 2.0 at follow-up, a 63 percent decrease. In contrast, the nonsurgical group had hardly any pain reduction at all.

Similarly, back function as measured by the Oswestry Disability Index showed a very large 60-point decrease, and remember that the FDA's criteria for significant decrease is just 15 points. In contrast, the nonsurgical group had hardly any change at all.

In the balloon kyphoplasty group no patients, no patient had worsening of the index fracture, whereas nearly every patient in the nonsurgical group had progressive worsening of the index fracture.

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37 percent of subjects treated with balloon kyphoplasty experienced a new fracture in the six months on follow-up, compared to 65 percent of patients in the nonsurgical management group.

The second study enrolled 60 patients with osteoporosis. All subjects had chronic fractures, and by chronic I mean fractures aged greater than one year. 40 subjects underwent balloon kyphoplasty and 20 underwent nonsurgical management. As in the previous study, the patients were very well matched at baseline, including for sex, age, bone marrow density, number of prevalent fractures and concomitant illnesses.

On a 100-point pain scale, subjects receiving kyphoplasty had an 18-point increase, whereas those treated with nonsurgical management had hardly an increase. Activities of daily living were improved. Height, patients treated with balloon kyphoplasty had a 12 percent increase in vertebral body height whereas those treated with nonsurgical management had an 8.2 percent loss. In the balloon kyphoplasty group 12.5 percent experienced a new fracture and 30 percent

of the patients with nonsurgical management experienced a new fracture. Putting this study together with the previous study shows a statistically significant decrease in the rate of new fractures in patients treated with balloon kyphoplasty when compared to nonsurgical management. And not shown on this slide, there was also a statistically significant reduction in back pain visits to physicians over follow-up from nine visits on average in the nonsurgical group to three visits on average in the surgical group. In summary, these two studies provide strong evidence to support the effectiveness of balloon kyphoplasty versus nonsurgical management, and help to answer question number one that the panel has to consider with respect to the quality of the evidence. The gain in functional outcomes of these two studies are consistent with the entirety of the literature on kyphoplasty. In addition, they provide strong evidence suggesting that in comparison to nonsurgical management, kyphoplasty may reduce the rate of subsequent fractures. Thank you.

DR. MCNEIL: Thank you very much.

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Dr. Garfin.

DR. GARFIN: Hello. I am Steve Garfin, professor and chairman of the department of orthopedic surgery at the University of California, San Diego. I specialize in spine surgery. I am here speaking for kyphoplasty patients who have obtained benefit from this procedure. My expenses are being covered by Kyphon, for which I am a consultant. I and/or my department have received financial support from Kyphon, but also from the NIH, VA, and many companies, some related to today's topic. I am past president of the North American Spine Society and the Cervical Spine Research Society. I coordinated the American Academy of Orthopedic Surgeons spine educational courses for many nears. I am a deputy editor for Spine. I review articles for many orthopedic and spine care-related journals. I have previously been invited to participate on FDA panels for orthopedic devices including kyphoplasty. I have participated in and have co-authored papers on innumerable spine clinical trials. I was the first person separate from the inventor to do this procedure, which I have performed regularly with excellent results

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since 1999. Today I'm going to be presenting some information on a two-year multicenter prospective study looking at clinical outcomes following kyphoplasty. 19 centers were involved, 16 community, three university, all had an IRB approval, all patients signed informed consents. There were over 200 painful thoracic or lumbar fractures treated, 155 patients entered into the study. As one would expect, most were female and in the obvious Medicare range with an average age of 77. Fracture age, almost half or more had over two months of pain, all had failed nonoperative care. 100 patients were followed for two years. None of the patients had disabling back pain secondary to other conditions. The pain scores were very high preoperatively and fell dramatically immediately after kyphoplasty. Activities that we asked the patient to record were days at bed rest for a month and mean days of activity interfered with by pain. Rapidly following kyphoplasty, there was a significant return to their activity. We measured activities of daily living, and three points to look at here are bending,

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lifting and standing for an hour. Pretreatment, the patients had marked limitations in function and inability to perform functions. Immediately following treatment or at least when they were able to be recorded and tested, they had dramatic improvement in their ability to lift, bend and stand. We used SF-36 outcome data, we looked at physical domain and mental health domain. There was a dramatic improvement from pre to post treatment, 20 to 40 points is markedly statistically significant. Of importance to me, the one factor that didn't rise was the general health. We would not expect our heart, kidneys or other areas to improve, which adds, to me, validity to the entire study.

In summary, these patients were highly debilitated pre-treatment, much more than I anticipated from the literature or until the data was seen. There was to me a very compelling, convincing, rapid, marked, sustained improvement after undergoing kyphoplasty that lasted the two years of the study and there were no procedure-related adverse events. It is clearly relevant to Medicare and this aged population and throughout the community. This study, when

combined with all the available literature and scientific presentations that I have read and heard over the years, has convinced me that kyphoplasty is the appropriate and perhaps the conservative care option for many of these debilitated elderly individuals to get them and their families a healthier and happier quality of life.

Thank you for the opportunity to present my data and to participate in this new and unique format. If there are any questions that I as someone who has performed these procedures can address now or later, I will be glad to try.

DR. MCNEIL: Thank you very much, Dr. Garfin. Dr. Jolivette.

DR. JOLIVETTE: Good morning. My name is Dan Jolivette. I am the medical director at Kyphon and a board certified pediatrician. I have 35 years of clinical research experience, including ten years as investigator and 20 years as a researcher in industry. I am currently the medical director at Kyphon.

I'm here to discuss with you the balloon kyphoplasty literature and to respond to all five questions. There are approximately 120

articles in the English literature easily identified on MEDLINE using the search term kyphoplasty. 28 of these report clinical outcomes for at least ten patients. As a group, these studies include over 1,500 patients treated for pathologic vertebral body fractures due to osteoporosis or related to cancer. In addition to the concurrently controlled studies described by Dr. Cher earlier, there are 14 prospective and 12 retrospective studies. These studies measure a wide range of clinical inputs including pain, ambulation, three different validated stability measuring tools and the widely used SF-36 quality of life questionnaire in addition to height restoration and angular deformity. Positive outcomes were demonstrated following kyphoplasty in each of these outcome measures in virtually all studies in which they were measured.

Turning to safety, as part of our 510K submission for kyphoplasty, the FDA requested a safety comparison between balloon kyphoplasty and vertebroplasty. This analysis was last updated in July of 2004. When we performed a MEDLINE search for all English language articles on the terms kyphoplasty and vertebroplasty, we found 77

kyphoplasty articles and 363 vertebroplasty articles. We limited the analysis to only original articles including results for more than ten patients and where there was a clear indication of whether the complication was procedural or not. The resulting analysis included 18 studies of balloon kyphoplasty and 39 for vertebroplasty.

The overall procedure-related complication rate included both bone cement-related and non-bone cement-related complications. For kyphoplasty, the rate was 0.9 percent among 897 patients and for vertebroplasty it was 5.44 percent among 2,400 patients treated. This is a statistically significant difference between these two groups.

In summary, the clinical outcomes of over 1,500 patients followed after kyphoplasty are documented in 28 settings. The positive clinical effects and outcomes demonstrated in the two concurrently controlled studies were marked and underscored the results in the 26 separate case series that have also been done. In each study the safety profile of balloon kyphoplasty was excellent. These studies provide a body of data

warranting a positive response to each of the five questions with a high level of confidence. Thank you.
DR. MCNEIL: Thank you. Dr. Dohm.
DR. DOHM: Thank you, members of this committee, for allowing me to speak to you about the evidence and the effectiveness of kyphoplasty. I'm Michael Dohm, a practicing orthopedic surgeon in western Colorado, and I come before you to present a clinical application of the evidence and practice. I am not a paid consultant for Kyphon. I did have them cover my travel as I was diverted from San Diego today where a minimally invasive spine meeting was taking place, but I think it's important to be here.
As a member of the evidence-based practice committee for the American Academy of Orthopedic Surgeons, in 1996 I attended our first national meeting regarding outcomes in Cambridge, and I heard a presentation which I've made part of my practice. The presenter spoke about outcomes focusing, evaluating patient outcomes in terms of patient satisfaction, function, technique or technical aspects of the care, and costs. The speaker was Dr. James Weinstein, who is present

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here today. I have been involved in following patient outcomes in my practice since that time. Through the Western Slope Study Group, a quality improvement organization we developed following Dr. Robert Keller's Maine Medical Assessment Foundation, I currently follow up on a number of IRB-approved studies. I present the following outcomes because I am confident in their validity and in the process of their evaluation. There is substantial evidence in the literature regarding vertebroplasty and kyphoplasty, as you have heard today. This study of patients with pathologic fractures, about 264 levels, is representative of what I have seen in my own practice. 52 patients were evaluated with pain visual analog scale and Oswestry. Preoperative and postoperative measures show statistically significant improvement in scores. This reflects the results I have seen in my own office with kyphoplasty. Patients were also evaluated in terms of physical, social and emotional function utilizing the SF-36, as you have heard described today by Dr. Mark, Dr. Lieberman and others. These findings, again, show significant changes in

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patients undergoing kyphoplasty in terms of preoperative and postoperative findings. The challenge, then, is to refute this data or to produce a better study when discussing outcomes. If the fracture is an active lesion, one which has cellular activity and response to apoptotic change, then these patients benefit from this surgical intervention, I am confident that these studies show a net health benefit for these patients. This study has evaluated the results of 56 candidate patients with multiple myeloma and metastatic tumors. 22 patients had kyphoplasty without complications. There was pain relief in 84 percent of them within 24 hours, a significant decrease in pain medication utilization one month post-op, and no mortality. We have a cancer center in Grand Junction, and this again reflects what I see in my practice.

I perform ten to 14 surgical procedures a week, which include kyphoplasty and which represents fewer than ten percent of the patients that I evaluate and treat weekly. I have a general orthopedic practice and have been in the same place for 14 years. I have about 120 patient encounters a week. I treat patients

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conservatively, I manage their osteoporosis primarily, and I intervene when necessary. I believe I represent practicing physicians. I follow both operative and nonoperative patients, and I have performed kyphoplasty since 2001. I know the literature and am acutely aware of the evidence. I believe there is substantial evidence to support the utilization of kyphoplasty and have included this in my algorithm for treating vertebral compression fractures.

I am also a member of the Western Orthopedic Association, a board member. At a meeting in San Antonio three years ago, a 73-year-old orthopedist was recognized for never missing a meeting in 45 years. In his address he stated there were four significant advances in orthopedic surgery, anterior cervical fusion, total hip and knee replacement, and kyphoplasty. I concur. Nothing is more heart warming than hearing my patients' families, thank you for giving us back our mother, which is truly in reality my patients. Please help our patients and help to promote and advance best practice. I believe the evidence clearly supports the utilization of kyphoplasty in vertebral compression fractures, I believe that

both basic and clinical science support this, I believe this for my patients, and I believe this currently is best practice. Thank you.

DR. MCNEIL: Thank you, Dr. Dohm.

Dr. Marks.

DR. MARKS: I'm Dr. Michael Marks, an orthopedic spine surgeon from Norwalk, Connecticut, and am also the immediate past president of the Connecticut Orthopedic Society. I'm speaking today on behalf of myself and all the patients I treat in my community, the spine surgeons of Connecticut, and I also work as a consultant for Kyphon. I own no stock in Kyphon or any other orthopedic device company. I do act as a consultant to other device companies besides Kyphon. I paid for my own transportation to today's meeting.

I am a community-based orthopedic spine surgeon based in Norwalk Hospital, a 220-bed institution in Norwalk, Connecticut that sounds very similar to Grand Junction, Colorado. I have been performing kyphoplasty since June of 2001 and in those years have operated on more than 250 patients. I could present 250 anecdotal stories about my patients but we would probably be here

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all day, so instead I will address two specific topics.

The first topic comes from an article by Crandall that was published in Spine in 2004 that looked at acute spinal fractures and determined that fracture age does not affect the response to kyphoplasty. A summary of the study looked at 86 vertebral compression fractures in 47 patients. 40 fractures were less than ten weeks old and 46 were greater than four months, with a mean age of 74, obviously Medicare age. The pain scores decreased equally in both groups. Vertebral body height can be restored in both of these groups but it seems to be better obtained in the acute group. There were no complications related to the procedure and kyphosal correction could be achieved in both of these groups.

John Ledlie and his partner have produced a long-term follow-up of kyphoplasty, recently accepted for publication in the Spine Journal. They concluded that in two years patients demonstrated sustained benefit from kyphoplasty. In this study they investigated 117 patients with 151 osteoporotic fractures. 77 with two-year follow-up with the mean age, again, of

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77. They found complete pain relief in 65 percent of these patients acutely and 86 by three to six months. They found a definite decreased need for pain medication, greater than 10 percent height was restored in 90 percent of fractures, and this height restoration was maintained after two years, and they found no complications associated with it.

They also interestingly looked at ambulatory status, which I think is definitely one of the questions before us today with respect to mobility, and they found that the mobility to fully ambulate increased from 44 percent preoperatively to 85 percent at one week and 88 percent at two years.

To sum up, kyphoplasty in my practice works extremely well. I like Dr. Dohm have many, many patients and their families that come thank me for doing something to benefit their family member. It works well in both acute and chronic fractures to decrease pain and achieve some correction of vertebral body collapse, which obviously as an orthopedic surgeon is one of the tenets that I was taught early on. The beneficial results of kyphoplasty definitely improve

functional status on a long-term basis. I want to thank you for allowing me to present today.

DR. MCNEIL: Thank you very much, Dr. Marks. Dr. Talmadge.

DR. TALMADGE: Good morning. I am Karen Talmadge, and my financial interest is that I am the chief science officer for Kyphon. I want to summarize how the scientific literature answers the panel's questions on the use of kyphoplasty. As background, my Ph.D. came from the department of biochemistry and molecular biology, and I've conducted post-doctoral research in other labs and I have been involved in the science of kyphoplasty since 1992.

As you've heard from Dr. Gold, osteoporosis creates multiple health effects independent of pain. Patients with acute and painful vertebral fractures who are managed nonoperatively have poorer functional outcomes and remain impaired five years post diagnosis. As you've heard from Doctors Belkoff and Lieberman, the spinal deformity continues to get worse because each uncorrected compression fracture increases the risk of further fracture due to changes in the mechanics of the spine.

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As Dr. Jolivette has noted, there are now 28 balloon kyphoplasty studies involving 1,510 patients. Eight of these studies showed marked, sustained and significant improvement with chronic fractures. 14 show the same marked, sustained, consistent improvement with acute fractures. Due to the similarity of outcomes, I will not distinguish them. Taken together, these studies show significant improvements in every clinical end point from the earliest time, seven days, sustained out to two years. This sharply contrasts with the literature on outcomes of nonoperative care for patients with osteoporotic compression fractures. This literature provides strong evidence that balloon kyphoplasty is superior to nonoperative care in the short term. The two concurrently controlled studies discussed by Dr. Cher show that pain and function are improved after kyphoplasty while pain and function when managed nonoperatively drops, and the subsequent fracture rate is significantly lower with follow-up at six months. The other 25 studies show the same consistent benefits. I apologize but part of my slides don't appear to be showing up, so it

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confused me a little bit.
Similarly, ten studies provide strong evidence that the benefit is maintained long-term. The scientific data should provide this panel with a high confidence that the balloon kyphoplasty studies are valid. Among the three published trials are the two (inaudible) studies and the multicenter study described by Dr. Garfin. There are 13 additional single-center prospective studies. 27 studies address short-term outcome, ten address long-term, and the studies use seven different effectiveness measures.
The panel can have high confidence that the scientific data on short-term outcomes are valid. The two concurrently controlled studies show superiority and the remaining 25 studies are consistent, including 16 studies that measure ambulation and other functional status.
The panel can have the same high confidence in the scientific data of valid long-term, as the ten studies are consistent with each other and with the studies showing short-term benefits and (inaudible).
Based on this literature, the panel can have high confidence that kyphoplasty will

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positively affect ambulation, functional status and vertebral height short term as well as long term. The risk of significant adverse events in all of these studies is low, 0.5 percent. There are no studies addressing mortality, but there were no perioperative deaths in this clinical literature, and given that nonoperative care is associated with excess mortality and increased spine deformity, the panel can expect kyphoplasty will reduce mortality based on its safety and in conjunction with its ability to reduce (inaudible).

The key question for the panel is, will kyphoplasty produce a clinically meaningful net health benefit for patients with vertebral body compression fractures compared to nonoperative care? The clinical literature is clear. Patients treated nonoperatively get worse. Patients treated with kyphoplasty get better and stay better.

Doctors Dohm, Marks and Garfin have confirmed that these results can be generalized to the Medicare population and to community providers.

