MultiJurisdictional Contractor Advisory Committee (CAC) Meeting Transcript

Moderator: Dr. Craig Haug
March 20, 2019
12:00 pm CT (1:00 pm ET)
Confirmation # 4983205

Operator: This is Conference # 4983205

Operator: Good afternoon, my name is (Roche) and I will be your conference operator today. At this time I would like to welcome everyone to the Multijurisdictional MEDCAC conference call.

All lines have been placed on mute to prevent any background noise. After the speakers' remarks there will be a question and answer session. If you would like to ask any question during this time, simply press star then the number 1 on your telephone keypad. If you would like to withdraw your question press the pound key. Thank you.

Dr. Haug, you may begin your conference.

Craig Haug: Thank you, operator, and welcome, everyone, to this contractor advisor committee meeting, aka CAC. Our purpose today is to obtain advice from CAC members and other subject matter experts about the strength of the published evidence on percutaneous vertebral augmentation, specifically for osteoporotic vertebral compression fractures and other added diagnoses.

In addition to discussion, participants will vote on pre-distributed questions. All speakers must have completed and returned the disclosure statement. The meeting is also open to the public as observers.

Just a quick review of the topic, osteoporosis or lower bone density causes fractures from normal activities like coughing or bending over; it affects 50 percent of people over 50. One quarter are vertebral compression fractures which can cause pain and other morbidity comparable to a hip fracture. Treatment options range from non-surgical such as analgesics, limited activity, bracing and physical therapy to procedures such as percutaneous

vertebral augmentation today's topic. Vertebroplasty is the percutaneous injection of bone cement under image guidance into the fractured vertebral body. Kyphoplasty adds balloon tamponade to create a cavity prior to cement injection. Both are meant to immobilize the fracture, reduce pain and improve alignment all basic tenets of fractured treatment.

Successful small European studies introduced the vertebroplasty to the U.S. in 1993, and by 2007 encouraging observational studies led to medical society endorsement in painful fractures refractory to medical management. Subsequent early open label randomized control trials including VERTOS, FREE, VERTOS II and others found the benefit of vertebral augmentation over non-surgical management. However, the lack of blinding meant these results were vulnerable to placebo effect.

Two high profile randomized control trials published in the New England Journal in 2009 addressed this vulnerability by comparing vertebroplasty to a sham procedure. Both studies found no statistically significant benefit of vertebroplasty. Consequently, some national organizations and professional societies withdrew or curbed support; others, citing methodological flaws, largely discounted the studies. Medicare coverage continued, but claims data showed the percent of vertebral fracture patients getting augmentations drop from 24 percent so about a quarter to 14 percent between 2008 and 2014 a 42 percent drop.

The VAPOUR trial published in 2016 attempted to address the methodological flaws of the New England Journal studies including with what they considered to be closer to a true sham, subcutaneous not periosteal anesthetic injection. VAPOUR found a significant benefit of vertebroplasty over sham in patients with acute fracture defined as less than six weeks, in severe pain defined as at least seven on a 10 scale, especially among patients symptomatic enough to be hospitalized. The authors concluded that vertebroplasty is superior to true placebo and controls severe pain in acute fracture.

In 2018, Vertos IV essentially replicated the VERTOS II study, acute fractures with moderate to severe pain, but addressed the lack of blinding in VERTOS

II with an active sham or a control treatment similar to the New England Journal studies (pedicle periosteal infiltration). Although the reduction in pain score was clinically and statistically significant in both groups, scores did not differ between groups. The authors concluded that the results suggest periosteal infiltration alone in the early phase provides enough pain relief with no need for additional cementation.

Also in 2018 a study of Medicare claims data by our co-moderator Dr. Joshua Hirsch found that lower percutaneous vertebral augmentation utilization was significantly associated with a four percent increase in propensity adjusted mortality risk.

Finally two very recent systematic reviews were not supportive of vertebral augmentation. The 2018 (Cochrane) review of 21 trials concluded the data does not support a role for vertebroplasty for treating acute or subacute osteoporotic vertebral fractures in routine practice. Correcting for open trial biases will likely drive any benefits observed towards the null in keeping with findings from the placebo controlled trials. A 2019 systematic review and meta-analysis by the American Society for Bone and Mineral Research taskforce concluded "Vertebroplasty does not work to relieve pain from the fracture and kyphoplasty should generally only be done in the context of a placebo control trial."

This is obviously a very cursory overview of the tentpole literature. Doubtless, we'll hear of other studies and other interpretations of these studies. Because the recent spate of negative publications partially instigated today's meeting, I think some assume our goal is to eliminate Medicare coverage, not true at all. Our goal is to determine what's best for Medicare patients wherever that leads. To get there however we want to hear from all sides. Both proceduralists and non-proceduralists have equal standing in management of patients with osteoporotic vertebral fracture.

And now I'd like to ask Dr. Hirsch, if they've opened your line would you like to add anything?

Joshua Hirsch: Yes, thank you Dr. Haug. Hello everybody my name is Josh Hirsch. I've been doing vertebral augmentation since the 1990s and work in Boston, Massachusetts.

I think Dr. Haug provided the necessary background of what led NGS to schedule this Mecca. I would say to the folks on the call that there quite a few people as this is multijurisdictional. As Dr. Haug mentioned, there are probably three different groups on this call. People who are here to be informed although probably everybody would do well to keep their mind open and be willing to be informed, there are people who would think of themselves as proponents of vertebral augmentation and other people who are not supportive of doing these procedures.

I think with the incredible amount of data, it's fair to say that both of the groups who are thinking that they're either for or against the procedure believe themselves to be data driven, and in their minds are making supportive comments for patient care in this vulnerable population that gets osteoporotic compression fractures. It's our hope that we foster a respectful dialogue so that people who are here to be informed are able to make the best data driven decision.

Dr. Haug shared with me this morning that 100 people have filled out disclosure paperwork. We're not certain whether that means 100 people wish to speak today. We would point out that everybody who filled out disclosure paperwork could speak but should not feel obligated. There are multiple subject matter experts from all aspects of this debate who have agreed to participate in this discussion today.

So anyone who filled out the disclosure paperwork should feel free to comment but otherwise does not necessarily have to comment. We will surely cover all aspects of the six questions in detail in the upcoming session. With that, why don't I hand it back to Dr. Haug for the first question?

Craig Haug: Thanks Dr. Hirsch. Before starting the discussion I'd like to go over the voting question format, one familiar to those who have participated in CMS's MEDCAC. To both maximize discussion time and have the most informed votes possible, I'm going to ask people to vote after not during the meeting.

CAC members and invited subject matter experts have had at least a week to review the final voting questions. A couple of days ago we sent out an Excel version which should make it easier to understand and log votes. For each voting question please use the following scale identifying your level of confidence with the score of one being low or no confidence and five representing high confidence. Some questions have what seem like multiple choices, each is actually a sub-question which should be scored individually on the scale of one to five. Please use whole numbers only.

The first four questions are vertebroplasty specific followed by an identical kyphoplasty set of four. Within each set of those two sets of four are three questions directed at augmentation skeptics. Questions nine and 10 are directed at augmentation advocates, neither vertebroplasty nor kyphoplasty specific. The last four questions, 11 to 14, are for advocates and skeptics alike. One clarification on question 13, how confident are you that each of the below specialists should be involved in a decision to use vertebral augmentation? I meant that to be as part of a multidisciplinary team consensus.

Also some people sent in answers ahead of time in some cases even on draft versions of the questions. To ensure everyone's answering the same questions with the same explanations in mind, we're only counting votes submitted after today's meeting. Please mark your score directly in column B on the spreadsheet next to each question and return it to your MAC ideally via e-mail rather than the snail mail. Only aggregate not individual scores will be published so don't be shy.

Any questions on the format? Operator if we could see if there's any questions on the format that I've explained.

Operator: At this time if you would like to ask a question, please press star then the number 1 on your telephone keypad. Again that's star then the number 1 to ask a question. We'll pause for just a moment to compile the Q&A roster. And your first question from the line of (Patricia Darrow) with professional surgery.

Craig Haug: Thank you.

(Patricia Darrow): Oh, hi. The sheet that I have in front of me I printed out this stuff so I could have it like handy. It just has the questions in blue and yellow and then the answer one to five column that's where we put the numbers?

Craig Haug: Yes, in column B you should be able to -- and again ideally you would do it on the Excel file so everything can be handled electronically and make it easier to tabulate quickly and more accurate, because if we have to transcribe written information you know there's always a chance of getting it wrong.

So yes column B in those yellow or blue spaces you can put in a one, two, three, or four, or five. If they're blacked out that means that's not a voting area.

(Patricia Darrow): OK, thank you.

Craig Haug: OK? All right.

(Patricia Darrow): Yes.

Craig Haug: Next question.

Operator: And your next question the line of (Gordon Mortensen).

Craig Haug: Yes go ahead, is there another question?

(Gordon Mortensen): Yes the question was answered so I'm good thank you.

Craig Haug: OK. All right I don't see any other questions in the queue operator so I guess we'll go on. Besides the voting questions there are six discussion questions. As the operator mentioned press star 1 to enter the question queue.

The first time speaking and I'll have to remind people of this I'm sure give your name, specialty, state, affiliation and importantly any relevant just relevant conflict of interest. So not necessarily all your conflicts of interest that you might list generically but just any that are relevant for this topic. Subsequently if you make another comment, I think just your name will suffice and actually the operator I think announces that anyway.

Please keep comments evidence based and focused and as Dr. Hirsch said respectful (I know there's a lot of passions on each side), and limited to a few minutes so as many as possible have a chance to weigh in. Today we have the great benefit of 16 subject matter experts, many have been nationally known and many nominated by an alphabet soup of national specialty organizations you'd probably recognize.

So in the interest of time I'd ask the many CAC members on the call, again this is because this is a national CAC in effect there are a lot of them, to first give them a chance to address your points before weighing in. So with that let's go to the first discussion question which is a branch of question five. How confident are you that there is adequate published evidence that augmentation, vertebroplasty or kyphoplasty, improves health outcomes, symptom status, function ability, health related quality of life over non-surgical management in select cases of osteoporotic vertebral compression fracture? And the discussion question is if the result of questions one and five was at least intermediate confidence, as defined as at least three or more in that scale of one to five, please discuss clinical parameters that would impact the choice of kyphoplasty or vertebroplasty? Dr. Hirsch, can you kick us off on this one?

Joshua Hirsch: Thank you Craig. There are multiple trials on vertebroplasty versus active and/or passive control sham and Dr. Haug listed them in his introductory remarks. Kyphoplasty has not been similarly studied but it has been studied in the, open label FREE trial.

The question comes up whether or not we should look at vertebral augmentation all the same vertebroplasty and/or kyphoplasty or whether there is a difference in how we should think of them as they relate to maximized medical management. As a result, we would like these questions answered for both vertebroplasty, kyphoplasty and then as they relate to each other.

Craig Haug: OK operator, if we could see if anybody has a question on this.

Operator: At this time if you would like to ask a question, please press star then the number 1 on your telephone keypad. Again that's star then the number 1 to ask a question. We'll pause for just a moment to compile the Q&A roster.

Craig Haug: Yes and I should say not necessarily a question but a comment to the question.

Operator: Again if you would like to ask a question, please press star then the number 1. We do have a question from (Craig Layman).

(Craig Layman): Yes hi, I apologize this is a simple question which is I don't have the Excel spreadsheet, I just have the various PDFs with the questions. So is there a way for somebody to send me the Excel spreadsheet to record my vote?

Craig Haug: Sure, we'll definitely get that done.

(Craig Layman): Thank you.

Operator: And there are no other questions at this time.

Joshua Hirsch: As Dr. Haug mentioned, the use of the word questions may be slightly modified to be questions or comments. Unless everybody feels that they're comfortable to answer these questions, we have multiple subject matter experts who can speak to these various questions.

Craig Haug: Operator, I see there's somebody in the queue if you could…

Operator: And your next question from the line of Douglas Beall.

Douglas Beall: Yes it's Douglas Beall interventional radiologist from Oklahoma. I'd like to take Dr. Hirsch's comments in reverse order. There has been literature most prominently meta-analysis from (inaudible) comparing vertebroplasty and kyphoplasty. There are other meta-analyses as well that come down to three basic differences between vertebroplasty and kyphoplasty.

So you know one vertebroplasty is consistently less effective in terms of pain. And in the meta-analysis it was statistically significantly less effective in designating quality of life differences. And the third is mortality difference and this doesn't come from the meta-analysis, it comes from the most recent

article by two by (Edmond) and one by (Ong) stating a significant consistent reduction in mortality of kyphoplasty over vertebroplasty.

So in reverse order, kyphoplasty hasn't been studied against sham, kyphoplasty has lots of open label trials. Vertebroplasty in terms of adequacy of evidence has been compared against sham but the issue there is was brought up by the Cochrane analysis and the response to that by Dr. (Bill Clark) recently where these were heterogeneous groupings of level one trials put all together and analyzed in one trial.

And so this kind of violates the Cochrane analysis protocol so this was a breach of protocol and this was recently published. So I think these comments in terms of heterogeneity and combination of level one evidence these can't be combined. The two New England Journal articles from 2009 in fact have been categorized as level two articles by the (Anderson) (inaudible) meta-analysis in 2013 using the preferred reporting items and the levels of evidence for primary research as disbursed by North American Spine Society.

So these are challenges that you can't combine heterogeneous groups into a homogeneous meta-analysis and call it a (Oxford) level 1A.

Joshua Hirsch: Thank you Doug. Are there any additional comments on the queue?

Operator: There are no questions at this time.

Joshua Hirsch: Craig (inaudible) perhaps Dr. Beall mentioned it but and I missed it, but Dr. Beall did you have any conflicts of interest that you wish to divulge?

Craig Haug: Operator, if we could open his line again. That was my error for not catching that.

Operator: And at this time please press star 1 on your telephone keypad Dr. Beall.

Douglas Beall: Thank you I have numerous conflicts of interest, quite a few in fact. The good summary of that is generally a collaboration with medical device companies for technology development.

Craig Haug: But you also I believe have specifically have been a consultant for Medtronic, right?

Douglas Beall: I have Medtronic, I have Stryker, Smith & Nephew, DePuy Synthes, Johnson & Johnson. So I have numerous, I have roughly 30 conflicts of interest listed there and these are all listed in their entirety. And there are such things are nonfinancial conflicts of interest as well so I have a whole bevy of them.

Joshua Hirsch: Thank you Dr. Beall.

Craig Haug: Any other comments on this particular topic kyphoplasty versus vertebroplasty. I think in general a lot of the society comments about augmentation in general lump them together. Dr. Hirsch, do you think that's incorrect or correct?

Joshua Hirsch: I think that is correct and thank you for asking. I want to be careful as a co-moderator to not to inject too many of my own opinions so I'm being a little careful in my comments. But I will say that historically the vertebral augmentation thought again not amongst proponents of one procedure versus the other was that the pain relief was equivalent between vertebroplasty and kyphoplasty.

And because the pain relief was equivalent and for a long time that was really one of the leading considerations of whether we judge the procedure to be successful or not, it seemed appropriate to lump together vertebroplasty and kyphoplasty and I think strong arguments can be made for still doing that. Today, after all in 2019, the main reason these procedures are done in osteoporotic patients is for pain relief.

Dr. Beall who's really made the only comment thus far did point to certain studies that have highlighted differences between vertebroplasty and kyphoplasty. Whether that leads to societies changing their practice parameters and guidelines going forward to differentiate the two I do not know. I would wonder if there are any more comments though since Doug made his.

Craig Haug: Operator I think we have another commenter.

Operator: We have a question from (Alan Brook).

(Allan Brook): Yes, hi thank you very much for putting everything in this context. One quick comment is that the earlier trials were comparing the sham injections of lidocaine and the vertebroplasty patients. Just to make it clear for people who didn't -- don't do the procedure that both populations did very well. It wasn't the fact that the vertebral augmentation or vertebroplasty did not work that's one important point.