We appreciate the chance to provide an

overview of the kyphoplasty issues at this meeting. In further support, we submitted a more detailed analysis of the clinical research in writing, and we are pleased to answer any questions the panel may have about our verbal or written remarks.
DR. MCNEIL: Thank you very much.
Dr. Evans.
DR. EVANS: Hello. I'm Avery Evans, I'm an associate professor of radiology and neurosurgery at the University of Virginia. By way of disclosure, I paid for my own travel arrangements. I do receive royalties from Cook and Cardinal on various vertebroplasty products. I would like to start off by echoing Dr. Belkoff's comments and frustrations regarding the lack of prospective randomized controlled trials when it comes to vertebroplasty. I would like to note, though, that if you look in the literature, fewer than five percent of surgical procedures are ever subjected to that level of scrutiny.
Secondly, I would say it's not necessarily for lack of effort that there are no prospective randomized controlled trials. Over

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six years ago in Tampa, Florida, my research group designed a randomized controlled trial, and over the course of a year we tried to enroll patients who would be randomized to vertebroplasty or to conservative therapy. I interviewed over a hundred patients. I got two patients to say that they would be in the trial. One patient randomized to vertebroplasty, she went home that afternoon with no pain, fully ambulatory. The second patient randomized to medical therapy, she went to bed rest. She died three weeks later from complications related to bed rest. In the course of a year, interviewing a hundred patients, I could not get enough patients. And that was six years ago, I was the only patient in town who did vertebroplasty. These days if you try such a setting, patients will go across the street to somebody who will do it.

So, we couldn't do that study and we did this one instead. This is 72 patients that we evaluated prospectively with a validated questionnaire. 161 patients were interviewed and 72 consented to complete the study. Patients then completed a questionnaire and were reassessed at one week and six weeks after vertebroplasty, they

served as our controls. We measured differences in self-reported pain and distress after vertebroplasty, differences in pain and distress at the first and second follow-up intervals, and mean scores for 24 activities of daily living based on a one to five scale. The mean age of the patients was 74 years, 80 percent were female. None of these patients suffered symptomatic complications, nine percent had asymptomatic leakage of PMMA into adjacent soft tissues. Results, visual analog scale, the mean pain reported pre-vertebroplasty was 5.8, post-vertebroplasty was 3.5, and that was significant as you can see. The reduction persisted between the first and second follow-ups. The ability to perform all ADLs was increased without pain or with little pain for all activities except for doing gardening. The majority of this improvement was sustained and this data is seen graphically. You can see that pain on the visual analog scale averaged 5.8 and that decreased to 3.5, and that was a stable decrease between the first and second follow-ups. On the adjectival scale you see the same thing, all these results were statistically significant.

Activities of daily living, such things as wash dishes, drive an automobile, climb stairs, lift light objects, lift heavy objects, you can see the difference between the baseline, which was the unshaded area, and then the follow-up number, and every single activity increased significantly between the vertebroplasty and the first follow-up, with the exception of doing gardening. So in conclusion, in this prospective nonrandomized trial, vertebroplasty resulted in a substantial lasting reduction in pain and improvement to perform activities of daily living. Thank you.

DR. MCNEIL: Thank you very much.

Dr. Mathis.

DR. MATHIS: Hello, I'm John Mathis. Thank you for the opportunity to come. I would like to just first say I'm sorry that I only get four minutes, and Dr. McNeil, because I speak so slowly, I really think I should get ten. I have had the opportunity to work for Kyphon, Orthopeda, Stryker, all of which I had financial relationships with. Stryker paid for my travel. I represent the American Society of Spine Radiology, and I'm a professor and chairman of the

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department of radiology at Virginia College of Osteopathic Medicine in Blacksburg, Virginia. My research colleague, Steve Belkoff, we've written one book, have another book in print, 18 peer reviewed articles on vertebroplasty and 14 chapters. I was fortunate to work with Dr. Jensen, Dr. Kallmes, Dr. Evans, we introduced vertebroplasty in the United States, and I've been to the University of Maryland and Johns Hopkins. The things I want to talk to you about today are a little different from the other people because basically they stated very well the fact that we think this works. This is cement augmentation of bone fracture, it does appear to relieve pain in the appropriate set of patients. What I think is misstated here and I think is taken awry is, is there vertebroplasty and kyphoplasty. I don't even think kyphoplasty should be a term, I think it should be balloon-assisted vertebroplasty because both of them relieve pain based on the augmentation with cement. If you take out a gall bladder, it doesn't matter whether you take it out with a scalpel or with a laser; at the end of the day it's the gall bladder removal that makes the

difference. At the end of the day, it's the cementation of the bone, and that's the only way we've found so far to make the pain go away. And you hold a critical opportunity to do damage or to do positive to this whole process, and that is how you decide to reimburse for these procedures. Everyone here has spoken in favor of the fact that it seems that this relieves pain acutely. But if you decide to reimburse a dollar for the vertebroplasty and three dollars for what is called kyphoplasty or balloon-assisted vertebroplasty, as Dr. Belkoff has already said, there are multiple other ways to get height restoration, including vertebroplasty. But if you reimburse a dollar for vertebroplasty and three dollars for kyphoplasty, you will decide whether or not physicians use one or the other, because if it takes no more time and as past representatives have already said, there is no difference in the time to do the operation, then I won't do vertebroplasty anymore, I will do kyphoplasty, because in the same amount of time in my lab I can make three times as much money. You will decide where we go forward and whether or not we get the appropriate research that we need. And

right now, what we need is when do you use kyphoplasty or when do you use vertebroplasty, what patients are appropriate and what patients are not. Patients selection is key to this whole process. I thank you so much for being here, your involvement in this process is very, very important. Thank you.

DR. MCNEIL: Thank you, Dr. Mathis.

And finally, Dr. McKiernan.

DR. MCKIERNAN: I have no conflict of interest to disclose and my employer, Marshfield Clinic, paid for my transportation costs.

Today we have heard reports of dramatic pain relief following vertebral augmentation and seen images remarkable showing height restoration. As you conduct your inquiry into the quality of the scientific evidence pertaining to vertebroplasty and kyphoplasty, I ask you to consider the following three issues.

This is a standing lateral radiograph of a two-week-old osteoporotic vertebral compression fracture on the left slide, and moments later the same fracture in a supine position. This vertebra demonstrates dynamic mobility. This is a standing lateral radiograph

of a 14-month-old fracture and moments later the same fracture in the supine position. This vertebra defines that mobile fractures contain clefts. And finally, this vertebra plain will illustrate intravertebral void in the supine position. Clinical researchers must therefore account for that portion of the vertebral height restoration due to mobility before it can be ascribed to any other mechanism.

There are several methods for reporting vertebral height restoration. If a four-millimeter depression superior end plate is followed by a three-millimeter restoration, one could say that this three millimeters constituted a 75 percent vertebral height restoration. Using this same method, if a 25-millimeter depression superior end plate is followed by a five-millimeter elevation, compared to the greater elevation, this reporting method would assign a 20 percent height restoration. This reporting method termed percent of lost height restored with inflation numerically favors a small magnitude of height restoration in myelofractures. Unfortunately this reporting method is still commonly used.

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Finally, journal editors should require disclosure of anterior, middle and posterior vertebral heights when reporting height restoration because a vertebra may fail in the middle portion, and yet there may be no change in anterior height. Even with complete height restoration, there's been no net change in the anterior vertebral height or angle. Without knowledge of all vertebral heights, claims of vertebral height restoration solely based on middle height may not be clinically relevant. In the interest of time, I will skip this.

So, what is the quality of the scientific evidence addressed in our literature? I call your attention to this article, published last month in the Journal of Bone and Mineral Research. The authors conclude that kyphoplasty reduces pain and improves function, a conclusion I think is supported by facts with which I don't agree. Unfortunately, the authors report on only middle height and use the percent of lost height restored method that we previously discussed. In the discussion section, these authors perpetuate the misconception that mobility

is only transiently seen in only very recent vertebral compression fractures and cite less than four weeks old. The support for this is apparently found in references 35 and 36, which are from my group. We do not perform kyphoplasty, we perform vertebroplasty, and our average fracture age is four months. The notion of less than four-week-old fractures appears nowhere in the text of either of our articles.

Finally, towards the end of the discussion section, the authors provide five references to support their assertion that pain relief and vertebral height restoration are not correlated in the vertebroplasty literature. Both references 25 and 26 have no mention of vertebroplasty in their titled text. 34 is an ex vivo evaluation of the Kyphon balloon, and 39 is a study of epidural cement leak damage, and 40 is a review article that doesn't address the issue of pain reduction.

In summary, I ask the committee to consider the following points when deliberating the quality of the scientific evidence. Is the issue of dynamic mobility rigorously addressed? Is their accountability in vertebral morphometry?

Is there integrity in reporting? Are the results clinically relevant, is the procedure cost effective, is it science or is it marketing?
DR. MCNEIL: Thank you very much, Dr. McKiernan. Dr. Phurrough, did you want to make a comment?
DR. PHURROUGH: Yes. Just a comment, if I can get the microphone turned on. Thank you. I apologize for not mentioning this at the beginning of this session. The purpose of this panel is to address the evidence and to make recommendations to CMS as to the quality of the evidence, and this panel will not make recommendations as to whether we should or should not change any payment methodology, whether we should or should not make a coverage decision, whether vertebroplasty should be reimbursed at a higher level than kyphoplasty. None of these questions are pertinent for this particular panel. The panel is solely to answer the question, what's the quality of evidence and what does that evidence show.
So as we go throughout the day this afternoon and have discussions, we won't be addressing those questions. Even though those are

important questions to be addressed, those are in the purview only of CMS internally and we will look at the recommendations on the evidence that the panel makes today and use that as we make determinations in the future about coverage and payment. I just want to make sure that is clear, and I apologize for not making that clear earlier.

DR. MCNEIL: So we have three public speakers, Miss Haley, Domescus and Lavasseur. So, you will each have two-and-a-half minutes and maybe the first speaker is here, Mary Haley, and if Cindy Domescus could step up front so she will be ready.

MS. HALEY: I don't think Cindy is going to speak after all.

DR. MCNEIL: Okay.

MS. HALEY: I'm Mary Haley, and I'm the vice president of reimbursement for Kyphon. The questions today relate to both vertebroplasty and kyphoplasty in relation to conservative care. I have had the opportunity to work with the local Medicare directors throughout the past years for coverage and one of the opportunities I have had is to work with the medical directors, the staff members, clinicians

in establishing coverage policies at the local level, and there is one policy that was just published recently that I think brings some of these points home, both on conservative care, but more importantly, for the treatment of both vertebroplasty and kyphoplasty.

They recognized that delay of either treatment pending response to medical management may not be in the best interests of the patient, and in those instances where the provider feels it is medically reasonable and necessary to proceed to treatment, either procedure immediately or within a brief time after the vertebral fracture occurs, the medical record must clearly document the justification for the decision. This is one of the Medicare providers that covers 11 states that has acknowledged the fact that the medical management may not be in the best interest of the patient and that either procedure may actually be considered good care. Thank you.

DR. MCNEIL: Thank you very much. Is Brooke Lavasseur here? I guess everything has been said then. Okay, let's see. At this point, it's probably reasonable to break rather than to start asking questions of the presenters. Let's

do the following. We will reconvene at 12:30 and then from 12:30 until about one we will ask all of the speakers or some of the speakers, we'll ask them questions, really clarifying questions about their presentations. Subsequent to that, starting at one o'clock, the panel will largely deliberate internally, with maybe an occasional question from the audience, but I don't really expect a lot of interaction between us and you after one o'clock or shortly thereafter. So with that in mind then, I would encourage the panel over lunch to get the questions sharply in order, and we will start back at 12:30. Thank you.

(Luncheon recess.)

DR. MCNEIL: Welcome back everybody, I hope you had a relaxing lunch, a little bit less fast, a little bit slower than the morning. Before we reconvene, I'd like to ask Jonathan Weiner to introduce himself, he came in a little bit late.

DR. WEINER: Hi. I'm Jonathan Weiner, a professor at Johns Hopkins School of Public Health. Sorry I was late, but the dog didn't like my car. Anyway, I have no conflicts of interest.

DR. MCNEIL: Thanks, Jonathan. Here we

are. The idea now is for us to ask the panelists for clarification of any issues that we didn't have a chance to after their discussions and at the end of that time, we will start our deliberations. So, who would like to go first?

MR. QUEENAN: This question would be directed to any of the speakers who are practitioners who use both of the two procedures being discussed here, and the question is, when you have a particular patient, how is it that you decide which procedure to use?

DR. LIEBERMAN: I guess I'll lead off on that. I'm Isador Lieberman, from the Cleveland Clinic. There are a number of issues that go into the decision-making that I look at, the first of which is the chronicity of the fracture; the second of which is the duration; third, the underlying physiology or metabolic process, is it tumor or osteoporosis; the fourth of which is the patient itself, what does the patient really need for that?

If they've got just a super end plate fracture which hasn't really collapsed down and they're what I call an at-risk patient, and it's at the thoracolumbar junction, then some kind of

vertebral augmentation in the form of a vertebroplasty may be the appropriate way to go with it. If on the other hand it's a complex deformity, if it's a tumor patient with a big hole in there already, if I'm concerned about where that cement is going to flow and it's significantly collapsed, then I will want to reduce the anatomy, restore the alignment, create that cavity, and then fill that vertebral body up for biomechanical and deformity purposes.

DR. DOHM: I'm Mike Dohm again. In private practice in Colorado, for me it's evolved to the point where patients that can't undergo a general anesthetic for vertebroplasty, if they're medically unable to tolerate a procedure like that, I still don't feel comfortable doing kyphoplasty under just a local. At this point I have colleagues that do that all the time very successfully, it's just personal preference. But in decision and my operative approach, for those patients who have had multiple lesions in the past and it's just a palliative procedure, I feel much more comfortable having them go the vertebroplasty route. If they're a very active individual, if I think that I can intervene with reduction of

fracture and then fixation, that's when I perform a kyphoplasty.

DR. HIRSCH: Josh Hirsch, Boston. I came to kyphoplasty through vertebroplasty, I believe they are both equally effective, and I believe the complication is equal as to both procedures under anesthesia that is similar to conscious sedation, unless the anesthesiologist prefers them to undergo general anesthesia. To that end, I think that the times that I use kyphoplasty are when I really, really want to push for height restoration. I think that as previous speakers, when the patient is frail, et cetera, I lean much more towards vertebroplasty because I can get in there quicker.

DR. PHURROUGH: Before you leave, why would you want to do kyphoplasty when you really, really wanted to do height restoration? What leads you to want to do height restoration?

DR. HIRSCH: That's a very complex question that I try to answer all the time, and I'm still working on it in my head. The work by Dr. McKiernan and colleague Tom Budzuski stressed that with vertebroplasty, as has been my personal observation, you can achieve outstanding height

restoration with percutaneous vertebroplasty. To me the jury is still out on this issue of the value of sagittal realignment. However, I think that at times when there's a compelling argument for trying to reduce the kyphosis you may want to do it in that fashion.

I will further share with the group that in my experience, prior to doing kyphoplasties I had done many, many, many vertebroplasties, and the pain relief does allow patients to stand up straighter by itself, and I think that in and of itself precludes the kyphoplasty. As I said in my comments, vertebroplasty and kyphoplasty are sort of a continuum and both work spectacularly well in this population, so vertebroplasty would continue to be the primary treatment.

MS. STARMANN-HARRISON: What percentage of your patients receive each type of procedure?

DR. HIRSCH: I haven't regularly looked at that, it's a valid question. I would suspect it's two-thirds vertebroplasty and one-third kyphoplasty and its equivalents.

DR. MCNEIL: I'm sorry, Josh, could I just follow up? I'm still a little bit confused

about this height restoration. We learned this morning that it's three millimeters. So, of the third of your procedures where you do kyphoplasty instead of vertebroplasty, or whatever that number you just gave was, what proportion of that group is for height restoration and what are the indications for the others?

DR. HIRSCH: Say that one more time.

DR. MCNEIL: Well, I think you said a third of your patients have kyphoplasty; and then you also said that you push for kyphoplasty when you're looking for height restoration, and Steve asked you under what circumstances that was the case. Given that the height restoration is three millimeters or so, at least that's what we heard this morning, that would apply to one-third of the patients, and that one-third of the patients is a fraction, then, that really need that three millimeters. What do the others need?

DR. HIRSCH: That's fair. Of course it's fair. Let me be clear about this. There have been many recent advocators for treatment with kyphoplasty over the years. I believe vertebroplasty and kyphoplasty to be equally safe and effective treatments, particularly for pain.