The second one is many of the populations who get vertebroplasty instead of kyphoplasty are sometimes sicker and they're more difficult patients to control, and the devices for vertebroplasty are much cheaper than anything implanted into vertebral body or with balloons. So they're -- even though you can lump them all together and say they have very good pain management wise there are slight differences.

And the literature has always captured that but the people the surgeons who do these procedures know these subtleties, and over the last multiple decades the efficacy of these is very hard to tweeze out based on the literature alone. But clearly both have good safety profiles and they clearly have efficacy at least the literature that I've read.

Joshua Hirsch: Thank you Allan. I think Dr. Brook's points can be encapsulated into two major thoughts. The first is in talking about the trials that worked to demonstrate its equivalency, it was really the act of control arm doing well and perhaps that's a difference with the VAPOUR trial that Dr. Haug had mentioned in the beginning.

And the second point would argue that vertebroplasty and kyphoplasty would likely potentially still be lumped together in the clinical guidelines with one difference between vertebroplasty and kyphoplasty being the cost of the procedural implements itself.

Craig Haug: Thanks Dr. Hirsch. Operator we have Dr. Beall coming on again.

Operator: Your next question comes from the line of Dr. Beall.

Douglas Beall: OK let me try to encapsulate the differences. There's two sets of differences. So, one is improvement in pain and a statistically significant improvement in quality of life of kyphoplasty over vertebroplasty. That's (inaudible) meta-analysis. The other one is a statistically significant improvement in mortality and morbidity of kyphoplasty over vertebroplasty that's the (Edmond) paper, second (Edmond) Paper and that is a paper by (Ong) published last year.

Another difference between kyphoplasties and I know we want these in but there is differences in approved kyphoplasties with implants is from the (SAKOS) trial meaning there's a statistically significant benefit over an implant augmentation in that trial for pain, for height reduction, and for decrease in adjust (level) fractures of implant reduction, titanium implant reduction improvement but statistically significantly better than doing kyphoplasty so hopefully that will encapsulate the differences.

Craig Haug: Dr. Beall, do you think that vertebroplasty is superior to just the periosteal injection active sham that was used in a number of the trials that did not show a benefit?

Douglas Beall: The real problem is there's heterogeneous grouping here. And if you tell the difference, if you setup a study to determine difference there's a clear difference but the study has to be done correctly. For example the VAPOUR trial established a difference so the VOPE trial was not discussed in the most recent Cochrane analysis and we…

Craig Haug: VOPE was not published, right?

Douglas Beall: It was published but not in a public arena, it was published as part of somebody's thesis so and we do have access to that manuscript. So the difference is clinically relevant reported difference. So the difference between that was clinically relevant (between) the reported groups is different than a mean subject mean difference.

So if you take the mean differences between groups, if you take Vertos IV for example the mean difference between groups and that the sham was a 4.75 point reduction in pain. You add to that which is inappropriate as according to

(Forar and Kat), this has been recommended against doing exactly this but you add minimally clinical important difference to that of 1.5.

Vertos IV had a 6.25 point reduction in pain that was necessary to show difference. To put that into average scope and scale so people can understand what I'm saying is that there's nothing in medicine that does that. I looked and analyzed hip arthroplasty so hip replacement data is at 4.8 and anterior cervical (inaudible) by a fusion of the cervical spine is all at most a 5.1 point difference. So my point is by comparing the group mean differences and looking for a difference plus MCID, it creates an impossibly high bar.

And there's no literature, none that I looked through with the exception of kyphoplasty that beats that 6.25 and I'm referencing the EVOLVE trial of a 6.3 point reduction in pain. I'm also referencing the largest registry in the United States, United States vertebroplasty vertebral augmentation registry that was done by Society of Interventional Radiology they had a 6.7 point reduction in pain.

But other than those two differences, kyphoplasty there's no nothing we do in medicine no surgery, no medication, no treatment that we do, that would best that impossibly high bar of Vertos IV. And that comes from the difference between the average means rather than a clinically relevant response difference.

Craig Haug: But didn't just the periosteal infiltration reach that level also?

Douglas Beall: So here's another important difference, periosteal infiltration does not reach the same difference. So the average reduction in pain for the 2009 New England Journal articles was about the same, Buchbinder reduction in pain was at 2.3, the (Kallmes) I'm referencing lead authors was reduction in pain of three.

The reduction in pain in (Feraneski) trial Vertos IV was a 4.75, so these are very heterogeneous. And let me reference the vertebroplasty reduction in pain for example in the Buchbinder trial was at 2.3. So we have a real methodology problem because in the United States registry, the average

reduction in pain all across the country with all the participants the mean reduction was at 6.7.

So that's almost three times the benefit for vertebral augmentation that we get every day around the country as compared to the Buchbinder trial for vertebroplasty, and it's more (inaudible) that of the (INVEST) trial.

Craig Haug: I understand that in the 2009 studies, one of the criticisms was the patient selection criteria were not that good, but was in the VERTOS IV. Again just to be clear that the active sham and vertebroplasty both had basically statistically insignificant difference. Are you saying that somehow the sham group was different than the non-sham group in VERTOS IV?

Douglas Beall: So no Dr. Haug. What I'm saying is to use the difference, the mean difference between the groups takes a much higher number. So let me compare VERTOS IV versus the Buchbinder trial. Buchbinder also used the mean difference between groups; vertebroplasty and sham had 35 and 38 patients.

Statistically if you were to analyze that paper and plan this pre project, you would need 120 patients in each group instead of 35 and 38 could detect that MCID. So there's no way at 78 total patients you can get that when what you need is 240. And so for VERTOS IV they had more patients, but the critical error is they still used the main difference between the MCID, which creates what I was saying previously a 6.25 point betterment of vertebroplasty. There's -- that's an impossibly high bar.

There's -- you could have put whatever compared to sham in VERTOS IV and come out with a negative trial, including a cervical fusion, arthroplasty, pain pumps, neuromodulation, epidural injections, (RF ablation). Anything that we do …

Craig Haug: You're saying if there was a small difference that it would require to be much more powered to show that difference?

Douglas Beall: Yes. And this has been described I mean the VAPOUR trial for example was published in (Lancet), they used a clinically relevant difference between the

means between the groups. And that was powered they had a little bit of in excess of 120 patients and that was statistically significant.

And they had a reduction significant reduction in pain at a predefined time point, and that was statistically significant. They also used a different sham but the point is the VAPOUR trial compared the mean difference, the clinically relevant response between the groups and was able to determine a clear statistically significant benefits of vertebroplasty over sham.

And the Buchbinder trial for example it would have needed three to four times as many patients for each group to determine that, it's -- and for the VAPOUR trial it's the same thing it's an impossibly high bar. Having said that, the Cochrane analysis included these two heterogeneous groups in one meta-analysis, even though they were very different they used a different technique, different patient population, and different statistical significance calculation.

And last time reading through the Cochrane analysis this is a breach of their own protocol, and this again was published very recently. The Cochrane analysis was published to try to correct their previous error again in 2000 again November as compared with April and there's a Cochrane vertebroplasty misrepresentation article published in as an evidence based medicine analysis very recently.

Craig Haug: OK.

Douglas Beall: And yes, this was a British medical journal evidence based medicine.

Craig Haug: All right, thank you. Yes, I'm sure we'll be coming back to you. So operator if we could get to the next question.

Operator: Your next question comes from the line of Robert Kettler.

Robert Kettler: Hi this is Dr. (Kettler) with (WPS) and we're having trouble hearing the speakers. I wonder if everybody could speak up a little more please. That's all I have.

Craig Haug: OK. It sounds OK to me. Any of the other CMDs on the call or anybody else having trouble hearing?

Male: No, I hear it great.

Craig Haug: Trying to see how widespread this is.

Male: We hear it fine.

Male: (No we hear) very fine.

Craig Haug: OK, sounds like it might be a local issue. And then operator if you could open the line of the next person, but I have a question for that person before she speaks. Is this Dr. Pawlak?

Anne Pawlak: Yes it is.

Craig Haug: OK, we don't have a disclosure form on file for you. Did you fill out one?

Anne Pawlak: Just what I have with my normal (take) CAC five not for this particular meeting.

Craig Haug: OK, you're a CAC member?

Anne Pawlak: Yes.

Craig Haug: OK. If you could send us in one of those, but in the meantime if you could just give us the information any conflict of interest that you have on the topic before you comment?

Anne Pawlak: Yes, no conflict of interest whatsoever. I'm a neurologist at -- in Michigan with Michigan Institute for Neurologic Disorders. The only question I had I know we've been talking about pain management and pain control with the kyphoplasty versus vertebroplasty can anyone answer for me two things?

One, what is the difference in motor activity like a Modified Rankin Scores with these individuals is there a difference? And then the second is, what is the difference in dollars that we're talking between these two procedures?

Craig Haug: Dr. Hirsch, do you have an answer?

Joshua Hirsch: So I'll answer how I would from just my own thoughts, this is not things I've validated. First of all thank you for asking the question. I don't think that a Modified Rankin Score would typically be applied in this population, unless we were looking at stroke rehab patients which would be a fairly uncommon group to consider for augmentation.

So I don't know of any literature that specifically is using that, but that could be my own ignorance of such a paper and I would invite other subject matter experts. With respect to vertebroplasty and kyphoplasty, the question is probably somewhat nuanced. There are equipment cost differences and also Medicare reimbursement differences therefore I wouldn't want to be quick in answering.

I would also say that I recently saw data that suggests that kyphoplasty long term compares favorably with vertebroplasty in terms of overall cost whereas there is a higher upfront cost that mitigates over time. Where I saw that I can't remember and I don't remember the specific reference.

There is existing literature in Vertos II for example that does compare in euros the cost of people management of vertebroplasty versus conservative therapy. And while the cost was a little higher, again over time that certainly mitigates. These are thoughts from my head rather than specific answers to your questions, so if other subject matter experts could answer the CAC member please feel free to press I think its star 1.

Anne Pawlak: So there is nothing that no literature that talks about improvement in pain versus how well they're doing their activities of daily living not just for stroke just in general?

Joshua Hirsch: No, I think there's extensive literature about that in all the trials, but we wouldn't compare it. I thought you were asking specifically against the six point mRS. I only use the Modified Rankin Score as it relates to stroke but that may be a limitation of my own practice.

Anne Pawlak: Yes it doesn't have to be just with mRS, any type of just talking about is there any difference in the motor activity getting back to (ADL) that type of thing between the two procedures?

Joshua Hirsch: So I mean there are numerous -- all the studies study quality of life and things of that sort. I want to be careful about answering with respect to motor skills and in the comparisons of these different procedures vertebroplasty versus the actual comparator which is conservative therapy or kyphoplasty against the actual comparator.

So we're removing the studies that looked against sham because that's not something that one would do in real life practice. There are tremendous advantages in terms of return to function quality of life et cetera when the procedures are compared with conservative therapy. In the equivocal trials against sham, one did not see that type of sustained difference but as I said one can't do sham in the clinical arena. There were some trials of vertebroplasty versus kyphoplasty, but I don't want to speak to them with respect to how those folks did with respect to differences in motor skills or quality of life.

In general, I would say that to get back to an earlier point, when people would think of vertebroplasty or kyphoplasty they would think of them both as having a significant impact on improvement of pain and functional outcomes versus the traditional comparators, which would be what one could get in clinical medicine which is conservative therapy so both would be expected to compare favorably to conservative therapy.

I wouldn't want to comment on vertebroplasty versus kyphoplasty in terms of motor skills for the reasons outlined above. Does that answer your question?

Anne Pawlak: Yes, thank you very much.

Joshua Hirsch: Pleasure.

Craig Haug: And Dr. Pawlak, well Dr. Beall looks like he wants to weigh in on this also. Dr. Beall if you have something specific to this question, but otherwise we're going to move on. Operator if you could open his line.

Douglas Beall: Largest registry U.S. registry is 792 patients, it had pain improvement from an 8.7 to a two in terms of numerical rating score and pursuant to your question had a Roland-Morris disability improvement from a 21 to a seven. So this is mean functional improvement, so hopefully I'd like to touch on the cost of the procedures.

Typically a kyphoplasty kit is roughly $1,500 more than a vertebroplasty kit and this is a rough just statement I realized that. There's two papers one by (Ong) and Osteoporosis International in 2012 that showed it takes two years but the medical management of vertebroplasty because it's less effective in terms of pain reduction, then at the two year crossover kyphoplasty becomes more effective cost effective than vertebroplasty.

And the other articles by (Andsga Lang) published in Spine in 2014 and that delta all is at four years where the overlap between kyphoplasty becomes more cost effective than vertebroplasty so it's quality (treatment) effect.

Craig Haug: Thank you Dr. Beall. OK, I think at this point we'll move onto the next question. Doesn't appear anybody else being in the queue. The next one is directed again at I think advocates of augmentation.

The topic question, before we get to the discussion question, the overarching question is number 10. If at least intermediate confidence (in other words greater or equal to three), was noted in question one or five (in other words, you are confident that kyphoplasty or vertebroplasty improves clinical outcome), how confident are you that there is adequate evidence each of the following non-surgical management intervals be attempted without success before augmentation? Zero days, one to seven days, one to three weeks, three to six weeks, or greater than six weeks. And again when you get to the voting each of these you would give a number too.

For the purpose of this discussion, we want to get a feel for where things stand as far as those who believe in augmentation, how long should the non-surgical management be tried? I think for Medicare coverage now most of the MACs have something on the order of six to 12 weeks.

It does seem like that the trend of the main research which I cited in the introduction is focusing more and more on the acute fracture which would be less than three weeks. I know that there's difference of opinion on this and also there's some thought that maybe there's different indications for different time periods.

The discussion question is for each interval above that receives intermediate confidence, in other words greater than or equal to a three, please discuss clinical parameters that would impact length of non-surgical management.

Dr. Hirsch, you want to kick this off again?

Joshua Hirsch: Yes, I think actually it's a really great question. When we started doing this so many years ago, this seemed like such a dangerous procedure and we all had this notion that fractures will heal therefore in our own guidelines we pushed for the notion of failing conservative therapy.

And in fact in my clinical practice I offer conservative therapy not infrequently in discussions with patients and consultations that we have in advance of consideration for any augmentation. I think that Craig makes an important point and it's that with some of the publication's there's been a trend towards talking about sort of the hyper acute phase.

And while it's not published and I think we should be careful in terms of talking about results, there has been effort to differentiate acute from chronic fractures and there is an ongoing trial looking at chronic fractures in this case vertebroplasty versus sham. What I would say is that Dr. John Barr and colleagues and I was one of the colleagues tried to tackle this question a number of years ago what is a failure of conservative therapy?

Is it defined by time? Is it defined by severity of the symptoms? Does it mean someone who's been admitted to the hospital and can't be discharged? And this was an effort to get at the sticky idea of what does it mean to fail conservative therapy as there is no standardized definition of conservative therapy. And that was a real effort by Dr. Barr at that time.

More recently a multispecialty group was brought together, all people that do augmentation, using the RAND/UCLA approach working with a company called Ismar and again I was involved in this research, this group of 11 experts really downplayed the relevance of time feeling that again, the situations should be thought about in terms of failures of other points rather than specifically time.

I think this is a very hot topic and important discussion, really one that consensus has been driving towards the idea that this question needs to be addressed for a number of years.

So with those introductory comments, Craig, do we have anybody in the queue?

Craig Haug: Yes we do and before we get to that though, I would say that I misspoke and defined acute as less than three; that's the sort of hyper acute that you were talking about which does seem to be the focus. In the VAPOUR they emphasized the hyper acute population, but definitionally I think acute is still defined as anything less than six weeks.

And as far as the definition of a failed non-surgical management question 12 does get to that, and says how confident are you that there is sufficient published evidence that each of the below is a reliable valid and meaningful indicator of failed non-surgical management? And then each to be individually scored, pain precluding ambulation, pain precluding physical therapy, unacceptable side effects from non-surgical management, progression of vertebral height loss, persistence of at least moderate pain and worsening kyphosis. And many of those were derived from society comments.

I think we have four in our queue now. Operator, can we get to the first question or comment. Operator.