In my practice, therefore, I will limit the patients that I believe will benefit from height restoration, and also using kyphoplasty for myeloma preferentially. I think that, again, the issue of height restoration is a complex one, and I don't mean to sound redundant on this point, in that the patient-physician interplay is extremely important, again, and Tom Budzuski has an article about this with vertebroplasty, I think showing 108 percent of post-treatment height versus preliminarily, meaning I think there's further stretching possible with vertebroplasty. I believe in terms of, however, the likelihood of a priori thinking you're going to achieve height restoration (inaudible) other products, at least in my mind afford a greater opportunity to achieve that height restoration. I believe in my practice, some of the early work was done using portable C arms, et cetera, but I really push these balloons and push the treatments. But I think this is something that should be studied further actually, because this issue of restoration is driving a lot of what we do.

DR. MCNEIL: Further questions?

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DR. ONDRA: I was wondering about alignment locally, regionally and globally, and that was my question earlier to Dr. Lieberman, does height restoration and the importance of that in any way translate to kyphosis restoration at a body level or a regional level? And before we say that this is it, I want somebody to make it clear to me what data do we have to show a benefit over vertebroplasty.

DR. HIRSCH: I would answer in two ways. One of the presenters, and I can't remember which, stressed very clearly the importance of how you measure height restoration, so I would encourage in future studies us to consider which, and that would be relevant to determine (inaudible) to the vertebral body.

To the other point, I think it is clear to me that any of the family of treatments for pain will correct what I think you're calling global kyphosis. In my opinion, patients who are hunched over are often in that position because they are in terrible pain. So relieving that pain will help, and I don't believe most people in this room, at least on this side, dispute any of these procedures do, and I think often will correct a

lot of the kyphosis, and I think that's valuable.
DR. RESNICK: Just to clarify an issue in my mind, we have as our charge to evaluate the literature as to whether or not either of or both of these treatments are effective for relieving pain following vertebral body fractures, and so the comparison theme is, I don't know why we're dwelling on it. And with the discussions of the subsequent vertebral fractures aside, it seems to me that in terms of patient outcomes and functional outcomes from either or both of these procedures, the question is whether you believe that either kyphoplasty or vertebroplasty have demonstrated adequate efficacy for relieving pain.
DR. HIRSCH: I'm delighted to retake my seat.
(Laughter.)
DR. MCNEIL: Well, one thing I would like to be particularly careful of, since we only have a limited number of minutes for questions, so that we don't need to hear the same answer from several people. That would not aid us in our deliberations.
DR. DOHM: If I can just speak to outcomes, as far as the outcomes question, you

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know, again, after Dr. Weinstein's discussion in the '90s and our societies looked at the outcomes and guidelines and the algorithms. In my practice, daily I look at Maine analog scales, I look at some form of measurement that most patients do. And what's unfortunate is I'm in private practice, and as a clinician-scientist, fewer than ten percent of us are clinician-scientists because with the demands of practice, it is so difficult to be able to report to you in some sort of a written format that shows how the patients do.

So I can look at other people's study and give you my anecdotes, but I would be more active if I had the opportunity, which is, you know, talking to these patients and looking at their pain scales and looking at their forms of reports, their activities of daily living.

I looked at 50 or 60 patients of mine that I presented to our community about two years ago, and we found that two to four percent of those were tumor, the rest were osteoporosis-related fractures, and in terms of activities of daily living, everyone did better, about 85 percent or better. If we asked someone

whether they wanted to have the procedure or not, again, it was about 85 percent that would have undergone the procedure again, and I know they had some statistically significant changes in their lives. I mean, that's what's obvious. The hard part is really measuring that in terms of getting something to compare it to. I, again, I follow these patients with nonoperative care and again, I operate on fewer than ten percent of the people that I see in my clinic. I think I've got like 50,000 patient hours in the last 12 years, and these patients do a lot better with that, and I can show them that, compared to nonoperative treatment.

DR. MCNEIL: Dr. Weinstein?

DR. WEINSTEIN: I guess I was interested in more of a process issue from the patient's perspective. Radiologists do patient care differently that orthopedic surgeons and neurosurgeons, and I guess one of the problems I see in the literature is this follow-up issue. And I'm wondering if there is a difference in process of care for patients based on discipline. We don't talk a lot about it but I think some of the literature is limited by the practice style,

the ability to collect data in different ways, because as you alluded to, it's not very easy to do. And I wonder what our obligation is to undertake these things, what our obligation is to see patients, evaluate them and then to collect information longitudinally in what way, given the different disciplines. I think the panel would like to understand how you do that.

DR. DOHM: I think this should be a standard of care and I'm just surprised and dumbfounded that this isn't a standard of care. I have to find IRB approval just like anyone involved in the study, and then many people don't participate because it's very onerous, so it's not a standard of care yet, but I hope to God it will be in the next ten years.

I know from being involved with the American College of Surgeons, the VA system, which is now 132 hospitals, are participating in the national surgical quality improvement project, they all have to do that to have the same electronic medical record. The American College of Surgeons has bought this and is trying to move it into the private sector but running into difficulties. CMS is trying to do the (inaudible)

project, that's another problem. We talked about our own registries, that's another problem. So none of us seem to collaborate well enough together to get preoperative data, hospital data and postoperative data, and that would be my hope, that we could all work together to do that.

DR. MCNEIL: Could I just clarify that? I didn't hear that as the question, I heard the question slightly differently. I thought I heard, why are there differences in practice style post whatever, and why aren't the individual specialties or physicians within those specialties responsible in the same fashion for collecting those data to make sure that what they say is really correct. Is that where you were going?

DR. WEINSTEIN: It's really, there is this issue of cross-disciplinary, and I think we would be at fault for not looking at that. And how do you get your patients in your clinical practice? A radiologist might get them by referral or a different way, and patients get lost in that process and therefore get lost in the collection of data, and then it's passed on to the studies that we've seen. I suppose if I heard Dr. Hirsch versus Dr. Lieberman, I would get a

different answer of how they get their patients and how they follow that patient.

DR. DOHM: In my community, I am a primary care doctor and I see that patient and family members and everyone else from the time they're born until they are dead, so I'm like a family doctor. The interventional radiologists see them for this period of time because of the referral for anesthesia or physical medicine rehabilitation.

DR. MCNEIL: Did you have a different answer?

DR. MCGRAW: Hi, I'm Dr. Kevin McGraw, an interventional radiologist. As an interventional radiologist, we actually have a very busy clinical practice. Maybe ten years ago the interventional radiologists relied on referrals. Now there is a paradigm shift within our specialty to assume more of a clinical responsibility to see patients in an office setting, admit patients post procedurally, see them in follow-up and provide continued longitudinal care. This is something we do routinely in our practice, and I think I speak for the majority of interventional radiologists and

interventional therapy radiologists that we now have a dedication to clinical patient care and seeing them in an office setting and providing appropriate treatment. All of our patients for vertebral augmentation are followed out to one year post procedurally, and I think the majority of my colleagues also provide the appropriate care with that.

That's why, you know, I had a published study with 100 patients with a mean follow-up of 22 months that was part of the, it's in your literature packet. So I think there is a misconception about radiologists and interventional radiologists, and intervention neuroradiologists, because we do provide clinical care.

DR. MCNEIL: Dr. Resnick?

DR. RESNICK: I just have a question for Dr. Mark about the technology assessment. In every paper that has been reviewed, there has been a demonstrated positive effect of these augmentation procedures, and that's been consistent from European studies, radiology studies, orthopedic studies, et cetera. There have been today referenced three comparative

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studies with subsequent control, and really the only difference in the outcomes of those comparative studies was the duration of the effect. The Diamond study had a very short duration effect and the other two studies had much longer duration of effect.

Your conclusion at the end of your presentation is that the, you recommended that the procedure not be approved or not be supported through Blue Cross Blue Shield, and I was wondering how you came to that conclusion after reviewing the literature that we all heard.

DR. MARK: First of all, the review has been updated since, about eight months ago, and the additions to the literature are two-thirds of the observational studies. At the time of our initial review, there was only the one observational comparative study by Diamond which as you recall, showed a difference in the 24-hour outcome which dissipated as the control group got better at six weeks.

And I think part of the difficulty in one issue that has been, I wish maybe there was another person here to try to elucidate that issue, is the natural history of the types of

patients that are being selected to have that procedure, and that in our review and some of the background material that you have in the report and the additional background piece I did, I kind of tried to make an attempt to elucidate what the natural history of this condition is and kind of concluded that what I had at hand was of limited utility because of issues of comparability. These patients that had a workup, there were differences in clinical presentation and then they had been selected.

So the caution, I guess, and I think our own medical panel which reviewed this evidence, I think did weigh rather impressive changes in visual analog scales and other functions against the type of study design that was done. So the question was, can the magnitude of the effects be explained by all the other problems that we know about observational studies, such as just placebo effect. There is an issue with natural history, there's a waxing and waning and regression to the mean effect of when patients present to care. And I think the important issue was weighing, exactly weighing those two issues, and I think the decision kind of came down to, do

we really have a good handle on how these patients are selected out of all the patients that have back pain and, you know, basically that issue. We don't really have a good handle to fully understand the natural history of the patients out of all the patients that have back pain, so it was a weighing of that.

DR. MCNEIL: Dr. Fendrick, did you have a question?

DR. FENDRICK: I think my question would be a higher level question, a 30,000-foot question to the practitioners and the supporters of this procedure. And I'm impressed by your dedication and compassion to the patients as I listen to the human side of this story. But having personally been embroiled in several interventions over the years that were accepted in observational studies without adequate controls, that yet, a few of those studies when RCTs eventually were done were found to not be there. I'm going to ask you basically, what kind of assurances can you give me or us that vertebral augmentation, given the lack of adequate controlled trials that you all admit to, will not turn out to be like internal mammary ligation, the

gastric bubble, endoscopic meniscal repair for the knee, and I could keep going on and on and on, but examples where medical interventions have been widespread adopted and they've actually been shown to have limited benefit and in rare circumstances fatal, actually hurt patients in the end. And to specifically address this failure to be able to do the randomized trial, I think I need to hear a little bit more about the details of the practicality of not giving us the evidence that some of us might need to make an easier decision.

DR. DOHM: I asked my patients that. I said, look, I'm going to go meet with these guys in the next month or so, or whatever, and I said what should I say to the people that are listening, for you the patient. I had a lady a couple weeks ago where her daughter says, you know, this is just amazingly different now in looking at my mother, the way she is now, getting out, doing things, compared to how it was before. And I hate the anecdotals, I really do.

DR. FENDRICK: And I'll tell you, if there were studies 40 years ago that looked at women who underwent perithyroidectomy for asymptomatic hypercalcemia, so they were

asymptomatic but they were saying they felt better and they would have it done again. So we all, many of us believe in the strength of the placebo effect, and I hope that you and the others -- you're persuasive to an extent, but you can't tell me that your great hands, Michael Dohm, are enough to make those patients perfect.

DR. DOHM: No. I'm just a person, I recommend Joe America I think, or Josephine America, and the thing is, when I see these patients, I think I have a pretty cultured mind for trying to look at it in an evidence-based fashion and with a good scaffolding. And I've given my best efforts to have an infrastructure of data collection, and I think I do this better than most private practices in the country, and I do have some supportive data.

DR. FENDRICK: But it may not be good enough for me.

DR. DOHM: Well, no, I understand that. But I'm saying also, I've evolved. So now I treat these patients, I also do injections of the spine, I also do rhizolysis to try to cure the pain. So I have a pretty good idea of classification categorization, and these patients do better, and

I think the data does support that. Does it need more? We're just in the beginning.
DR. MCNEIL: Why don't we hear from the academic center? Cleveland does lots of studies.
DR. LIEBERMAN: Lots of studies, and I think we were also involved with the arthroscopic meniscal knee repair study and my recollection is that it is a good operation and it does work.
SPEAKER: Knee repair?
DR. LIEBERMAN: Knee repair, meniscal repair. We've got to define what we're looking at. You've got a room full of dedicated practitioners, as you pointed out, and the one thing that's stark to me is just the volume of patients that have been treated. These patients would not be coming back to us if this was a bad operation, if patients were dying, if they weren't doing any better. The biggest referral source for me is my previous patients. I don't know --
DR. FENDRICK: Didn't the same thing happen with hormone replacement therapy? I want you to raise the bar for me, please.
DR. LIEBERMAN: I showed you the results on 329 patients that were analyzed over and over again in as specific as we possibly can

get, and to discount that evidence because it's not randomized controlled trials, I mean, look, we still have very good objective prospective evidence with pre-intervention baseline information, post-intervention information, that showed statistically significant improvements that were carried out to one year and to two years. We can see that with both vertebroplasty and with kyphoplasty in multiple other ventures that we're doing at this moment. So we are dealing with a much larger picture, you can't discount it. What you're effectively saying is, the glass is three-quarters full, let's empty the glass.

DR. FENDRICK: Let's agree on that. I like the three-quarters full, don't get me wrong. Tell me a little more about your experience of this impossibility of doing the adequate control.

DR. LIEBERMAN: There have been a number of issues, and over lunch a number of us got together and we said let's go ahead and do it. But first and foremost right now is going to be the patients. These patients are going to come and they're coming for specific treatment. They come to me because they know that I was involved in developing the kyphoplasty and that's what I do

and that's what they want. When I tell them that they're going to be randomized, they're going to have to do this paper work, they walk out the door, they walk down the street and they find someone in private practice who's not going to put them through all that. That's what's happening, that's what's unfortunate. We should have thought about this seven years ago when we started out before getting to this point.

Now having gone through this, maybe the next generation of medicine will be able to do things a little more specific than we have.

DR. FENDRICK: Last comment. One of the greatest surgeons that I know of in the U.S., at least in this past generation was Maury Glesick of the Cleveland Clinic, who actually invented, or whatever term you use, use of the internal mammary artery for CABG, and was willing, after hundreds and hundreds and thousands of patients at the Cleveland Clinic, to do a randomized trial of CABG versus medical therapy, so it's not impossible.

DR. LIEBERMAN: I am very willing to do that, and I have tried five times, and each time we've come up with other issues where the trial just hasn't gone. Now, we've got a number of

individuals here, we all spoke over lunch and said let's do it, let's get together, we'll see what happens. I'm willing to randomize my patients. I do both procedures, I've got set criteria. I'm willing to take off my emotional hat because of what I believe is the right thing, to answer this scientific question that we haven't seen in seven years. And members of this panel, many of whom work with me, know that we tried this as desperately as possible. But the fact remains, there is still hundreds of thousands of patients that are coming to us demanding this treatment.

DR. MCNEIL: I'd like to make sure that we don't get stuck on this one particular component. Do you have something additional to add?

DR. EVANS: Just briefly. Avery Evans from the University of Virginia. Six years ago I tried to do that trial and I will just tell you, it is almost impossible to do. I would say at this point in time, it probably is impossible to do. Now other people can talk about that, it's unfortunate, it would be great if we could collect that data. I'll be frank with you. I think the only way we could possibly collect that data would

be for this panel to say that vertebroplasty and kyphoplasty will no longer be paid for, and basically force patients to enroll in these trials. It is a grim fact that you're facing, because I can tell you that I have been there, I have tried for years to get patients to agree to be randomized to no therapy, and they won't do it, especially when they can walk down the street and find somebody who's willing to do it. I agree with you, we want to do it, tried to do it, and it is nearly impossible.

DR. ONDRA: I have a question that may help get us out of this randomized controlled corner. Have you looked at ways other than randomized controlled trials to get at Class I evidence? RCTs are not the only route to Class I evidence specifically, and it is not necessarily appropriate for all types of procedures. Is there any thought into looking at something other than an RCT that will give you Class I evidence?

DR. BURKE: Like what?

DR. ONDRA: In a large population specifically, it is not necessary to do a randomized control trial. At the University of Minnesota and University of California, San

Francisco, there are statisticians that evaluate when you have a large enough number. There is a huge population of patients, this is a fairly common problem, and you could in all likelihood get to a large enough number that the absolute necessity and value of an RCT is no longer the only way to go about it.

DR. BURKE: You still need people who aren't treated for control for unmeasured covariates, so even in a large population if you're not measuring the unmeasured covariates, you're still in a box.

DR. ONDRA: But if you build in a study for this, because the point is, you can't get patients to do a randomized study, and I think that issue persists until you force people to do it.

DR. MCNEIL: I see several people on the floor, but Dr. Jarvik, did you have a comment specifically related to this?

DR. JARVIK: This is specifically related to the issue of the feasibility of doing a randomized controlled trial. As many of you know, Dave and I have been working on a randomized controlled trial for vertebroplasty here in this

country and have had tremendous difficulty in recruiting patients for the trial for a variety of reasons. One of them is just the issue that Avery Evans raised, that it's paid for in this country, so people have an alternative to entering into the trial, to get something for which there isn't excellent evidence that it works. However, there are other countries where they have done this work. In fact in Australia, there is an ongoing controlled trial for vertebroplasty versus a controlled intervention and they have been much more successful than we have in recruiting patients. I think as of a month or so ago, they actually enrolled over a dozen patients in a relatively short period of time. And so, I think it may be potentially feasible to do, but maybe the climate has to change.

DR. MCNEIL: I think I missed a hand.