Operator: Your next question comes from the line of Nelson Watts.

Nelson Watts: Yes hello, this is Nelson Watts, I'm an endocrinologist osteoporosis (person) in Cincinnati, Ohio. I represent the Endocrine Society, have no relevant conflicts of interest, also a member of the American Society for Bone and

Mineral Research whose taskforce report was quoted earlier as showing no benefit to vertebroplasty.

This an opportunity to highlight the heterogeneity of two sides of the question. One well, and the first question is or issue is if these procedures reduce pain what is the mechanism? And one could be stabilization of the fracture, but the cement creates an exothermic reaction as it cures so it could be heat.

But fractures are different. Where's the location? Is that a mild fracture, a severe fracture? Is there cleft? Timing is important and the procedures themselves sound like they're the same, but vertebroplasty on one hand is not the same as vertebroplasty in someone else's hand how much cement is put in, what type of cement.

And I was thinking what would happen if I had a painful vertebral fracture and someone asked me to be in a sham controlled trial and said if you don't participate in the trial we can go ahead and do the procedure anyway. I'm concerned that there's a selection bias for patients who may be less severely affected who would say yes to participation in a trial.

So as important as these numeric endpoints are, I would argue that it's unless you have much more homogeneity in defining what type and other parameters of the fracture and much more consistency in how the procedures are performed that we're not nearly as smart as we think we are. That's my comment.

Craig Haug: Thank you.

Joshua Hirsch: Nelson I want to just thank you. That's a really terrific comment highlighting several different important points. It is very hard to achieve a homogeneous population in any of these trials, and I do think that that has been a challenge as we've tried to do some of these that amongst the many other excellent points you made. Thank you Dr. Watts.

Craig Haug: Operator, we can get to the next commenter.

Operator: Your next question comes from the line of Dr. John Barr.

John Barr: Is my line open now?

Craig Haug: Yes.

John Barr: Good. Hi, I am an interventional neuroradiologist who practices at UT Southwestern in Dallas, and I'm a former president of the American Society of Spine Radiology who I represent today. I think all of these comments are great but there are two fundamental issues that we really haven't discussed.

One which is with regard to a waiting period that this would essentially be the only bone in the body that we consider a trial of doing nothing rather than fixation for a fracture. And the other is the issue of safety of this procedure. That has been questioned by some that this might not be safe or we don't know how safe it is.

And I would challenge that in fact now with 15 reported randomized trials, we know precisely how safe this is. From a recent presentation I gave at a meeting, there are 1,098 patients who were treated with augmentation in the 15 trials. Of those nearly 1,100 patients there are 16 reported procedural complications that's 1.5 percent.

And of those complications many are trivial, there are only two patients that had significant complications; one with osteomyelitis one with a respiratory arrest from sedation which is a 0.18 percent serious adverse event rate and the mortality in these 1,098 augmented patients is zero from the procedure.

So I think we have absolute ironclad data that this is an extremely safe procedure. You know how did we get to the question of waiting? In the beginning when we started doing this and I've been doing this now for 25 years, we didn't know how safe it was. It was a very novel procedure, so we tended to only treat patients who had exhausted all other traditionally accepted therapies.

As we understood how safe this was and became confident, we started treating patients earlier and earlier. I will also add from personal experience, both of my parents have had osteoporotic vertebral compression fractures for

a total of four between them, every single one of those fractures was treated within 48 hours of identification. Thank you.

Craig Haug: Dr. Barr, were they particularly symptomatic?

John Barr: Yes, they were in severe pain.

Craig Haug: Were they hospitalized?

John Barr: Actually yes my mother was hospitalized.

Craig Haug: OK.

John Barr: I will also speak to the lack of clinical follow up in some of the trials. My mother had an initial excellent response that lasted about 72 hours then she told me her pain had returned almost to baseline. I knew instantly what she had, she had a new fracture.

But some of the negative trials that we play stock in had absolutely no clinical follow up, so when those patients did poorly who knows what happened them. And all of us who do this know that having new fractures is extremely common.

Craig Haug: Thank you Dr. Barr. Dr. Hirsch, do you have any follow up there you want to say?

Joshua Hirsch: I think that Dr. Barr's paper is in the bibliography and the bibliography did make efforts to include lots of papers with different perspectives. I think that one of the debates that I helped launch and lost was the question of whether or not adjacent body fractures occurred more commonly after vertebral augmentation.

In the recent paper that was cited by our colleague from endocrine, there were questions raised about whether that question has been answered. But I would say that there has been no randomized control trial that I know of, that shows a statistically significant difference between either the control group or sham group and the augmented patients.

So let me repeat that, there has been no trial that has demonstrated the difference. And what that likely means is that there is a component of natural history involved in the development of additional fractures. And I think that's important because that is a question that comes up quite a bit with our clinical colleague from rheumatology and from endocrinology.

I know you mentioned there were four people in the queue, so I'll be quiet again.

Craig Haug: Thank you. Operator I think we can go to the next question or commenter.

Operator: And your next question comes from Deborah Tracy.

Deborah Tracy: Hello, can you hear me? Hello, can you hear me?

Craig Haug: Yes we can hear you.

Deborah Tracy: Yes, oh OK. My name is Dr. Deborah Tracy, I practice in Florida in the J9 jurisdiction. I've been a CAC member since 2007, I am board certified in anesthesiology subspecialty certified an interventional pain, fellowship trained in interventional pain by three separate organizations including the American Board of Anesthesiology.

I trained in vertebroplasty in 1999 and since then have done thousands of vertebroplasty and kyphoplasty and my practice is 90 percent Medicare. I practice in Hernando County which is one of the top counties for Medicare per capita, and the hospital I practice in is a 350 bed hospital that is 80 percent Medicare.

So I would like to address the neurologist question …

Craig Haug: Do you have any conflict of interest?

Deborah Tracy: I do teach for the Stryker Company maybe once to three times a year and that involves teaching other doctors how to do the procedure.

Craig Haug: OK.

Deborah Tracy: Is that adequate sir?

Craig Haug: Yes, yes please go ahead.

Deborah Tracy: Thank you. I would like to address the neurologist comment, and for this problem what we're dealing with is the sedentary restrictions of having a vertebral compression fracture.

And this is outside the domain of the literature that we have been reviewing, but we know from other literature in the osteoporotic literature that bone density declines two percent per week with bone loss most dramatic in the first 12 weeks for patients 70, 80 and 90 years old. Muscle strength declines one to three percent per day, 10 to 15 percent per week to have normal strength at three to five weeks.

And the patients are at risk of developing pressure sores, they have side effects from opioid analgesics, as they develop a kyphosis they develop rib crowding, decreased lung capacity, and their sedentary lifestyle can lead to DVT, pulmonary embolism and pneumonia. So I hope that for the neurologist who asked the question that answers it.

Additionally, the vertebroplasty procedure is basically putting a needle through the pedicle most of us use the transpedicular approach and then putting the cement in. The kyphoplasty procedure involves putting the needle in then a drill to drill through perhaps sclerotic bone then a balloon or a cavity cutter.

And this has been suggested to decrease the incidence of extravasation because you're decreasing the pressure within the bone, and this is what results in the increased cost. So the vertebroplasty procedure basically would move forward a little faster than the kyphoplasty procedure, and the kyphoplasty procedure would be more costly because of the extra equipment used.

In terms of what Dr. Beall commented on, I would further like to say that in the Buchbinder study of 2009, 67 percent of the patients came from a single site. I would wonder if the FDA would qualify this as a multicenter trial. And the primary variable was mean pain not responder analysis, so I would

question with the sample size they achieved if the FDA would require a responder analysis.

So I think what Dr. Beall said was that to achieve a difference of one point from the mean either way, the sample size in the Buchbinder 2009 study would have to be 120 participants per group and it was only 35 and 38 per group. So the means and the confidence levels are inadequate to determine the distribution of properties.

Again the sample size was too small, and I would like to refer you to the task force report the second task force report of 2019. We have Dr. Buchbinder and Dr. (Kallmes) as participants in that paper and they do say pretty strongly that sample size is very important on page seven bullet two and page 18, and they do say that the studies must have adequate power on page seven bullet nine and page 18.