Dr. Fessler, did you have a comment?

DR. R.G. FESSLER: It's specifically relevant to these issues, and that is, we've already said here repeated times that we lack the controlled studies and that we can't recruit patients. The other major issue that nobody said, these are tremendously expensive studies to do,

and nobody is stepping up to the plate to pay for them. So given those variables, and I'll direct this to Dr. Belkoff or Dr. Marks, because you guys were the most vocal against the available data, what data can we accept if we can't do a controlled randomized study, and particularly with the questionable ethics of doing that with surgical patients anyway, what can we accept?

DR. BELKOFF: Well --

DR. MCNEIL: There were two people, before you answer that question, it looks like there were two colleagues that wanted to add something.

DR. KALLMES: Well, I can say about this issue that everyone says we can't do it, and we had an NIH-funded trial, so there is money, $2 million to do it, and I know I'm terribly underfunded, but let me give you the specifics. We have been up and running for a year at two sites, one a private practice site in Asheville, North Carolina, and one at Mayo Clinic. We have screened 500 patients, of which about 90 were eligible, of which three enrolled, and a three or four percent enrollment rate sounds bad. I'm optimistic. As the gentleman from

Colorado said, he's their doctor, patients listen to their doctor. If the doctor comes to the patient in clinical practice and says we don't know, patients will enroll, as the study in Australia is learning. So it's not the appropriate time to throw up our hands and say it can't be done, we have funding to do it, but it depends on the clinical ethos of the investigators, which I think is substantially lacking in North America. It may happen overseas, but it may not happen in North America.

DR. MCNEIL: Jim, did you have a question for the audience?

DR. WEINSTEIN: Well, I would just echo Dave's point. I mean, I have been involved in a lot of randomized trials, we enrolled 2,500 patients in 11 states, some of which are in this age group. I would argue that it's also very difficult and you need a lot of money.

I guess my argument for the people presenting, though, even Dr. Avery, who had 70-some patients, had 89 that he didn't collect any data on, and that's my question. Why aren't we collecting data on those patients who didn't have the procedure? You have hundreds and maybe

thousands of them who would serve as some sort of control. I see no reason not to be collecting data on those patients. That is not an onerous task and I'm sure the money that the companies are paying would cover that.

DR. MCNEIL: Let's see now, we have a whole lot of people standing, and I'm trying to figure out what question they're answering.

DR. R.G. FESSLER: I'm still interested in Dr. Marks and Dr. Belkoff answering my question.

DR. GARFIN: I'm Steve Garfin from San Diego. I tried to develop a randomized controlled trial for kyphoplasty when it first started, at 25 centers, probably 20 academic and five community practice. They were all my friends, they were all committed to it. Nobody else in town did kyphoplasty but those people. I spent a year and a half developing the protocol which you saw today, which we enrolled after two years 40 patients. Halfway into the nonoperative arm, halfway into the procedure arm, there wasn't enough. The control group was to be nonoperative care, which included adding Fosamax or Actonel, giving them pain medication, controlled bed rest,

physical therapy. So we couldn't do that, so what we settled on, because we couldn't get patients to enroll -- I mean, after two-and-a-half years we had 50 patients at 25 sites. So we settled on this prospective arm, set it up, so the next group of doctors who started using kyphoplasty had to agree to get involved in this study, which was how that second group occurred, because there was no way to enroll patients in the first group. Now everybody is coming in on antirestoratives, now everybody is coming in already with some kind of treatment, and now everybody is coming in having read all this information on the web which says it works, and in fact it appears to work, I think the data you have heard today says that. I don't even know what the control arm would be in today's world, because everybody gets osteoporosis, whether they're 40, 45, 60, everybody's on Actonel of Fosamax, so the control arm is pretty much gone. So, I don't know how to do randomized trials so that's why, again, we set up this prospective arm which was the best I thought we could do to get some science looking prospectively.

DR. MCNEIL: Other comments? Is that

on the same issue?
DR. MARKS: Michael Marks, Norwalk, Connecticut. Maybe my practice is a little bit different in Fairfield County, but part of it also is that the average age of my patients is 80 years old. And to talk to some of these people and talk to them about the fact that we're going to randomize you to whether you're going to get a treatment or not treatment, in this day and age where there have been more than enough of these procedures done where these people know about the outcomes. I know it's not gold, but a month ago I had a woman come in to me saying she had had pain for a month, I'm not getting any better, I'm in my 80s, I don't know how many more summers I have to play golf, I don't want to wait any longer. So that would be somebody who would not have opted into the study, and just getting these people in is a very difficult aspect of this, and I know, Dr. Fendrick, you're shaking your head, but that's the reality of being in a community-based practice.
DR. FENDRICK: I need to quote Yogi Berra. Lumbar reduction surgery, I'm hearing it all over again. We were here sitting in this room

in a different format basically talking about how every one of the people that came to present to us after taking out a defective lung, that patients were playing golf and the patients were living these happy lives. And it took the courage and integrity of the clinical community to say, we need to find out whether this intervention actually helps patients. Our first cut showed that it was actually killing certain patients more than helping them. The trial in Denver in fact showed that this intervention that was taking off at similar rates as this is, with the same level of scientists of dedication and compassion, it turns out that all those people who came in with the same amount of zeal looked at that result from randomized trial and shook their heads saying, I'm really glad we did this study and I'm pretty surprised with what we found. I'm not discounting anything you're saying. I'm just saying it's one of those things that those of us who are shallow like me, who look across conditions, we've seen this so many times where someone has to take the point of view that this may not be right.

DR. MARKS: But I think the other issue that I hope you heard today is that there are

700,000 vertebral compression fractures out there. I think what you've heard from at least the community-based doctors is that we're probably operating on ten percent of the fractures that we see, so a lot of them are getting better, there are those that just are not getting better, and we have an alternative treatment for them.

DR. FENDRICK: A great majority of our 80-year-old patients don't have their tonsils because surgeons believed that was helpful as well.

DR. MCNEIL: You had asked Dr. Belkoff a question, is that correct?

DR. R.G. FESSLER: Yes.

DR. MCNEIL: He now has the opportunity to answer.

DR. BELKOFF: I forgot what the question was, but I will answer anyway. Basically, it's not what you guys want, it's what the standard is or how high the bar is set. I personally think that a randomized controlled study would be a nice thing to see. Barring that, I understand the complexities of that, I know there's a study ongoing, but oddly enough in France, where Dr. Germon tried to do a prospective

study, the problem he had was just the opposite, he couldn't get his primary care physicians to refer patients to him because they all thought it was voodoo and they wouldn't give him the patients to put the cement in to see if it had any palliative effect, and to this day they are still not reimbursed in France for doing vertebroplasties. So it's just the opposite. Maybe we can get together with France and ship people across the ocean.

But the next level, I think, and I'm not, although I will be soon I think, an epidemiologist, I don't know what the best controlled study would be. There was one option put out a while ago where you would allow patients to enroll, they would be assigned randomly to a conservative treatment group, but after a certain period of time they could cross over. I think, Dr. Weiner, you would be most qualified to answer this question as to what sort of bias that might introduce, but that would I think, as I see it, the compromise for evidence in saying that you give them a chance to try conservative therapy for a period of time. If the lady wants to golf this summer and things aren't working out very well,

that she can cross over, she can hold that hope out, and maybe we will al least get two or three weeks worth of data, or six weeks, and see if the fracture will heal on its own, and it at least gets us where the Australian study was. That's all I can offer, I don't know. It may be like a bottle of elixir.

DR. FENDRICK: Will it make my hair grow back?

DR. BELKOFF: It will cure lumbago, sciatica, bad breath and constipation.

(Laughter.)

DR. MCNEIL: So Dr. Jarvik.

DR. JARVIK: Yeah, briefly, that's how we conducted our trial, had a relatively short crossover time point of four weeks, so that people are actually guaranteed to get the procedure within a relatively short time period. And in some sense, that's the weakest point analytically of the study, but it also is a strength as far as recruiting and that is what everyone is going to get potentially with both procedures.

DR. MCNEIL: Dr. Sullivan, did you want to add to that? I want to be sure that you all aren't going to run out of time in terms of saying

important things to us, and that we've all asked you all the questions that we want. What question were you answering?

DR. MCKIERNAN: Just a comment on Dr. Fendrick's position.

DR. MCNEIL: Okay. So maybe we can make a quick comment, and then open it up for new sets of questions, and we will do this for about five minutes.

DR. MCKIERNAN: I think your concern is spot on, and my concern is that we reconvene in ten years and have the same bad data to go over again, we will have learned nothing. So I do think there is an opportunity that the correctly designed study can be done. For us it's money, but we're in a unique setting where everyone comes to see us, and my concern is that we don't need more data, we need better data. If we keep designing studies the way that we have been and are careless with patient selection, clearly with those measurements, outcomes, et cetera, we will be no smarter.

DR. MCGRAW: Kevin McGraw, Columbus, Ohio. I was part of two randomized placebo controlled trials, one was at Carolina Accutron,

and I was also part of Dr. Kallmes' NIH-funded trial. We have a very busy vertebroplasty practice in Columbus, Ohio where we do 500 procedures a year. To try to enroll patients in those studies, I interviewed 125 patients. They knew going in that they could cross over if they were randomized to the control arm of the study. Not a single patient wanted to be in pain for another four weeks before crossover. It's exceedingly difficult to enroll patients into a trial of that nature.

DR. MCNEIL: Thank you very much.

DR. BIAN: I'm John Bian from UAB, I'm an assistant professor of preventive medicine, and trained as an economist, and I just wanted to make a brief comment about are there any other ways other than RCT to assess the outcomes of the procedure. I firmly believe that RCT is the standard, but one step back, I think there are potential other methodologies, but each one with some limitation. Someone proposed to do an intent analysis, but the problem is there will be uncontrolled confounder. Someone could do that, but it's extremely difficult to define. It's a very nice technique in theory, but I found only

one article published in 1994, which one of the authors studied the outcome of (inaudible). For instance, there are other means which have other names, the epidemiologists call it case crossover analysis. In economics we call it individual (inaudible). So the one catch of this type analysis is you need to have repeated measurements, repeated treatment on the same individual over time, and you also like to observe variation in outcomes over time. I don't think this type of data is available at the present time because we're trying to do that technique, but we don't have enough patients who have multiple treatments or outcomes.

DR. MCNEIL: Thank you very much.

DR. LIEBERMAN: This is Lieberman, from Cleveland Clinic. Two quick comments just in response to Dr. Ondra and in support of my initial comments to Dr. Fendrick.

Is there something other than a randomized controlled trial? Well, this is right out of Spine, of which Jim Weinstein, the editor, is sitting right there. Is there a continued role of prospective observational studies in spine research, and the answer to this, or from this

editorial is yes, there are, if they are controlled properly and designed properly. And you've heard from my crowd, from Dr. Evans, Dr. Mathis, there's a number of names who have given us these prospective controlled trials with good information that shows objective outcome measures. Now, the second point is, why have we completely discounted the outcome studies from the drug trials that show that these patients with osteoporotic compression fractures get worse over time, that show that mortality is bad over time? Can't we somehow take that information and marry it to the information we have today and show, look, my SF-36s show us in two years these guys are doing better, they're much better than their baseline when they got there, and when you compare that to the historical controls, we do have evidence that this procedure, these techniques do help our patients. Thank you.

DR. HIRSCH: Josh Hirsch from Mass General. I wanted to address each of these questions, particularly Dr. Weinstein's about radiologists performing these procedures, but I held my tongue. This I think is really important to address because we wanted to do this trial.

This isn't lip service, I'm not on Jerry Jarvik's committee, and I believe in this stuff, I really do. I was on the active (inaudible) we don't do sham trials, through my IRB, and I was humiliated. I would like to make an anecdotal remark, which is that at 105, which is the oldest of my patients, six weeks is a long time. And I would also like to make the further observation, having stated that I believe in these studies and I also believe in these procedures, which is an obvious bias, but the point I tried to make before, conservative therapy does have its own risks and we shouldn't discount those risks. Two to four weeks of additional narcotics, of lying in bed, of enhanced hormones, shouldn't in my opinion be expected.

The final point I would like to make, though, I know it was only in abstract form, and I've offered to help them write it, we developed a very nice prospective study out of Stanford which I don't think I could do today. It was referenced, but not referenced as clearly in my opinion as Ed Kallmes's five patients, for the ability to do a sham trial. And I think it should be given at least equal weight to that because I

think it was a legitimate effort. Thank you.
DR. MCNEIL: Dr. Burke.
DR. BURKE: I think that pain is a very problematic outcome, it requires proper instruments, it requires that the instrument is administered objectively, which is important in its own right. I think back pain is very difficult and requires especially rigorous settings, and I think back pain more than any other problems has a host of issues that we've seen over the years, which demand extremely rigorous studies. I think there are some general problems with this data and I don't see how they are going to be overcome with these prospective or retrospective studies.
I agree with the Blue Cross assessment and believe there is questions to be made. I think there are powerful placebo effects related to the procedures. I think there may be patient selection biases at work here. I think the use of validated pain assessment instruments are required. I think that the issue of unblinded administering of the pain instrument is a critical problem. I think the natural history of back pain is not addressed. How are they controlling for

the medical management of these patients through this process? I think the issue of the Hawthorne effect, that just by doing something to these patients, by paying attention to them, you get a benefit, that's well known. I think there is confounding outcome covariates and I think these issues have not been addressed sufficiently to my mind.

I think there are a number of unanswered questions. What is the best comparison group? Which patients will benefit from the treatment? What are the best instruments used to measure the effects? Are we looking at systematic pain management as a comparison or are we looking at the ad hoc pain management? And then finally, what is the appropriate time interval for the outcome measurement.

DR. SULLIVAN: I have a comment and a question. So, the comment on alternative study designs, there's been suggested a couple. I would like to point out that in the late '90s, there was a paper published in JAMA using instrumental variable technique to investigate pulmonary artery catheterization and it was a very important study, and showed the use of an alternative methodology

rather than the randomized control trial. The problem, though, as mentioned, is you need people who didn't receive the technology for comparison purposes.

So, my question is, we're basically evaluating a lot of data here that are essentially case series, they're not trials, and what I need to understand is, what happens to the patients who drop out of the case series? Dr. Lieberman just suggested that we study his two-year SF-36 data. There's only 48 patients out of 329 at two years, that's a 15 percent follow-up. I would like to know if anyone can characterize for me the kinds of patients that aren't followed up and don't have SF-36s at the one-year follow-up, which according to your case series was only 30 percent of cases. So, can someone who has published these case series just help me understand the people who drop out who you don't have measurements on, tell me about them clinically.

DR. LIEBERMAN: One of the things we have to be careful about when we start looking at those percentage numbers, when we said that there were 48 patients at two-year follow-up with 72 percent of them, that meant that we had 55 full

patients with two-year follow-up, on which I only had full data on that 48, that's where that number 72 came from. Now the two-year follow-up, sure, is only a small portion of that, and those are patients I did way back in 1999 and 2000 and 2001 that we have continued to follow up as long as we possibly could.

Now we have lost a number of patients through attrition, some die, some move, some just don't bother coming back, but we have tried to follow as best we can. So those groups were divided down in that intact population according to those yearly breakdowns that we had there, so it's not that it was only 15 percent follow-up at two years, we had 55 patients or whatever that number would be to make that 72 percent or whatever it was that we had.

DR. SULLIVAN: I'm not sure you answered my question, to help clinically characterize the patients who you haven't followed up on for all those reasons, but in your graph here it's 48 patients that you have an SF-36 measure on when you say minimum of 24 months of follow-up.

DR. LIEBERMAN: Right. And there's a

percentage number beside that, I don't have it in front of me, but 70 percent right at the very top of that graph.
DR. SULLIVAN: There is no percentage there other than the one I calculated.
DR. LIEBERMAN: I don't know why that's not up there, but it should be. Of the 48 that we had, that ended up being 72 or 73 percent of the total that we had for two-year follow-up.
DR. SULLIVAN: Okay. Let's assume it was 55. So even 55 out of 329 is very few patients.
DR. LIEBERMAN: But those are the patients that we did very early on, those are the ones that I managed to follow through that still kept coming back.
DR. SULLIVAN: So back to my main point, can you tell me about those patients, were they sicker, were they healthier, did they not receive benefit from the treatment and decide that they weren't going to come back to you to follow up or participate in your study because they were off at a naturopathic healer or something?
DR. LIEBERMAN: We tried to follow those patients up beyond one year as much as we

possibly can. When they don't come back, I can't tell you why they don't come back. We tried to chase them up, and these are the best numbers that we could possibly do short of physically moving into each and every one of these patients' homes and seeing how they're doing. We tried as best we can and those are the numbers that I have, so I can't comment on what happened to them after or why they didn't come back.

DR. FENDRICK: But if they came back for a visit at one year and said they were less satisfied, there is something we would be able to see there.