Yet there's no commentary or thoughtful commentary on the inadequacies of those papers that are referenced later in the taskforce paper that analyzed how the literature should be provided. So I would wonder why they didn't reference the literature from 2009 as to its inadequacies. In terms of Dr. Barr comments, I would totally agree with Dr. Barr, it's really hard to define a fracture.

An acute fracture is something we never knew is there, it's acute it has marrow edema. But what I see here in this patient they can have a chronic fracture for years and then it becomes acute on chronic and it progresses. So another problem that's not addressed in the literature work is does the stabilization of the bone and the stabilization of the height of the bone improve the patient's future in terms of progression of the fracture?

In terms of our endocrinologist comment neuro-endocrinologist I think that's exactly right, one of the biggest problems in all the literature referenced is the homogeneity. And if further studies are recommended by the task force, I would recommend that the time of the fracture, the type, the integrity of the bone, if there's spinal stenosis. What I often see our people get a compression fracture fixed, if they come back and say oh my pain is worse

than ever I say well, you know here's where we did that. Is this where it hurts? Oh no that pain's totally gone, now I have pain in this place.

So I think one of the other problems in the literature is that there are no efforts to determine when the pain scale doesn't decrease if there are comorbid spinal conditions that are at different sites, or as Dr. Barr said if there are progressing fractures. I saw an elderly lady who was in a motor vehicle accident, she had one single fracture and we repaired that fracture but she didn't get better. Well we did an MRI within the two weeks of the repair and there was a fracture above it.

So I think that evolved infraction just fractured did not show itself until later on and was probably beginning to fracture at the point where I saw her. Thank you very much, I hope I didn't take too much time.

Craig Haug: Dr. Tracy one question, do you think that in VERTOS IV the groups were homogeneous enough to compare to reach a good comparison?

Deborah Tracy: You know right off I could answer that question later, but at the moment there was so much literature I really don't remember my opinion of that specific problem in that specific paper. But I can answer that at a later time for you.

Craig Haug: OK, thank you. Operator if we could go on to the next commenter.

Operator: And your next question from the line of Dr. Kathryn Park.

Kathryn Park: Hello, can you hear me?

Craig Haug: Yes we can, go ahead (inaudible).

Kathryn Park: Yes, so I don’t want to take up too much time. I am a pain doctor from Indiana board certified in pain medicine, and I specialize in treatment of spine. I agree with all the comments that have been already…

Craig Haug: Any conflict of interest, do you have any conflict of interest?

Kathryn Park: No I have no conflict of interest at all, I'm in private practice.

Craig Haug: OK.

Kathryn Park: Yes. So I agree with all the comments that have been made in favor of vertebroplasty, and there was one short study that showed there was an adjacent fracture. The study was 78 people I can't remember the name right now, there were seven adjacent fractures that occurred after vertebroplasty. That's the only thing that I think I saw that referred to any adjacent fractures that occurred.

So I agree that there's not enough research if there's a return of pain. There needs to be other studies performed and not just call it a failure of the vertebroplasty. And my own father suffered severely could not move, had vertebroplasty by interventional radiologists because I don't do them and he was he was fine within hours of having the procedure.

So you cannot deny this to patients who need it, we cannot deny it just because there is not enough literature. So that's all I need to say, thank you.

Craig Haug: Thank you. Operator, the next commenter please.

Operator: And your next question comes from the line of Dr. Patricia Byers.

Patricia Byers: Oh hi, I'm a CAC member. I don't -- I'm general surgeon representing the Florida chapter, I don't have any conflict of interest. I'm just curious about the studies that show no improvement of pain.

If those studies were done after the patient was on opioids for a period of time, would not that interfere with the patient's improvement because if you're on opioids for any more than a week or so now that we know about the opioid epidemic, someone would continue to think they have pain because of their opioid addiction no. So I was wondering if there is any studies that like teased that part out of it.

Joshua Hirsch: We could open up to subject matter experts, but I can probably help with this Dr. Haug. So I just want to clarify first the studies -- the basis of the challenge to vertebral augmentation and the Cochrane review and or the recently published paper in (JVMR) is not that vertebroplasty didn't work.

Vertebroplasty has historically worked in all of these trials, it's the performance of the sham arm. And I think that's just an important distinction that was made by one of the other subject matter experts earlier. And the subject of opioids is extremely important and clearly many of these patients are on opioids, and in fact in a different era many of us thought they really should be on opioids before we would go ahead and offer augmentation meaning that was considered an active part of conservative therapy.

Thankfully after years of thinking that and a lot of I think challenges to not thinking that way, I think the -- there's been an evolution and thought about what conservative therapy should look like. But I would say in answer to your question, clearly a large percentage of patients in the trials are on opioids and the -- one of the benchmarks that the trials use, is how well people do coming off opioids once they've been treated.

And I would say that across the plurality of real world comparator studies, vertebral augmentation offers a significant advantage in that case. I would open the comments up to other subject matter experts.

Craig Haug: Operator if we can go to the next commenter.

Operator: Your next question comes from the line of Dr. (Melissa Chambers).

Rene Chambers: Hello, this is Rene Chambers from…

Craig Haug: Yes we can hear you.

Rene Chambers: I'm a neurosurgeon at UAB, I'm representing the American Association Neurologic Surgeons and I have no conflict of interest. I would like to only reiterate the comments of both Nelson and Josh.

When they made what I think is one of the most important findings to date that is there are many unique combinations of clinical and imaging factors that might affect not only accurate diagnosis but also treatment choices. So I think this particular issue we've sort of skirted around it because as Dr. Hirsch pointed out we have so many randomized control trials, we have so many studies.

You know we have prospective and retrospective patient experience reviews. I think probably this has been addressed thoroughly by both the European and the American clinical care pathways that were developed by the multispecialty panel with the RAND/UCLA appropriateness method. You know Dr. Hirsch mentioned he was part of that, I was as well in the American pathway.

My point is there are so many different factors involved here. Presently we're talking about non-surgical management interval of time, and then as we go to question 12 we'll be looking at pain and its progression, loss of vertebral body height and its progression, progression of symptoms in general, impact on daily activities, advanced imaging findings and so on.

I think timing is just one factor among all of these in my opinion and my experience. You know we published in 2015 an article that's not on the list just the patient experience following over 200 patients, and I think the patient experiences significant rapid sustained reduction of pain, improved quality of life, reduced disability and a low complication rate. I think we've all agreed those are relatively common findings agreed upon findings.

I think that timely repair of the fractures indicated not only to prevent complications that Dr. Tracy pointed out associated with prolonged inactivity, but also just for humane and effective treatment of severe pain in the acute setting. But if we go to the literature, I think the clinical care pathways are the closest we can come to addressing each of these factors and each in their unique combinations to say yes, literature does provide reliable valid information to use for treatment choices. That's all I had.

Craig Haug: Dr. Chambers, you're familiar with VERTOS IV, right.

Rene Chambers: I am.

Craig Haug: So in that case the sham was similar to the New England Journal studies and was in itself a form of treatment, would you agree with that?

Rene Chambers: Now remind me I say I'm familiar with it. Is this the bupivacaine?

Craig Haug: Yes, and periosteal injection bupivacaine.

Rene Chambers: Yes, yes I think that is an active sham.

Craig Haug: OK. And they didn't find a statistical difference. I guess you could argue if you increase the numbers enough that maybe even a small difference would be statistically significant. Do you think that that periosteal injection should be part of the treatment algorithm in some form?

Rene Chambers: Part of the treatment of fractures?

Craig Haug: Yes, I mean it's -- it was an active treatment and its results were equivalent arguably to the vertebroplasty. So should that be tried alternatively to vertebroplasty or at least be part of…

Rene Chambers: I think you're -- go ahead I'm sorry.

Craig Haug: Go ahead I'm sorry. No you go ahead.

Rene Chambers: Well, I think those are two different treatments for two different problems. I think what happens is the injection introduces yet one more confounding variable into these trials, where is the bupivacaine going? Are you simply infusing anesthetic subperiosteally or are you providing a medial branch block? Are you injecting the facet joint pain, are you injecting into the musculoskeletal tissue and relieving myofascial pain?