DR. LIEBERMAN: Well, that's what we've got and that's why we've broken it down, and that's the basis of the paper that we submitted to Osteoporosis International. We've broken it down based as the whole group, the two-year group, the one-year group, and the six-month group, to look at that. So with each one of those groups, the numbers go up in terms of the follow-up and you can make some conclusions. In each one of those groups, we showed statistically significant sustained improvements in their SF-36 numbers across the board.

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DR. BURKE: You know, in cancer, I mean, you know, the follow-up that we look at, the people who drop out invariably have a worse prognosis, that's almost always found in cancer. That's in cancer, but I think in other fields, I think they have similar findings and many times the people who drop out are the ones with worse prognoses.

DR. R.G. FESSLER: My personal findings are very different than that, because I didn't follow a vertebroplasty group, but a lumbar fusion group for two years and at two years many of our patients weren't coming back to clinic. So we called them and we hounded them, and when we got hold of them what they said was no, I'm not coming back, I'm fine, leave me alone.

DR. ONDRA: I think it is a very different issue in cancer and other outcomes, and the follow-up or lack of it may be for different issues.

DR. LIEBERMAN: If I could just make one comment, I'd just like to clarify something with Dr. Burke. Vertebral compression fracture pain is very, very different than the degenerative low back pain, we're dealing with two different

animals here, so I'm not sure that I'm comfortable with that generalization and lumping all of this as back pain.

DR. BURKE: Well, I'll just answer. It's a slippery character and we have to be aware of that.

DR. LIEBERMAN: Granted, but they are two different patient populations and groups and etiologies of pain.

DR. RESNICK: Just a comment, if I may, actually addressed to Dr. Burke. We're not curing cancer here, we're not going to improve these patient lives for the rest of it, they still have osteoporosis, they're still 80-some years old, they're still going to have future problems. What we're doing here is providing immediate pain relief that appears to be lasting, which at two or three years out may have actually no benefit, where if you measure out two or three years out, but there is still an intrinsic benefit in that pain relief that you get for the avoiding that six weeks of bed rest or the morbidity associated with the initial fracture pain.

DR. BURKE: I mean, it may be that it isn't a durable effect, maybe it is. I wish I

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knew by the evidence.
DR. GARFIN: Steve Garfin, from San Diego. I presented two-year data on a multicenter trial and to answer you question, we know the numbers. We entered 155, I reported on 100. We know what happened to those 55, I have the breakdown. I don't have it right down here, but a certain percentage of them died, and the average age was 77 that we're dealing with, from unrelated causes reported on the two-year data. Some, like Izzie said, just felt good and didn't want to come back. Some didn't have a ride. Some developed other medical problems and were hospitalized elsewhere and just couldn't come back. Of the data points we had, which I didn't report because I didn't want to confound or deal with too many statistical variables, they followed the same standpoints, they followed the same parameters, they did all the same tests until they dropped out. They looked the same, demographically they looked the same datawise, but I didn't report them. But there were 55 that dropped out and we know what happened to all but five that we just couldn't track.
DR. MCNEIL: Go ahead.

DR. ONDRA: I have a different question and that's to talk about morbidity. Do you have any data on the role of morbidity and not having good control, the relative morbidity of nonsurgical treatment versus surgical treatment of those populations?

DR. LIEBERMAN: Are you looking at me?

DR. ONDRA: Any of you.

DR. DOHM: No, we don't have, and that's the point. We have all this other data that helps us with the impression that we are making a difference in these patients' lives.

DR. MCNEIL: Let's see. Jonathan, you had a question, or comment?

DR. WEINER: Yeah, building on short-term, long-term, the best that we've got out there, and I think Blue Cross identified it, were the comparative, not controlled groups, and one was in German and my German is not very good, but as it turns out, one was Australian and two were German, and I found another one in the Hopkins library coming out next month from Vienna, some of you may already know about that, Dr. Gross, and they're all either European or Australian. How are they doing that and we're not? Is the

difference that we're not paying for it outside of this context, or are they being tougher on their patients? Granted, these aren't perfect studies. The next one also is similar to the German and Australian, it's a comparison, prospective, two years, solid disability and pain measures, and again define that by the short-term.

DR. MCNEIL: Dr. Kallmes.

DR. KALLMES: I can address that. I've spoken to the investigators in Australia. I think what Dr. McGraw is here saying, Dr. Evans and Dr. Hirsch, they are the wrong people to be talking to. They are probably the worst people to be talking to, because they get the patient referred to them after seeing their internist, their endocrinologist, their rheumatologist. They come with this preexisting bias built in by the referring physician. The studies that are succeeding overseas are PIs, not a radiologist, but in fact endocrinologists or rheumatologists. So that's the reason, I think it's the physician. Again, patients listen to their doctors, but we are the wrong doctors to do that. You've got to reach out to the primary care people who will not instill bias.

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DR. WEINER: Do they have payers involved, do they mandate it?
DR. KALLMES: Australia has stopped paying for vertebroplasty.
DR. WEINER: How about Germany and Austria.
DR. DOHM: Just to follow up on Dr. Kallmes, what I'm seeing in my practice and again, do I have the statistics, no, but what I see is I'm an orthopedic surgeon in the era of managed care and we have a lot of managed Medicare. These patients need a referral to come to me, they are not just picking up the phone to come see me. And so by the time they get to see me, most patients have had, because of the time wait to get to see me, four weeks, six weeks, time to get the MRI and all the other stuff. It is rare for me to get a patient in the operating room to consider doing a kyphoplasty before six weeks. The simple fact is, there is just too much delay in the system. And if I have a patient who comes to see me who had pain and then comes back, and I've actually had it happen once in the four years, I cancel the procedure, because that was somebody who had a minimal depression fracture, it was five percent,

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they come in to see me, there wasn't a lot of deformity associated with it, the pain went away, so I didn't do the procedure. But almost every other patient, by the time it's six weeks, like the 80-year-old patient, or this past week, and I know it's another anecdote, the 90-year-old woman who has been having pain for six weeks, told me she needed to have the procedure done because she needed to take care of her handicapped 82-year-old.

DR. FENDRICK: We hear you loud and clear, but if you were just collecting the data on those people that were waiting to come into your operating room, we would be much more comfortable. Not even, no study design, just checking the raw descriptive data on six weeks of natural history would make a lot of us feel much better. Since I don't do trials in this area, I heard at least an inference that the companies that are supporting other trials, given that this piece of a case report form or data collection would be marginal over the larger studies that all of you are doing, hearing this makes me feel even more frustrated, knowing that you had the opportunity to collect six weeks entry data on these patients and haven't

done it. Now I'm not speaking to you directly, I'm looking to the community. You have all had that opportunity, whether the wait list in western Colorado is two weeks and in Cleveland it's four weeks, but the people who are not coming in that day, you could be collecting that data to the point that Jerry Jarvik's study at four weeks and six weeks, you might even have some really important information on what his control group might look like.

DR. MARKS: But I guess to me, and maybe somebody mentioned it before, the main issue is, and I think Izzie was saying before, a lot of us are more than happy to do it. I guess the question is, we need to put together an organized set of questions so that we're all on a large scale asking the same thing and gathering the same data, and then having a repository where we can basically submit that. Because I can tell you as a private practitioner, I don't have the financial resources nor the time to go ahead and do those things.

DR. FENDRICK: I've seen the same thing in cardiology, pulmonology, gastroenterology. I would recommend going to a very fancy resort with

12 of your colleagues and set up one of these registries that collect these data that we're talking about. It's not that hard to do and there's lots of examples in other areas that it's been pulled off.

DR. R.G. FESSLER: What about the data that was presented today? On the one hand we're saying you guys ought to collect it, and on the other hand we're seeing it presented right in front of us and we're saying it's not good enough.

DR. GARFIN: Steve Garfin, on Dr. Kallmes's comment. When we were failing in the prospective controlled RCT trial to get patients enrolled, we did go to three or four internist or endocrinologist or osteoporosis centers to get them to enroll the patients for us to avoid the surgeon's arm, and they couldn't do it either. This was back in '99. Because the patients went across the street to get vertebroplasty, we just couldn't get them in, even at the primary level.

DR. MCNEIL: All right. We will have just a few more questions for the audience. Did you want to add something?

DR. DOHM: I just would like to make

one comment with respect to the idea of registries, et cetera. I've had some involvement with that, and maybe Dr. Weinstein could comment as well, but for 30 years our American Academy of Orthopedic Surgeons has really looked at trying to have a joint registry, it seems pretty simple and it's analogous to doing this with the spine but it's a lot more difficult. There are so many personal issues that are at hand, and the difficulty now is we just met in Washington, D.C. for our academy in February. We worked three years on putting together the American Joint Replacement Registry, because every other big nation already has a registry for joint replacement and we thought it would be fairly simple to do. We have a contract with Eclipsis and Sun Clinical, they could come up with the software to sort of back us up and help us. We already have 13 hospitals that are IRB-approved across the country, University of Wisconsin, and something that simple, we can't do it. I think we're getting closer to the point of being able to, but it's just extremely difficult.

DR. MCNEIL: I want to ask one thing, and the question is as follows: It looks as if

however we criticize the design of the studies, we have some follow-up data to two years, and it's not a complete follow-up at two years or whatever the time frame is, so my question is the following: How can you be sure or what confidence can you give me that your last follow-up period, there isn't an increased incidence of adjacent fractures in the group treating these procedures? That was raised as one of the classical long-term complications, and I fail to see how you've convinced me that there isn't. I'm looking for data to the contrary, I don't want just thoughts.

DR. LIEBERMAN: Izzie Lieberman, Cleveland Clinic. We published in October of 2004 the follow-up that I referred to in my talk looking at 115 patients with 225 kyphoplasties, and we found an 11 percent incidence of remote and adjacent level fractures within the osteoporotic group. Within the secondary osteoporotic group, they had a 45 percent rate.

DR. MCNEIL: And what time period was that?

DR. LIEBERMAN: That was at 12 months minimum in that group of patients.

DR. MCNEIL: So, do you have anything

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out further than that?
DR. LIEBERMAN: Further, we haven't fully analyzed that, and that's part of the process that we're going through right now with that same group of patients.
DR. MCNEIL: So the original question, then, is what percentage of the total patients was that?
DR. LIEBERMAN: At that point in time that was 115 out of I think it was 175 patients that I had treated at that point. What we had done is excluded the myeloma patients out of that group, so it was the whole group that we had treated from I think it was April '99 to the 2001, actually I think it was 2002, in that span, we treated over 200 patients, and it was 11.25 percent up to 12 months, remote and adjacent, and about half of those were adjacent and half were remote at other levels.
DR. MARKS: Michael Marks, Norwalk, Connecticut. I actually looked at my patients during 2004 and it was in the fall because of the article in Spine by Freiberg which was quoted to you earlier. I looked at my first hundred patients who had then been out two years and I

found similarly that it was roughly 12 percent refracture. Actually it was 14 percent refracture rate for all comers and when I substituted out the secondary osteoporotics, my number turned out to be about 8 or 9 percent for those who had primary osteoporosis and 32 percent for these who had secondary osteoporosis.

DR. MCNEIL: Okay, do you have a number?

DR. CHER: Daniel Cher from Kyphon. As you recall from the presentation I gave, the two prospective controlled studies from Germany both addressed this issue. The first study showed a decrease in subsequent fracture rate with balloon kyphoplasty as opposed to nonsurgical treatment after six months.

DR. MCNEIL: Did it go out any further, 12 or 24 months?

DR. CHER: We are aware of one-year data which I believe have been submitted to a U.S. journal, I think they have been submitted, and they do show a statistically significant reduction in subsequent fracture rate at one year.

DR. MCNEIL: What's the raw number? I don't think I can relate to a reduction unless I

know what the control group is.
DR. CHER: It's actually in my presentation, I cannot recall. New occurred in 7 of 19 patients treated with balloon kyphoplasty.
DR. MCNEIL: That's at 12 months?
DR. CHER: That's the six-month data. And 11 of 17, if I recall the numbers, were 37 percent versus 65 percent. The other study, also from a German investigator that was published just last month, showed at 12 months, 5 percent versus 30 percent, and again, this is at six months. This one-year data is also available. Individually, both of these studies, the six-month data are not statistically significant reductions; however, when you put them together, they are statistically significant, and it's my understanding that the one-year data from the first study which has recently been submitted does by itself show statistically significant reduction in the rate of subsequent fractures attributable to balloon kyphoplasty, so there is actually data from concordant, granted not randomized, but concordant studies.
DR. MCNEIL: Thank you very much.
DR. FENDRICK: A brief final point is,

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not to sound like a broken MP-3 player since my kids don't know what a record is, but looking at the effective size that you have all presented in your nonrandomized controlled trials and the information that you find, I don't have my calculator here in front of me, but I will tell you that a randomized trial to show pain reduction would not have to be very large, and I think that's another thing, and I'll probably hear from the NIH-funded trials again, but I'm actually thinking that this, if you're plugging away at ten patients a year, I think you're going to be able to get the numbers you need to at least reach some of those primary end points much sooner than a lot of you people who feel that these studies cannot be done will actually happen.

DR. CHER: I agree that the study size not does not have to be large. I just wanted to note that the (inaudible) for subsequent fractures is roughly 0.3, so that's a 70 percent decrease from these two studies.

DR. MCNEIL: Yes, Josh.

DR. HIRSCH: Josh Hirsch, Mass General. I just want to make a quick point. I think Dr. Kallmes is right (inaudible) the committee, which

is far more expert on studies, I submit to you that you've told us that the studies are being done abroad and that they're succeeding. So why contemplate such a destructive change in how we're helping people now when studies will be available in I imagine a short period of time.

DR. FENDRICK: If the Australian study is negative, will you be willing to stop doing it?

DR. HIRSCH: I think I would submit to randomized controlled data if that went the wrong way, I have to be honest about that, and I have I hope stated my bias clearly. I accept it. I really believe in these procedures and for this reason I have trained many people to do these procedures, but I think I'm an honest practitioner, and if randomized controlled data comes against what I think, then I have to accept it as such.

DR. BURKE: But you know, we've seen that in cardiology, TPA (inaudible) worked and the American cardiologists didn't agree to that, and those are randomized trials in Europe, so it's not always like that.

DR. HIRSCH: The other half of my life is in cerebrovasculature and I've watched

controlled studies or studies of that ilk absolutely change practice in the United States. Those surgeons, one of them spoke how they now perform far more minimally invasive procedures in surgery. I would like to think that the community would respect the results of it. I will say this. I believe (inaudible) CMS or Medicare reimburses for these procedures will be unruly and disruptive to the patient that we treat. I'm at an academic center, they don't have my salary published, but I don't think I'm making money in doing these procedures; in fact, it probably costs my department that I do these procedures instead of more lucrative procedures. I've stated my belief, thanks.

DR. MCNEIL: Thank you very much. All right. Let me just make sure there are no other additional questions from members of the panel to the audience.

DR. WEINSTEIN: How are those studies supported, the European studies, who funded them? How are they funded?

DR. KALLMES: The one in Australia was funded by the government.

DR. WEINSTEIN: And the German studies?

DR. MCNEIL: Jonathan, do you have that?
DR. WEINER: By Kyphon Europe and the German government.
DR. MCNEIL: Other comments or questions? Did you have a question that you wanted to answer?
DR. TALMADGE: There were a couple questions that I wanted to comment on briefly. I would like to clarify with the panel that I believe that there is far more data on the outcomes of the natural history than is being appreciated right now. I point to a series of papers that have been published over the last ten years demonstrating how the osteoporotic condition impairs function and quality of life, and there's about ten papers that really are very powerful in terms of these outcomes.
And then in addition, more recently there's been a prospective study that was done where they actually have all the patients who had acute fracture and they followed them for two years, and the outcome that was measured was SF-36. And in physical function, vitality, social function and one other domain, there was no change

in the SF-36 scores in spine fracture patients for two years. There were some minimal changes in the other SF-36 domains but they did not in any way reach the case controls that were also part of that study, and they did not compare to the hip fracture patients which got better.

In addition, there is a separate cohort from Sweden that is available on the web, it's not yet published, but it's an ongoing study that confirms these SF-36 results. So I think there is a substantial body of independent data that says that the management, the nonoperative management of these patients in the near term doesn't address their symptoms and in the long term creates a deformity that impairs function and quality of life. So, that was that comment.

Also, I would just like to comment on some of these studies that have shown that treatments that were thought to work don't, and in particular I would like to mention Mosley, which was in the New England Journal of Medicine, it's the one that's referred to as the lavage study, the study of the arthroscopic lavage. And in that study, I'd just like to remind everybody that in that study, there was no benefit of the

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arthroscopic lavage itself or of the placebo treatment. So it wasn't that we saw a placebo effect, it was that we saw no effect.