I think these are two separate issues. I don't think that you want to compare vertebroplasty to this injection. I think as I was stating about the unique combinations of pretreatment findings, I think you have to do your very best to make an appropriate diagnosis and decide what you're treating. I don't think you just need to like the (Label) trial just take bupivacaine and inject it to then say well this was not the result of a relief in the INVEST trial.

I think these are just two completely different things. I think you'll muddy the water if you try to create a trial comparing sort of a random subperiosteal injection, to a procedure specifically to stop the fracture pain.

Craig Haug: Well I mean I just …

Rene Chambers: Does that makes sense? I think there …

Craig Haug: Yes, no but I would push back a little in that you know the authors of VERTOS IV themselves, again these were highly selected patients, and unlike the 2009 studies, I think the two groups were -- they were a better patient selection and presumably the periosteal infiltration wasn't so random.

They presumably did it in a consistent fashion and they themselves say the result suggests that periosteal infiltration alone in the early phase provides enough pain relief with no need for additional (cementation). So it seems like they're suggesting that should be one of the treatments that are tried and fail before vertebroplasty.

Rene Chambers: Yes and I would -- yes, I don't think I'm knowledgeable enough about Vertos IV to respond to that reasonably. But I would say I'd still go back to these clinical pathways and say I think you're throwing out the baby with the bathwater.

You're saying let's do a trial and treat them all like this, when you're not going back to these unique combinations of findings in these patients. And just like you pointed out, I think bottom line patient selection would be essential. I would be very careful not to treat a fracture that has caused kyphosis, caused postural change, caused you know all of the known problems we have with osteoporotic vertebral fractures and try to stop the pain with a bupivacaine injection when you're not treating the other problems.

Craig Haug: OK Dr. Chambers, thank you.

Rene Chambers: I don’t think that would be perfect.

Craig Haug: We've got people stacking up in the queue. I would just remind people that the question here is about the interval. Assuming that we agree that augmentation is useful, it's about the interval that should proceed, does the fracture have to be acute, can it be sub-acute, or can it be chronic?

Rene Chambers: And may I ask just I don’t want to take too much time, but Dr. Hirsch you're probably much more familiar with how the intervals were addressed in the RAND/UCLA appropriateness method paper. And I think they were divided zero to one, one to three, three to six and greater than six.

Again could you explain how that factors into the multiple combinations of treatment and if you think that publication addresses that adequately?

Joshua Hirsch: Thank you (Rene), I think you took over the job of co-moderator.

Rene Chambers: Sorry, sorry.

Joshua Hirsch: OK, I want to be respectful of the fact that we have a lot of people in queue. I'll say two quick things related to the questions that have been posed. The first is and I would make people aware that there is some background noise.

In order to be respectful of all the people that are on the call if you're not muted and not speaking please mute yourself. With respect to the RAND/UCLA study, we looked at multiple different parameters and it was actually a surprising and strongly held consensus opinion that timing should be deemed less important on these other factors.

With respect to the question that Dr. Chambers was answering for Dr. Haug, I think we can simplify Dr. Haug's question which is that if the sham trials demonstrated that the active control sham did better than expected, would that be a reasonable step on a clinical care pathway, not one that was employed in the RAND/UCLA trial but one going forward?

I have my own biases on the answer to that question which I actually shared with Dr. Haug but I think we should throw that back to subject matter experts.

Craig Haug: Thank you. Operator if we could open the lines for the next commenter.

Operator: Your next question from the line of Dr. (Jeffrey Coe).

(Jeffrey Coe): Yes hello, can you hear me?

Craig Haug: Yes.

(Jeffrey Coe): I'm an orthopedic spine surgeon in California, I represent the California CAC. I have no current conflicts although I did participate in the (CAS) trial about three to four years ago I had some research support, but again no current conflicts except for the fact I take care of patients with fractures.

So far I believe I'm the only orthopedic surgeon that has spoken regarding this, and the principles of fractured care have to be kept in mind. And I think there's meta-analysis and other studies that suggest that the mortality rates from vertebral compression fractures approach that of hip fractures.

And I think we have to understand and I want to reiterate the comment of the endocrinologist colleague who spoke earlier that this is a heterogeneous population. And I think all of these studies including this recent Vertos studies, but particularly the two very disproportionately high impact trials in 2009 Buchbinder and (Kallmes), have -- although the randomized controlled trials we've been seduced by the fact it's a randomized controlled trials published in prestigious journals.

And the reality is a definition of evidence based medicine is high quality randomized controlled trials and I'd venture to say and I'm disappointed with my own Academy for not calling these out that these are low quality trials with severe methodological flaws. The point that I'm making here is that, who in their right mind having severe fracture and severe fracture pain is going to make a flip of the coin decision on whether or not to participate in a trial like this?

These trials I admire them for trying to do these trials but they're very difficult, and I think the same probably applies to more recent trials. The trials that you want to look at for clinical evidence are trials that follow all patients that are either enrolled or not enrolled, and what happens to those much like the (Sports) trials that look at disc herniations.

And I know we were discussing science and anecdotal evidence in general, but the reality is, is if it doesn't pass the smell test something's wrong. Fractures hurt, they're painful. And granted some are less painful than others, and some have various stages in healing when they are diagnosed, but 101 old grandfather of my nurse practitioner was misdiagnosed for whatever reason.

He had severe pain, he had a relatively minor incident and he was on opiates and was died nearly of a respiratory arrest until he was finally appropriately

diagnosed and treated with a kyphoplasty. This was just last week these, are lifesaving procedures in patients. And if the science is bad we need to reject the bad science and move forward.

Craig Haug: So Dr. (Coe) let me ask related to the question on the table, how long would require non-surgical management before proceeding to augmentation?

(Jeffrey Coe): Very good. And the point I want to make it depends on the patient in the clinical presentation. If a patient is in acute pain and can't move, has impairment of (ADLs), has very poor scores on (ODI) or what other clinical measures use you will treat them more urgently.

If they present what's relatively minor pain, they're more functional then you can wait and try bracing and other measures. So it's a patient selection issue. Again the point I made earlier this is a heterogeneous population and it's a variable thing and I will offer this…

Craig Haug: Although I would say I think most of the studies have at least been moderate to severe pain, they haven't included minor pain.

(Jeffrey Coe): Well, I understand that. But pain is subjective unfortunately and what one patient perceives as severe pain is maybe more tolerated by others, and some folks will minimize their pain for various reasons because they don't want to be a burden on their families...

Craig Haug: Are you suggesting if they're reporting it as mild that we should still consider them as potential candidates?

(Jeffrey Coe): Well not necessarily, it depends upon other factors. If a patient says their pain is mild but they're stuck in bed and can't get up, so I'm not going to get out of bed it hurts too much but my pain's only a two out of 10, I'm not necessarily going to believe them if their (ADLs) are impaired and the fracture anatomy is appropriate and they have the appropriate imaging study.

So this has to be handled on a case by case basis from a point of view of active clinical practice. But from the point of view of the science, we have to be very careful about not getting seduced by randomized control trials that

are published in prestigious journals because quite honestly the editors and reviewers of these journals …

Craig Haug: No, I think we've covered the deficiencies. Yes I think we've covered the deficiencies you don't need to go over that. But sticking to trying to get...

(Jeffrey Coe): I understand.

Craig Haug: Talk about the length of non-surgical management, as I mentioned in the beginning I think most of the Medicare policies require six to 12 weeks approximately. Clearly there are some that you would do immediately if there are -- would there be any that you would wait six weeks or 12 weeks on?

(Jeffrey Coe): If the patient was functional, if the patient responded to let's say bracing and non-opiate medication, they didn't have significant deformity and I would say this is a reasonable option this fracture will heal. If it fails to heal properly and you're then delayed in my case I would perform kyphoplasty would be an alternative option and I do.

That's exactly how I clinically practice; it depends upon the acuity and the amount of impairment in the sub-acute and acute phase. Unfortunately while I see some hospitalized patients a lot of those tend to go to my (MRI) colleagues. Most of the patients I see are in the outpatient setting, and some of those settings are -- some of those patients are moderately impaired and some are less so.