And if you look at the observational studies, unlike the kyphoplasty and vertebroplasty, the observational studies in fact were mixed, and there were many that showed no benefit and some that showed some benefit, but there were very few studies with objective outcomes, and the randomized study has to have objective outcomes. So I do think that's a very different situation than we have right now where we have profound immediate changes.

And then I'd also like to just mention some unpublished data from the Women's Health Initiative, something that I have always suspected, which is, that study was performed in women who are 65 years of age, and all the observational studies were performed in women who were perimenopausal. They have now done a subanalysis and it will be published, showing that in the cohort in the first decade after menopause, that they have exactly the same outcomes as the observational studies, so when the patient populations were matched, the patients did in fact

do just as well in the randomized study as they did in the observational studies. So, thanks.

DR. MCNEIL: Thank you very much for those comments.

What I would like to do now is, this committee is blessed to have a number of methodologists, a number of practitioners, and a number of representatives from consumer and other groups here, so I would like us to talk to each other. I would also encourage those of you who are in the audience not to leave on the off chance that we have another question to ask you, but at this point we will be talking mostly with each other, and while we may throw out a question, I expect a lot of the dialogue to be among ourselves at this point. Jerry.

DR. JARVIK: I just have a quick question as to how best answer these questions. What parameters should we use to decide whether something is either poor or very good on these scales? Should we use, as you suggested, the Cochrane collaboration criteria or something else?

DR. PHURROUGH: Let me take a try at that. In all our decisions where we are grading evidence, we usually have a difficult time in our

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organization clearly defining exactly the standards that we use for assessing whether evidence is or isn't of good quality, and so we typically define that within each of our decisions based upon the particular type of process it is, the ability to gather information of the process and so forth.

We have some limitations in saying we will accept this, this and this standard, or we will accept American Academy of Dental Physicians standards, or we will accept NAOA standards, or any of those numerous organizations who establish standards, since our selection of one over the other would seem to be challenged with our being a government agency, selecting one over the other, so we have a difficult time doing that.

So this committee in general uses their own independent determinations of what they believe to be good and not good evidence, which in some cases does result in various members of the committee having different views of what is and isn't good evidence, and that's about as close as I can get to you. So you get the, you have the opportunity to decide for yourself what you believe to be good and not good evidence.

DR. RESNICK: Just on this subject, all the evidence that's been presented would be Class III or higher, it's all case series evidence, but I'm pretty convinced from the evidence that's been presented that short-term morbidity with these treatments, that these treatments help short-term morbidity resulting from compression fractures. So I'm fairly convinced based on poor quality evidence, so what number should I put there?

DR. MCNEIL: That's question three. There are two separate questions when you look at them, one is how good are the data, that's question two, and question three is how good are the outcomes. So it sounds as if you say the outcomes are pretty good short-term but the data aren't, it would be high for three and low for two. Yes?

MR. QUEENAN: I just wanted to make sure that I had the right understanding of what we meant when we were saying conservative care, and it wasn't clear to me whether that was applied equally or meant the same things as all the studies we heard about. Sometimes I heard the word nonoperative care, or some other terminology was used, so I just wanted to know whether this

committee had a common understanding of that term, since that's the baseline of things that we're considering.

DR. MCNEIL: Well, I think -- I'll start that, but I would like perhaps Jerry or Jim to add to this. We would have to read each one of the articles and look to see specifically what the authors meant by conservative care, but my sense from reading it was that it wasn't exactly the same in each study, but that it generally meant nonsurgery.

DR. BURKE: That's exactly right.

DR. MCNEIL: So whatever nonsurgery means, that is conservative. Any other comments?

MR. QUEENAN: So just to clarify, it did not include, I assume, other interventions that might for example be treating the osteoporosis along with pain?

DR. BURKE: It could have.

DR. ONDRA: I think perhaps a less confusing term would be nonsurgical care, because there are times that nonsurgical care is not conservative.

DR. WEINSTEIN: I've seen the nonoperative care that was given in the three

studies that people talked about, and I was wondering, what was the nonoperative care in those studies?
DR. MCNEIL: Do you have that, Jonathan?
DR. WEINER: It will take me a while.
DR. MARK: Barbara, I'll look too.
DR. MCNEIL: Okay.
DR. KRIST: In Diamond they talked about like giving Fosamax, calcium, and it was unclear whether they got physical therapy, and I don't see if they received that, but they talk about calcium, Fosamax, which is what I saw as the key interventions in there, and narcotics. I have it right here if you want to refer to it again.
MR. QUEENAN: Actually, maybe the question I should be asking, I can understand that it would probably vary from study to study. Since I am not a doctor or physician, I'm interested in knowing whether the experts here think that it matters to the interpretation.
DR. BURKE: Yes, it does matter.
DR. KRIST: I have it here, if you want me to read it. Calcium and (inaudible).
DR. MCNEIL: That's the Diamond study.

DR. MCNEIL: Did you want to say something, Dr. Burke, just to be explicit?
DR. BURKE: No. Just because if you're comparing something to something else, if you don't have, for example, systematic pain management done by pain professionals, you will get a very different quality of results in your comparison results, or if you don't do pain management at all, or if you let the surgeons do pain management, and most of these studies have no comparison at all, so it's moot.
DR. MARK: David Mark from Blue Cross. Just briefly, the Kasperk study says that both groups, both the observational and the surgical group received medical treatment daily, standard dose of bisphosphonate, calcium, vitamin B, and a recommendation for supervised physiotherapy once a week, but no other evidence about compliance, adherence, stuff like that.
DR. MCNEIL: Thank you.
DR. WEINSTEIN: One of the things I'm having a hard time with, I think Josh may have taken my comments and thrown them away about radiologists, but the issue is that this is a problem confounded by different disciplines caring

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for different parts of the disease. It is a metabolic disease and hormone replacement therapy or calcium therapy, monitoring those things in a clinical practice, versus an intervention that's technically done by an orthopedist, neurosurgeon or a radiologist, and I think the issue of the comorbidities that are often associated with older people, none of these results are adjusted for baseline differences, none of these results are adjusted to my knowledge for comorbidities. There's just so much confounding here because of the management of these difficult patients, and I think that's part of the problem.

I don't think they are able to do these studies well because these patients are in different places and different kinds of practices that don't seem to me, this is the first time I've heard of a radiologist running a clinical practice, I didn't know that was occurring so I apologize, but I think that's an unusual occurrence in many places. So if you manage osteoporosis, you manage their fractures and if something happened, I suppose you would do their surgery, I don't know.

The issue is that these are complicated

patients that require co-intervention by lots of disciplines. I think Dr. Garfin tried it once with the metabolic people, with the idea that that may be where the people should be enrolled from, and I think that's actually probably right. Primary care doctors and endocrinologists are probably the people who should be enrolling these patients in trials for the interventionalists. I feel like I am a clinical trial (inaudible) funded by NIH for spine problems and it is not easy, but it clearly is doable. And the reason it is, it doesn't work is because of us, the clinicians, and not having that echo poise that Dr. Talmadge talked about. But I also think in this particular population, because of the comorbidity and multiple disciplines that are needed to care for these patients, it creates a lot of difficulty in actually setting this up, and I would argue that the failure was in thinking this out ahead of time and how to actually follow that process for the benefit of the patient, not for the benefit of treating one fracture or three fractures, but treating that patient. I think that's where these data just get lost on me, and the fact that I can't come away with more than

level one data.
But that compassionate need to take care of the patient in pain, obviously as a physician, we all feel that compassionate need, but does compassionate need drive science or does science drive compassionate need, and what often happens is compassionate need drives treatment, and science then comes back like the bypass or something that Josh was mentioning in oral surgery, where there is a tremendous compassion for doing the procedure, the randomized trial doesn't work. It didn't mean there weren't a lot of editorials in the New England Journal about it filled with compassion, but that procedure is no longer being done for the most part.
DR. WEINER: To build on Dr. Weinstein's statement, a comment as a professor of public health. Usually on these boards I make a comment that I don't really care about the neurosurgeon, orthopedist or interventional neuroradiologist, it's about the patient, it's about the population.
And I would urge the committee to read the letter from Dr. Sam Ho, the medical director for, to the best of my knowledge, the largest or

second largest Medicare HMO organization, a very thoughtful letter that says hey, it seems to work, but that's not enough. And I think as we move toward, we ain't seen nothing yet, you know, before the baby boomers come on board, as we move toward limited resources, that we need to get this right and people need that meeting at the high end retreat you talked about, and it needs to be across specialties and also with outcomes researchers and CMS at the table. It needs to be population-based and I would encourage you to look at that. Dr. Ho says yes, it seems to work, but that's not good enough.

I also want to ask the questions but not right now, it's really more of a statement, but when does it work, for whom, what are the indications? There are lots of questions, you know, once, twice, three times, we can't pay for it all. And then in the end result, does it really improve the life, and can we pay for it. And Dr. Ho's bottom line, by the way, is we need to start collecting data because it's not good enough just because it seems to work.

DR. R.G. FESSLER: I think that if in fact we want to get it right, we're ignoring a

significant question that we would have to answer at the same time, and that is the patients we're talking about treating are the patients that failed nonsurgical therapy, I'm not going to call it conservative because that's an oxymoron. When you get acute epidural hematoma, conservative therapy is surgery and aggressive therapy would be ignoring it and letting the patient die. In this case our alternative to treating those patients who failed nonsurgical therapy is an open thoracotomy, an open laparotomy with multiple level instrumentation posteriorly. If we want to get it right, we've got to randomize those patients too when we do the study.

DR. KALLMES: I wanted to address the question about who's doing it and when, and just that, I have some insight because I wasn't there at the beginning with Dr. Jensen. She had that seminal paper in 1967 which has been cited 276 times in the literature. About three years ago I read the paper and I made a list of ten things that were outright, well, I called them lies, they were wrong in my opinion, how much cement to use, how many needles do you put in, who do you treat, does the physical pain matter. All these things

have changed in our practice and elsewhere, so it's a very dynamic practice. How do you select the patients? We don't even know.

So there is, you know, we have all these papers where the mean pain goes from 9.5 to 2. I have been in the exam rooms with those patients. They're 80 years old and they say, you ask if they have pain and they say I can't really tell you. Is it a ten, yeah, it's a ten. So I think there is a lot of bias in how we collect these data. When they come back, they say how are you feeling, what's the best your pain has been? I'm a practitioner, I believe in the procedure, I really do, but I'm on the inside and I know what the data are, and they're probably not as good as people are standing up there saying they are.

DR. PHURROUGH: Being just a country doc having practiced in Texas and the rest of the United States, I'm not real clear on what individual criteria are for deciding a patient is ready to get the kyphoplasty or vertebroplasty. Dr. Fessler, you just mentioned patients who have failed conservative care, and yet we have talked a lot about this is also an acute procedure and can relieve acute pain, and then we talk about

patients who are two weeks or four weeks or six weeks, or is it all of these patients? If it's indicated as a procedure after failed conservative care, which we've heard some people mention, and there is a different data set we would need to evaluate that, and if it's indicated as an acute procedure, how do you decide whether all patients who show up immediately with a compression fracture are acute, are they all indicated for one of these procedures, or what is indicated? I'm confused, so someone help out this country doc here.

DR. KALLMES: Dr. Jensen deserves the credit for attempting to develop this in North America, and back then we admitted the patients overnight, you know, all our patients came from neurosurgeons, patients had to have failed six weeks of medical therapy, they had to be on narcotics. And now it's similar to diagnostic vertebroplasty. That is to say, we don't know where your pain's coming from but let's give it a try, so things have really slipped. If you're doing 500 vertebroplasties a year, you know, what is your selection criteria? It's highly different. People say the physical exam is very

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important. Dr. Jensen and I published, saying you have to have localized pain to the spinous process when you came through the door to be a candidate, and you know, we had no good physiologic mechanism for that. We hired a nurse practitioner after a couple years and every single patient that came to our door had pain on palpation. I watched her palpating these patients and it was excruciating to watch.

So, we don't really know how to select patients. The fact of the matter is if you have an MRI that has edema, you're in. That's the great thing about doing vertebroplasty, you've got to be a card-carrying fracture patient. There is none of this, well, you really have to have an MRI, and it's basically, I would say that 99 percent of patients had an MRI and if there's edema on the MRI, they get the kyphoplasty or vertebroplasty, that's the fact of the matter. I think it's also subjective back pain and so forth. But I think duration of pain, Dr. Diamond studied (inaudible) patients, and a lot of people do patients out of the ER now. Is that the right thing for a patient? I don't know. How long should we wait? I don't know.

DR. MCNEIL: Dr. Jarvik.
DR. JARVIK: I think that he misses an incredibly important question as to patient selection. Everybody who was up today or most everybody said that selecting the right patient to do the procedure on is important. The problem is, I don't think we have the data to say who are the right patients. The best particular is probably who's going to get better with vertebroplasty, they're probably the same as who's going to get better without vertebroplasty, you know, duration, is likely important, age, I mean, there are lots of covariants which are worth looking at. But I am not convinced and the problem is we don't have a series with a control group to say, well, yes, there clearly is a difference between those treatment options.
DR. MCNEIL: Could I ask, which way does the age go that you're referring to?
DR. KALLMES: I was very surprised to see that one of the Kyphon studies, Kasperk I think, greater than one year pain for all those patients. That's not practice in the U.S. I mean, one fraction of our patients have had pain for more than a year, so we don't treat chronic

fractures. I think that, you know, six weeks is probably, six to 12, that's where we get the patients.

DR. PHURROUGH: Does mobility have any bearing? A couple people mentioned, and I think it was the Kasperk study that said you have to have this immobile sitting, supine --

DR. KALLMES: To my knowledge, it has no role in vertebroplasty practice, it may be in kyphoplasty practice, but having dynamic fracture is just the cure-all, and I --

DR. PHURROUGH: Do all these produce disparate results if they don't have these particular findings?

DR. KALLMES: No. People have published that cavities do better and, you know, (inaudible) necrosis, and that's very underdiagnosed. If you look at a plain film, it's great to have a cavity, but when you put cement in you frequently see cavity, but nobody has studied that, and it's usually felt to be a good prognostic indicator, patients tend to do better with cavity, although in our data patients get more subsequent fractures if they have a cavity.

DR. MCNEIL: Dr. Resnick.

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DR. RESNICK: I have a comment regarding what Dr. Kallmes just said regarding the Diamond study. We have been discussing how the Diamond control population did better than any other control population, including the patient population cited or reported by Hall, the medical cohort patient population, and is probably because they were acute patients and people are going to get better in the first couple of days, first couple of weeks after a fracture. So I think that in terms of the (inaudible), it seems that the majority of the studies that show benefit, at least the comparisons are looking in the subacute to chronic in the U.S. population.

The other comment I wanted to make is that while it is true that we don't have high quality evidence, it also is true that we probably don't want to throw out the baby with the bath water in terms of this procedure. A large, 15,000-some-odd patients with kyphoplasty and I don't know how many thousands of patients with vertebroplasty have at least documented very good changes in the SF-36, Oswestry, and visual analog pain scales, and those changes have been persistent. Now we can't claim that eventually

patients in controls may or may not have gone there, but based upon the Diamond and Hall study and the small comparative series from Germany, it seems that the controls are durable and yes, it's not high quality evidence, but the absence of proof is not the proof of absence.

DR. MCNEIL: Dr. Weinstein and then Dr. Burke.

DR. WEINSTEIN: I was thinking that patients with these painful compression fractures, it's very hard for them to do flexion and extension x-rays, I probably wouldn't put them through that at 70 or 80 years old.

I think the other issue is how is this data collected on these people, who's actually collecting the data in these practices. Having collected thousands and thousands of data points, this system is just paper and pencil. What do they do with missing values? None of the papers talk about data issues, crossover issues, failures, things that happen in every study, it happens in everyday practice. I mean, we can't have all good results. And so the point is, I've seen patients in my own practice who've benefitted from this technology, but is that an excuse not to

do a good study? And so, I'm struggling with yes, we don't want to throw the baby out with the bath water and not help out our patients, but that's not in the absence of doing good science.

DR. MCNEIL: Dr. Burke.

DR. BURKE: There is a good reason why we go to blinded study designs. I mean, you know, when we did the psychology experiments, the investigators who were interested in a good result get good results, okay? That's well known. That's why we blind, that's why we double blind studies, for exactly that reason. None of these studies as far as I know are double blinded, because you couldn't double blind them. So the investigators are interested in a particular result. We know, and studies have been done, that you can get good results if you don't randomize and blind your patients. Secondly, who's going to benefit from the treatments? I brought it up earlier, the only way to know is to have a set of necessary and sufficient entry criteria in patients in the study, that's the only way you're going to find out who is going to benefit, you can't just take all comers.

DR. MCNEIL: Did you want to add to

that, Dr. Resnick?
DR. RESNICK: No.
DR. MCNEIL: Jerry.
DR. JARVIK: A somewhat separate question, which is, we've heard that one of the strongest predictors of having another fracture is having a first fracture, and we see in these various case series and cohort studies persistent good functional status and lack of pain development down the road, and I'm just wondering, why aren't we seeing sort of recurrent pain, you know, you know, in people on follow-up. A fair percentage must be developing pain, or doesn't that happen separately?
DR. KALLMES: I was going to talk about subsequent fractures. At Mayo, 40 percent of our patients are reduced, they have already had vertebroplasty. On the one hand you can say that's great, that means they love us, we really do a good job. I'm just, I was ignorant about Dr. Lieberman's study with these surveillance radiographs so we can catch all the fractures or not, but we know that we're undercatching all our fractures and still have a very high bounce-back rate.

DR. FENDRICK: You don't mean reduce, you mean a second fracture?
DR. KALLMES: Yes. I have the only paper of the six -- I'm sorry, retreatment at the same level, that's extraordinarily rare, but patients get fractures at other levels.
DR. MCNEIL: 40 percent?
DR. KALLMES: Yeah. Actually in our trial I know this because that was the exclusion criteria in 40 percent of the patients, they had already had vertebroplasty and they come back with recurrent pain from their new fracture.
DR. MCNEIL: I just want to make sure I understand. So 40 percent of your patients come back?
DR. KALLMES: No, that's not what I'm saying. Of patients that we see, we've already treated about 40 percent of them, but we've treated 500 patients over five years, so we see patients as far back as five years. So I don't mean to say that there is a 40 percent refracture rate, I don't know what our refracture rate is because we don't do surveillance radiographs. We only get the painful ones that come back, and there are numbers all over the map in the

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literature, from as low as 8 percent to 67 percent, I don't know what the number is.

DR. MCNEIL: Would 8 to 10 percent seem low to you?

DR. KALLMES: I don't know, I have not systematically looked into that. I would be surprised if it were as low as that because I think it depends on how well they're treated with medical therapy. Are they all getting teriparatide, probably not, but if they are, then I would say 80 percent is high, and if they aren't, I would say it's pretty low.

DR. FENDRICK: One of the things that's positive to the observational trial is, I think I would disagree with Dr. Jarvik a little bit, but one of the good things that you could use in observational studies is actually predict the likelihood of a positive effect of that intervention. Now that doesn't say that it wouldn't also happen in the control group, but you don't need a control group in Dr. Lieberman's study since he has such a richness of data that I imagine that you have too, Dr. Kallmes, that you could actually say that the people who may be in danger, if you have the variables and there are

various standards, maybe there is something, certain variables, and when people are treated at time zero, that would predict that all of them do well or none of them do well. So that's something that you could really do a couple of studies as you move forward, to find something about, I don't know, the mechanics or height or age that would preclude some people right off the bat.

DR. SULLIVAN: I've never done this before, which is disagree with Mark in a public forum, which I'm pleased to do actually.

DR. MCNEIL: Feel free.

DR. SULLIVAN: The only thing, I would say I think he is mostly right, but you have to be able to have better follow-up to be able to do what he's suggesting, and with the follow-up that I'm seeing in these series that are extremely poor, you can't do what Mark is suggesting. In theory you can if there is better follow-up data.

DR. BURKE: Well, it's not even that, because you have to control for covariates and more confounding factors, and in order to do that, you have to have a lot of sample size to see the effect.

DR. RESNICK: Just getting back to

methodological concerns, Dr. Burke mentioned that the only way to answer the question would be to have a priori entrance criteria to randomize the patients as possible. As we've heard from Dr. Kallmes, they only had a three percent accrual rate and out of a hundred patients they screened, only three patients signed on. When we were doing our fusion guidelines, we saw that in the methodology that of 1,500 eligible patients, 30 were selected to do the study, and you would immediately knock that down to a case series type level of evidence.

DR. BURKE: That's correct, but on the other hand it talks to the generality of your study rather than the comparison itself, because you randomize you can still make comparisons, but how generalizable the treatment would be is limited by the two patients which you enroll.

DR. KALLMES: I would like to respond to that, that's an excellent point. If we ever do the trial, I think we would have a tremendous selection bias in patients with less pain, the pre-procedure pain level would be extremely low compared to the 9.5 in most studies and I don't know how to get around that. Our custom is four

weeks, it might possible in 48 hours, is that good enough for the panel? You know, is 48 hours of natural history okay? You might need to come back to that level to get patients in excruciating pain.

DR. MCNEIL: I would like to ask a question of the clinicians and that is, suppose either of these procedures diffuse widely, even more widely than exists right now, just pretend. Apart from cost, what would be your worst fear about health outcomes?

DR. ONDRA: One of the standards that I think is fairly used, but my concern really is, what is the morbidity of treatment versus the morbidity of nontreatment in that first six-week to 12-month period, where at least the Class III to V data suggests there is a pain benefit? We're sort of getting involved in debating the relative plausibility of RCTs in this population and perhaps we're a little off track here.

DR. MCNEIL: Could I just push you a little bit on that? There are a whole bunch of possible side effects that occur in the first short term. Are some of those, if we start doing this procedure more and more, have some of those

really been overlooked? I forgot what we said, like emboli of the brain or whatever?

DR. ONDRA: Those are the things that we talk about, embolism of the brain, narcotic use, pneumonia rates, pressure ulcerations of the skin between different populations, the need for surgical intervention for extrapitation, there is a whole host of things that would be very important, not just how much height restoration, you know, how much angulation, and I think we're missing some of the important parameters.

DR. MCNEIL: Is that because we just don't have enough patients on whom those data have been reported?

DR. ONDRA: I don't think we have collected the data.

DR. MCNEIL: There has been some, there's the FDA review. I was trying to figure out, again, Jerry, you told me about a brain embolus, didn't you?

DR. JARVIK: No, it was a septic emboli, but I actually think there is relatively good evidence about the safety of these procedures and you can get that information from case series about the procedure itself, if you have good

follow-up. But down-the-road complications, my biggest fear actually is probably subsequent fracture rate, which I'm actually somewhat surprised at the cohort data from the German study that suggests lower rates of fracture, and I would like to see more.

DR. ONDRA: And there is a nonexisting control group.

DR. MCNEIL: Okay.

DR. FENDRICK: One thing I need to hear from the interventionalists, I think it was glossed over because there was probably a variation of practice in this need for general anesthesia. These are old folks. I'm not worried about safety in all the things that were listed on all the slides in the cohort study, but I heard one physician only does locals for vertebroplasties, some people do them for kyphoplasties, a lot of local, some people use general anesthesia. I think I really kind of heard from all the experts saying on pain and outcomes that they're guessing, because it has never been compared, that many of the outcomes are going to be comparable. When I have a choice to put a 77-year-old person of any type under a local

or conscious sedation versus general anesthesia, I think this is huge, and I don't think that has been discussed at all in terms of the potential downside risk of one or the other.

DR. KALLMES: We do all ours under moderate sedation and that has been fine. I would be interested to know how the radiologists feel about conscious sedation, I think Josh said. I don't know, but I'd be interested with conscious sedation.

DR. FENDRICK: There were some slides in the documents and general anesthesia is rare, is that your --

DR. KALLMES: For vertebroplasty, yeah.

DR. FENDRICK: I'll try to speak English. In practice, not in the experts' hands, is there a difference in anesthesia choice between the two procedures and if there is, I think if all other things are equal, it's important for us to know, because the risk of anesthesia in an 80-year-old in terms of local versus general.

DR. KALLMES: Dr. Lieberman said he did 90 percent of his under general anesthesia, I think.

DR. LIEBERMAN: Yes, but that's just a

breakdown. Part of that is practice location, whether I do it at an outpatient facility versus an inpatient facility. Part of that is also my anesthesia colleagues, they're a lot more comfortable with an 80-year-old face down with a tube in under general anesthetic than they are with an 80-year-old face down under neuroleptic; if something should happen, they can't intubate that patient, so they insist that we do it more often under general than under local.
DR. KALLMES: Even for vertebroplasty?
DR. LIEBERMAN: Even for vertebroplasty, yeah.
DR. KALLMES: That's unusual, though.
DR. LIEBERMAN: Now again, it's practice location. The anesthesiologist will say well, if we're doing it in the angio suite or we're doing it over at Carnegie or Beechwood, I don't want to drag my anesthetic machine over there, so it's okay to do it over there under local anesthesia.
(Laughter, followed by inaudible colloquy.)
SPEAKER: There has been one death I know of from myocardial infarction, there's been

several cases of paraparesis, the one case series (inaudible) some of these series, I think Dr. Cadu mentioned the (inaudible). And then I worry about the long-term secondary fracture rates, which we've heard from Dr. Lieberman being 11 percent in the primary, 45 percent in the secondary osteoporosis, and Dr. Freiberg, 26 percent, with 53 percent in adjacent segments. As we get an older-aged population that will live longer, what will be the implications of that in taking care of these patients? I don't know, but those are things that try to answer your question.

DR. KRIST: I was going to say that as a family physician, I see a different group of patients than the severity of patients we're hearing about for this procedure. But more of my concern, and some speaker already said it, is that patients who you wouldn't really think about doing this on will receive it. So most of these studies, they're saying that people have been on six weeks, or one or two weeks of medical management, and failed therapy diffuses a lot more. And as patients expect this or learn about it, as physicians know about it, then a whole group of patients we wouldn't even think about

doing this on, will receive it. In my community we're sending the patient to a radiologist, that's the group in our community who does it, I just write a referral for them to go get vertebroplasty, and they come back and have had it done. It's not a very systematic process for figuring out who gets it and who doesn't.

DR. R.G. FESSLER: Jim, I want to respond to some of your concerns, because I think they may not accurately represent the implications of the data. You said there was in 75 percent, but in fact only one percent or 1.5 percent are symptomatic. You know, my concern actually is, and before I go into that is whatever the percentage is, 10 to 40 percent, whatever the refracture rate is, that may not be any different than the natural history of the disease, and that may be all that we're seeing, the fact of natural history of osteoporosis in an aging population. So my concern is that in the hundreds of patients that I have done and in following them over the years, it's my distinct impression that in fact morbidity and mortality is lower in these patients than it is if you let it follow its natural history, and I'm afraid of missing that

fact by talking about the potential morbidity in minuscule percentages when we do know that morbidity of an 80-year-old patient who's bedridden for six weeks is.

DR. WEINSTEIN: I think Dr. Talmadge from Kyphon did a nice summary of sort of what's happening in the osteoporosis literature and associated with these nontreated patients, I think she's right, that there is a significant morbidity. I was trying to answer the question of what the concerns are and I think the cement leakage, although many argue it is not a problem, I don't know. I mean, in most cases it turned out not to be a problem.

But as we're having this open discussion, when I looked at the Medicare guidelines for doing the procedure and the stuff that was in the material that was mailed to us from the June 15th, 1999 document about what are the indications, what are the procedures under Medicare's rules and how this should be done, it talks about, and I quote, "The decision for treatment should be multidisciplinary and take into consideration the local and general extent of the disease." And I sort of thought about that as

what I was getting to before; health care today is not about just a discipline taking care of a patient, but that's sort of the way we practiced for a long time, and I think this is an example that osteoporosis is a disease that is more than just an interventional type of problem, but clearly the new medications are going to have a role as was just pointed out, and the evaluation of osteoporosis with MRI, and what I worry about is we talk about these things in isolation of the patient as a whole, which wasn't the intent of the coverage here.

And I don't know how that would help this, but my understanding is that we would have thought about a multidisciplinary approach to this problem and not sort of sending it to the guy who does this, or helps with the pain, and if we do a lot of medicine, maybe we would have had the ability to treat and follow these patients a little bit differently. I think the physicians who are responding today and are talking about their results all have altruistic goals and have no malfeasance of trying to do something wrong, they are trying to help patients.

But the system, we cannot pay for

things, and I would argue this is under your guidelines as well, certainly if a long-term reduction study and other things were done under protocol and paid for, $75,000 a case for that one reduction study, there is no reason we couldn't continue on getting the kind of data that we need to help these patients in the right way. I think this talk is circular and all of us involved in trials realize how difficult this is, but that's an excuse to not do it. You have the ability to set the guideline and the rules to help pay for things that aren't being done, to collect the data and come back with an answer, it sounds like pretty quick given the number of these things that are being done. So I would argue that given your directive in '99, we haven't really followed that and we need to consider doing that with payment, and get the answers and come back and discuss it. Otherwise, we're just going to be going round and round in circles.

DR. BURKE: I mean, as a doctor practicing in the community too, the heterogeneity of pain management in the community is quite large. Some docs do a great job in pain management, some docs do a terrible job in pain

management, and that in itself is a tremendous bias. It seems to me that if you're putting it in the context of professional anesthesiologists or whatever, who specialize in pain management and look at this procedure after they have had the pain management, and in coordination with systematic professional pain management, we might see something better.

DR. MCNEIL: That's a control group. So, Jerry, tell me what the sample size you needed for your RCT, what was it?

DR. JARVIK: It was originally powered at around 280, is that right?

DR. KALLMES: 294. Our primary outcome was a Rowley scale, a modified Rowley scale, it was not pain, and it was my belief that the Rowley changes, but with vertebroplasty we go from about 19 of 23 to 11 of 23, so I think 294 is, and doing all the control interventions, they might go to 19 and 11 as well, but I think it's probably over, and 294 was the quickest.

DR. MCNEIL: And what was the end point?

DR. KALLMES: I'm sorry, we have another dirty little secret, one-month crossover,

you could cross over after a month.
DR. JARVIK: And we were following out for a year.
DR. MCNEIL: Okay. Sean.
Dr. SULLIVAN: Just to comment on the sample size, remember the reduction series study that was powered to 2,500 patients initially which had a 25 percent crossover, and they experienced a five percent crossover, and so they were able to (inaudible).
DR. KALLMES: Let me say that the impediments to doing prospective research on vertebroplasty is much less today than it has been in the past, at least from a regulatory standpoint, because until cement was approved for vertebroplasty, and Kyphon affiliates were the first ones to get it, but that made my life so much easier because I didn't have to wait (inaudible) and now you have much more leeway on what kind of study design you can do, a lot of people have mentioned difficulty with the IRB, so you can be more creative with study design.
DR. MCNEIL: Other issues? Comments? Well, if that's the case, then we should perhaps go to the questions. So what I'm going to do is,

you all have cards.
DR. KALLMES: We are nonvoting members, but we vote?
DR. PHURROUGH: Everyone does, and we will determine how to count.
DR. MCNEIL: Okay. Assuming everybody has one, two, three, four and five, and if you don't, please say so. I will read the questions, first for vertebroplasty and then for kyphoplasty, and then everybody will just raise the number that they think reflect their opinion, and keep it held because we have to have basically two people count it, right?
So the first question is on vertebroplasty. How well does the evidence address the effectiveness of vertebroplasty for patients with compression fracture as compared with conservative care, realizing that there is some ambiguity in what conservative care is, going from one, poorly, to five, very well? Just hold up your scores.
(All six voting members voted two; of nonvoting members, four voted two, one voted three, and two voted four.)
DR. MCNEIL: And I'm not voting.

DR. PHURROUGH: I notice some of you straining to write these numbers down. We will produce those and they will be available for you as soon as the meeting is over. You can still strain if you want, but you can also relax.

DR. MCNEIL: Now this question relates to data, not outcomes. How confident are you in the validity of the scientific data on the following outcomes with respect to vertebroplasty for patients with, and I'm first going to ask about acute and subacute compression fractures, so asking about the data, short-term morbidity, again, one to five?

DR. RESNICK: In terms of this question, are we referring to the short-term morbidity of the procedure or the short-term morbidity of the fracture? Is this an efficacy or is this a safety question?

DR. MCNEIL: This is an efficacy question, is it not?

DR. WEINER: And from here on you're going to ask us twice, once for acute/subacute and then a second time for chronic?

DR. MCNEIL: Yes, acute and then chronic, would that be easiest? Do you want to go

down or across?
DR. BURKE: Either way is fine.
DR. MCNEIL: I will go down. So, how valid are the scientific data with respect to short-term morbidity for acute and subacute fractures?
(Of the voting members, one voted one and five voted two; of nonvoting members, one voted one, one voted two, three voted three, and two voted four.)
DR. MCNEIL: How about long-term morbidity? Long-term morbidity is two or more years.
(Of the voting members, one voted one and five voted two; of nonvoting members, one voted one, three voted two, and three voted three.)
DR. MCNEIL: How about mortality?
DR. SULLIVAN: Is that 30-day mortality?
(Inaudible colloquy.)
DR. MCNEIL: Hold on.
DR. PHURROUGH: This particular question is asking the validity of the data in measuring these particular outcomes in patients

who have undergone vertebroplasty, so it is the effect of vertebroplasty on mortality.

DR. MCNEIL: Remember, this question number two is about the data and our belief in the goodness of the data. Question three is about the effect on these various outcomes, so how good are the data is question two. So how good do the data describe the effectiveness of this procedure on mortality?

DR. R.G. FESSLER: But that doesn't answer the question.

DR. PHURROUGH: It could have no effect at all, it could have a terrible effect or marked increase in mortality, and if there's no data, then you would vote one on that question, if the data that has been reviewed has no information on mortality at all, then your vote is one. If there is no data on mortality for vertebroplasty, then your vote is one. If there is some data, you are not comfortable with the data, then something higher than one. If there is really good data on the effect on mortality, then your answer would be five.

The next question will say how does vertebroplasty affect mortality, the outcome of

mortality, and if you say there is no effect, then your answer is five. So this question is, is there data, and the next question is, what's the effect on the outcomes. So we're just talking about is there data.

DR. KALLMES: On acute and subacute.

DR. MCNEIL: Correct.

(Of the voting members, three voted one and three voted two; of nonvoting members, one voted one, four voted two, and two voted three.)

DR. MCNEIL: Were they any data on mortality, just as an aside?

DR. PHURROUGH: You can't challenge the vote.

DR. MCNEIL: I can't challenge the vote, I'm sorry. All right. So, this question relates to the data on mobile and functional status, again, acute and subacute.

(All voting members voted two; of nonvoting members, three voted two, three voted three, and one voted four.)

DR. MCNEIL: Now pain, pain relief.

(Of the voting members, five voted two, and one voted three; of nonvoting members, one two voted two, two voted three, and three voted four.)

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DR. MCNEIL: Now we're going to do the very same questions with regard to chronic compression fracture. So, the data on short-term morbidity. And remember, chronic, according to this particular set of definitions is defined on the back as greater than six months.

(All voting members voted two; of nonvoting members, four voted two, three voted four.)

DR. MCNEIL: How about long-term morbidity?

(Of the voting members, one voted one and five voted two; of nonvoting members, one voted one, five voted two, and one voted three.)

DR. MCNEIL: Mortality?

(Of the voting members, three voted one and three voted two; of nonvoting members, two voted one, three voted two, and two voted three.)

DR. MCNEIL: Mobility and functional status.

(All voting members voted two; of nonvoting members, six voted two and one voted three.)

DR. MCNEIL: Pain relief.

(Of the voting members, five voted two

and one voted three; of nonvoting members, four voted two, two voted three, and one voted four.)
DR. MCNEIL: Now we're going to move to question three, which goes from the data to the actual effect on outcomes. That question reads, how likely is it that vertebroplasty will positively affect the following outcomes?
DR. RESNICK: And positive effects is high?
DR. MCNEIL: Very likely is five, yes.
DR. JARVIK: If you thought there was not good evidence, on this scale of not likely to very likely, if we don't know the evidence, what are we supposed to say?
DR. BURKE: If there is no good evidence, then the likelihood of effect --
DR. JARVIK: But there still may be, you know, good evidence. You may be convinced in your heart of hearts that it's going to work without good evidence.
DR. MCNEIL: Then you would vote five.
DR. BURKE: That's this question here.
DR. MCNEIL: Then you would answer a five, Jerry, but you would be wrong -- that was a joke. Okay. So for your acute and subacute

compression fractures, short-term morbidity, in your heart of hearts.

(Of the voting members, two voted three, three voted four, and one voted five; of nonvoting members, one voted three, one voted four, and five voted five.)

DR. MCNEIL: Long-term.

(Of the voting members, one voted two, three voted three, and two voted five; of nonvoting members, one voted one, two voted three, and four voted four.)

DR. MCNEIL: Mortality.

(Of the voting members, two voted one, one voted two, and three voted three; of nonvoting members, one voted one, four voted three, and two voted four.)

DR. MCNEIL: Functional status and mobility.

(Of the voting members, one voted three, four voted four, and one voted five; of nonvoting members, three voted three and four voted five.)

DR. MCNEIL: Pain relief.

(Of the voting members, one voted three, two voted four, and three voted five; of

nonvoting members, one voted three, two voted four, and four voted five.)
DR. MCNEIL: Chronic compression fracture, same thing, short-term morbidity.
(Of the voting members, one voted three and five voted four; of nonvoting members, five voted three and two voted four.)
DR. MCNEIL: Long-term.
(Of the voting members, four voted three and two voted four; of nonvoting members, one voted one, five voted three, and one voted four.)
DR. MCNEIL: Mortality.
(Of the voting members, one voted one, three voted two, and two voted three; of nonvoting members, one voted one, one voted two, four voted three, and one voted four.)
DR. MCNEIL: Mobility and functional status.
(Of the voting members, four voted three and two voted four; of nonvoting members, five voted three and two voted four.)
DR. MCNEIL: Pain relief.
(Of the voting members, one voted three and five voted four; of nonvoting members, two

three and five voted four.)
DR. MCNEIL: So, the next one is a net health benefit, how confident are you that vertebroplasty will produce a clinically important net health benefit for patients with compression fracture compared to conservative care, and we will first do acute or subacute.
(Of the voting members, one voted two, three voted tree, and two voted four; of nonvoting members, one voted two, two voted three, one voted four, and three voted five.)
DR. MCNEIL: How about chronic?
(Of the voting members, three voted two and three voted three; of nonvoting members, one voted two, three voted three, and three voted four.)
DR. MCNEIL: Moving on, how likely on the basis of the literature presented is it that the results of vertebroplasty in the treatment for relief of pain and improvement of ability to function for patients with compression fracture can be generalized to the Medicare population?
(Of the voting members, three voted two, one voted three, and one voted four; of nonvoting members, four voted four and three voted

five.)
DR. MCNEIL: Okay, how about to physicians in community practice?
(Of the voting members, three voted two, one voted three, and two voted four; of nonvoting members, one voted two, one voted three, four voted four, and one voted five.)
DR. MCNEIL: So, we've got the tally and we are not going to allow anybody to vote twice on this particular subject. We're going to go on now to kyphoplasty, so it's exactly the same set of questions, I think, and some of you would probably like to just use ditto.
DR. BURKE: I move that we use the same set of results for the second voting.
DR. ONDRA: Second.
DR. MCNEIL: Any discussion? Is there anybody who disagrees with the motion?
MR. QUEENAN: The motion is for all of the questions?
DR. BURKE: Same set of questions, same results.
DR. WEINSTEIN: I was just thinking about the morbidity, it would change my score on that question.

DR. BURKE: Then let's do it.
DR. MCNEIL: Okay. So, the first one, how well does the evidence address the effectiveness of kyphoplasty for patients with compression fractures as compared with reasonable care -- conservative care, I'm sorry.
(All six voting members voted two; of nonvoting members, three voted two, two voted three, and two voted four.)
DR. MCNEIL: So, how confident are you of the validity of the scientific data on the following outcomes, for kyphoplasty, for patients with acute and subacute fractures? Short-term morbidity.
(Of the voting members, five voted two and one voted three; of nonvoting members, four voted three and three voted four.)
DR. MCNEIL: Long-term.
(All six voting members voted two; of nonvoting members, one voted one, four voted two, one voted three, and one voted four.)
DR. MCNEIL: Mortality.
(Of the voting members, three voted one and three voted two; of nonvoting members, one voted one, five voted two, and one voted five.)

DR. MCNEIL: Mobility and functional status.
(Of the voting members, five voted two and one voted three; of nonvoting members, three voted two, two voted three, and two voted four.)
DR. MCNEIL: Pain relief.
(Of the voting members, five voted two and one voted three; of nonvoting members, two voted two, two voted three, and three voted four.)
DR. MCNEIL: So now we'll do chronic compression fractures, same set of indications, short-term morbidity.
(Of the voting members, five voted two and one voted three; of nonvoting members, two voted two and five voted three.)
DR. MCNEIL: Long-term.
(All six voting members voted two; of nonvoting members, one voted one, four voted two, and two voted three.)
DR. MCNEIL: Mortality.
(Of the voting members, three voted one and three voted two; of nonvoting members, one voted one, five voted two, and one voted five.)
DR. MCNEIL: Mobility.
(All six voting members voted two; of

nonvoting members, four voted two and three voted three.)

DR. MCNEIL: Pain relief.

(All six voting members voted two; of nonvoting members, three voted two and four voted three.)

DR. MCNEIL: Moving to question three, how likely is it that kyphoplasty will positively affect the following outcomes when compared to conservative care for patients with acute and subacute compression factors, same set, short-term morbidity.

(Of the voting members, two voted three, three voted four, and one voted five; of nonvoting members, three voted three, two voted four, and two voted five.)

DR. MCNEIL: Long-term.

(Of the voting members, one voted two, two voted three, and three voted four; of nonvoting members, one voted two, four voted three, and two voted four.)

DR. MCNEIL: Mortality.

(Of the voting members, one voted one, two voted two, one voted three, and two voted four; of nonvoting members, one voted one, three

voted two, two voted three, and one voted four.)
DR. MCNEIL: Mobility and functional status.
(Of the voting members, one voted two and five voted four; of nonvoting members, six voted three and one voted five.)
DR. MCNEIL: Pain relief.
(Of the voting members, one voted three, three voted four, and one voted five; of nonvoting members, one voted three, three voted four, and three voted five.)
DR. MCNEIL: Okay. We will move to chronic compression fractures, same thing, short-term morbidity.
(Of the voting members, two voted three and four voted four; of nonvoting members, six voted three and one voted four.)
DR. MCNEIL: Long-term.
(Of the voting members, one voted two, three voted three, and two voted four; of nonvoting members, one voted one, five voted three, and one voted four.)
DR. MCNEIL: Mortality.
(Of the voting members, two voted one, three voted two, and one voted three; of nonvoting

members, one voted one, five voted two, and one voted four.)

DR. MCNEIL: Mobility and functional status.

(Of the voting members, three voted three and three voted four; all seven nonvoting members voted three.)

DR. MCNEIL: Pain relief.

(Of the voting members, two voted three and four voted four; of nonvoting members, four voted three and three voted four.)

DR. MCNEIL: Okay. Now, how confident are you that kyphoplasty will produce a clinically important net health benefit for patients with a compression fracture as compared to conservative care, acute or subacute compression fracture?

(Of the voting members, one voted two, three voted three, and two voted four; of nonvoting members, one voted two, three voted three, and three voted five.)

DR. MCNEIL: Chronic.

(Of the voting members, two voted two, three voted three, and one voted four; of nonvoting members, two voted two, four voted three, and one voted four.)

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DR. MCNEIL: Okay. Based on the literature, how likely is it that the results of kyphoplasty in the treatment of relief of pain and improvement in the ability to function in patients with compression fractures can be generalized to the Medicare population?

(Of the voting members, three voted two, one voted three, and two voted four; of nonvoting members, four voted four and three voted five.)

DR. MCNEIL: And to physicians in community practices.

(Of the voting members, two voted two and four voted three; of nonvoting members, three voted two, two voted three, one voted four, and on voted five.)

DR. MCNEIL: We have one more piece of business before we finish, and that is to start with the right hand of the table, and we will ask people for a sentence or two about why they made the judgments that they made, and if the spirit moves you, you can say ditto occasionally.

DR. WEINSTEIN: Ditto.

DR. MCNEIL: But not you, you're the only one who can't.

DR. WEINSTEIN: Thank you for having us. I think the participants in this panel spoke to the limitations of the literature. We have clinical practice and we have the science of clinical practice, and as we look back on the past we always like making it better than they currently are, but that's the state of the art and I voted the way I did because of the state of the art as it exists today.

DR. JARVIK: I want to primarily echo that. I voted what I thought was based on the existing evidence and my hope is that this will be an opportunity for CMS to improve that evidence by partnering essentially with clinical trials.

DR. KALLMES: Much as I would have liked to have given more information on the patients in our study, as a clinician, I have I think fairly high confidence that the procedure works.

DR. RESNICK: I believe these are promising and effective procedures that have to be better documented.

DR. R.G. FESSLER: My decisions were based on two different criteria. First was the scientific question and that was based on my

evaluation of our literature as it exists. The second question was what do you think is actually going to happen to these patients, and I based that on my own personal experience following all of my patients with vertebroplasty, with preoperative evaluation and evaluation at six weeks, three months, six months, one year and two years, and those evaluations include visual analog scores, Oswestry disability, and SF-36, including their neurologic exam.

DR. SULLIVAN: First, I would like to thank everyone for the invitation to be here, and also say that I appreciate the rigor of the process. I have been the chair of a multistate private health plan P&T committee for ten years, so this process has been really eye-opening for me and I think I'm going to take some things back for the way we do P&T.

With respect to my voting, I think I was influenced most spectacularly by the very poor follow-up in the data that we saw relative to assessing effectiveness. With respect to mortality, I think I probably gave low scores because I didn't see any data and scored low because of that. I'm not a clinician, I have no

experience with the procedure or patients or family members with this procedure, so I was very focused on the data that I saw.

MR. QUEENAN: I wasn't particularly impressed by the data and would like to see it improved. On the other hand, as a patient or patient representative, I think we need to listen to the patients, and having heard about them and from them, I think that really helped me that this procedure really does work and will work, and I think that needs to be taken into consideration.

DR. WEINER: I would second that the patient input and obviously clinicians who really do the care. On the other hand, if I were to base it on my scientific knowledge, we have two or three ED studies of 30 or 40 each in other countries, so I think that something that affects tens of thousands of lives and spends millions of dollars, I hope that CMS will work with the NIH, and I think it should be more than maybe, I think it's really incumbent, and it's going to be even larger when the baby boomers come on board, and the science has to be done to do the right thing and see where these cards may fall.

MS. STARMANN-HARRISON: I would concur

that the scientific data is sorely lacking, but I also think we have to listen to the clinical experts and we also have to keep in mind that improvements in patient care have to be at the forefront of what we do, so with that in mind, my votes were in that order. We do need improvements in the scientific data, and I guess I would look to CMS if there was any assistance that they could provide, they have the database to do that.

DR. ONDRA: I agree very much with what Jim said, the second thing, not the ditto. And I also agree that we do have a mandate in a sense of what we need and I can only hope that the funding to effect that mandate is somewhere in existence.

DR. KRIST: I'll echo what others have said here, it certainly looks promising, some of these findings and these trends are relatively consistent, but I think we need a better designed study, preferably an RCT.

DR. FENDRICK: I'm impressed by the dedication and passion of the key opinions here, and we hear you loud and clear that, at least taking the votes that I could see, that we are moved by and confident that if you do the right studies, the outcomes that you think are going to

happen are likely to happen.
DR. BURKE: My votes were based on science, and it's just not proven.
DR. MCNEIL: Well, any additional comments? Okay. Steve, do you have some final words?
DR. PHURROUGH: Yeah, and this is the final comments about where we go from here. First of all, I want to thank the panel. We purposely choose people who have various opinions so that we have this type of vigorous debate so that we can bring the issues to the forefront, and this kind of debate is the debate that we're looking for, and I just want to thank the panel for being open and willing to challenge each other with the different issues. I think it also brings to the forefront sometimes the challenges of bringing the methodologist and a clinician together to get the kinds of data that we want.
You know, the field of orthopedics has moved a long way in the last several years in collection of data, you've always done an incredible job in collecting data, you've done a better job of that I think in the last several years, but I think perhaps what you heard today

where we've introduced a technology and we're now saying you need to go back to the beginning of that technology, or we should have at the beginning of that technology and done the appropriate studies. And use that for things that are beginning now, what are the new technologies that are coming into the field of orthopedics today, and that we try to do the right studies today, and not having this panel meeting five and seven and ten years from now and saying we don't have the right data. So I challenge you to look at those kinds of things, whether it's looking at the development of protein, or whatever it is that's happening in orthopedics, let's look at doing, what are the appropriate studies, and let's do those trials so that we're not rushing out a technology before we know what its risks and benefits are.

And finally, we have some information, we have some recommendations on quality of evidence and as I mentioned earlier, we have no open national coverage determination and had no plans to open a national coverage determination for this. We will take this information back and digest it and see what is the next step for us.

We are certainly interested in stimulating in any manner that we can further collection of data. If you have some ideas that you would like to bring to us in a manner we could help with, we are more than happy to sit and listen. We don't fund the administrative cost of doing trials, so if you want administrative money for doing a trial, we are not the people to come to. If there is a way that we can work to stimulate those trials through helping meet clinical costs or through our reimbursement coverage process, we are certainly willing to entertain that. We also have some relationships with our sister agencies at NIH and AHRQ, so we would be more than happy to entertain those kinds of questions and see if we can stimulate that to occur.

I do expect that over the next several weeks to months, we will produce some type of guidance document that will discuss what we think about how evidence ought to be developed in this particular field of spinal disease, and those are always put out in draft form and we will look for your comments on that.

Now to the assembled groups, thank you for your attendance, thank you all who presented

and spent your time. We think this has been very helpful, we look forward to these, I enjoy these, and I thank you for helping us doing what we think is the people's business here in ensuring they get the appropriate treatments. I thank you, and have safe trips home.

(Whereupon, the meeting adjourned at 3:21 p.m.)