And I had one patient that was literally held captive recently in a skilled nursing home totally misdiagnosed, she was sent off for pain management and held prisoner in a skilled nursing facility, until I made the diagnosis of a compression fracture and treated her. She escaped from there, signed up AMA and I treated her and she went home and was extraordinarily grateful for that. So there's a lot of misdiagnosis unfortunately.

Craig Haug: Thank you. Operator, if we could open the line to the next commenter.

Operator: And your next question is from the line of Dr. (Allan Brook).

(Allan Brook): Hi, I spoke earlier. I want to reiterate what the orthopedic surgeon just said. The standard of care is usually when you find a weight bearing fracture that presents so most patients who have asymptomatic fractures in the spine most in the thoracic because they're not weight bearing don't usually present to the emergency room or to the doctor's office with pain or disability.

So there's no other bone in the body that's weight bearing but that doesn't get treated once they present. Now, treatment can be more conservative if the patient understands what the risks and benefits of the procedure are and they're able to move and go on with their daily activities and they can deal with pain management with a non-narcotic type of pain medication that was reasonable.

In addition, most times a patient with weight bearing bone that's fractured they treat it for not only the pain management inactivity but so it doesn't get deformed. I think it was the Vertos IV trial or Vertos trial that showed that when a bone is augmented in the spine it doesn't continue to fracture over time and get more deformity. Other trials have supported that as well.

So there's more than one issue involved not only the pain and that should be treated just like any other standard of care in weight bearing fractures when it presents if clinically indicated just like the speakers before said, and clearly it'll prevent further deformity. I think that's well documented in the literature. Thank you. Any questions?

Craig Haug: Dr. (Brook) as far as the time of the question again the length of non-surgical management, do you have any views on that in particular how…

(Allan Brook): Oh absolutely. When patients present with a weight bearing fracture that's painful or debilitating, every place in the body whether it's your ankle or your knee or your hip you treat it when it presents unless bracing it or standard NSAIDs or some other pain medication can have them go on with their daily care of life.

So the sooner you treat it the less deformity you'll have and the higher quality of life they'll have.

Craig Haug: Would you ever wait six to 12 weeks?

(Allan Brook): If a patient presented incidentally and we saw the fracture because of imaging and it wasn't painful and it wasn't deforming them or stopping them from daily activities, I would advise them this is the fracture you have, these are the methods we can treat it.

But if you're doing your daily activities and it's not very painful, I could easily see waiting six weeks or following them closely and advise them that osteoporosis management is vitally important too, that physical therapy in a very controlled way is important and three, is not to lift things that are heavy and advise them on how to grasp things like from the ground. So you need to be taught how to do the daily activities in a safer fashion.

Craig Haug: So you wouldn't if somebody had persistent, OK if somebody had persistent moderate and severe pain and it was still limiting them you wouldn't just stick to an arbitrary length of six or 12 weeks?

(Allan Brook): Absolutely not, this is not a cookbook; we are not baking a cake. If the patient or family has a say in it and they really need to understand what the risks and benefits are to both doing nothing and to treatment with most weight bearing fractures have. The standard of care is to treat them early to prevent deformity. Thank you.

Craig Haug: Operator next comment.

Operator: Your next question from the line of Dr. (Steven Deprima).

(Steven Deprima): Good afternoon, can you hear me?

Craig Haug: Yes.

(Steven Deprima): OK. CAC representative from Florida. I am an interventional neuroradiologist and I have no conflicts of interest. Just a quick comment about the Vertos IV study which has been brought up a few times, while it was designed to be more robust I have a couple of concerns with this methodology and I was wondering if Dr. Haug also shared my concerns.

They included patients over 50 years old instead of a classic proxy for osteoporosis of older age. Number two, they treated more than one vertebral compression fracture if they saw them at the same sitting. And lastly, while they initially enrolled patients with pain up to six weeks, because of enrolment problems they halfway through the study they expanded that indication to pain up to nine weeks.

Does anybody else share those concerns with methodology?

Craig Haug: I read that recent Clark paper that was published last week that mentioned that because of delays even though they were billed as acute i.e. less than six weeks, in some cases they were nine weeks or maybe even a little bit more I forget the exact wording. So yes, that would be concerning.

As far as the multiple fractures, I think they did one to three and I don't know that that's a real outlier. And obviously the age I don't know what the average age is but obviously we're talking about Medicare eligible patients here so…

(Steven Deprima): Right, and they took patients (inaudible).

Craig Haug: Yes. Yes Dr. Hirsch, do you have any comments on that on those things?

Joshua Hirsch: Yes, I mean I need to state a bias which is that I'm an author of the Vertos IV trial. I think regarding Dr. Deprima's concerns. I would caution that multiple levels are common in vertebral augmentation trials. Also, surrogates for osteoporosis go well beyond age. And there is no question that you are correct that the indications were expanded perhaps inadvertently but they were expanded beyond the six week set critique by both yourself and Dr. Clark is correct.

Craig Haug: And Dr. (Deprima), I have to go back to the question. As far as the length of non-surgical management currently the standard in Medicare is more like six to 12 weeks before proceeding to vertebroplasty. Do you have any feelings about what that length should be if any?

(Steven Deprima): Yes I do. My personal experience I would say that my treating of chronic compression fractures has not been particularly good with in terms of improvement post procedure. But I would say that before I'd consider treating

somebody three to four months out, they would have an MRI that showed persistent edema and physical findings consistent with that compression fracture or in this day of age of pacemakers or bone scan.

There would have to be something additional imaging wise, advanced imaging wise to help guide me that that could be still an active fracture as opposed to just a chronic fracture with normal bone marrow signal.

Craig Haug: Thank you. Operator next comment.

Operator: And your next question from the line of Dr. (Mark Alson).

(Mark Alson): Hi there, this is (Mark Alson) from California. Can you hear me?

Craig Haug: Yes.

(Mark Alson): OK. I'm a diagnostic radiologist in California, I'm a CAC member. I do not do these procedures. I just had a question based on something Dr. Haug that you were asking about on the periosteal injection of bupivacaine versus vertebroplasty. It would seem to me that an injection of an anesthetic while it may or may not work wouldn't be as durable and has anyone looked at durability of that arm versus vertebroplasty?

Craig Haug: Well the VERTOS IV study lasts for a year. Dr. Hirsch I think at least as far as the follow up in the VERTOS IV it was durable. Am I right on that Dr. Hirsch?

Joshua Hirsch: You're correct yes.

Craig Haug: Was the follow up a year?

Joshua Hirsch: Yes.

Craig Haug: OK. Now as far as wearing off, one would think that the anesthetic would wear off well before a year.

(Mark Alson): Yes, that was my question.

Craig Haug: Did you have any comment on the length of non-surgical management that would be appropriate?

(Mark Alson): The only comment I would have again just from seeing patients anecdotally, again I don't do these but having had relatives that have had them and such, to me I think what you heard from my colleague the (orthopod) here in California makes the most sense to me. I think you treat patients on a clinical basis.

I think the timing is less important than the clinical presentation and how the patient's doing. That would seem to make sense frankly in all of medicine to me.

Craig Haug: Although again the point was brought up that in general fractures get immobilized right away in other areas of the body. I mean there's definitely been a trend away from passive external fixation via cast, where the body or the limb has to be inactive for a period of time, and more to immediate active internal fixation which would seem analogous to augmentation.

(Mark Alson): Yes, which makes sense to me in an older osteoporotic patient because if you limit them, if you cast them, if you make them on weight bearing you're just going to lose more bone which I think in someone of the ages that we tend to be talking about is a bad idea in general so I would agree with that.

Craig Haug: OK. But that was put out there as a question why should this treatment of these type of fractures be treated differently than other types of fractures? But thank you for that comment. Operator if we go to the next commenter.

Operator: Your next question from the line of Dr. (Lance Ryan Smith).

Craig Haug: Dr. Reinsmith before you proceed I couldn't find you on our list of that you submit a disclosure? Are you a CAC member?

(Lance Reinsmith): Yes, I'm a representative of the American College of Radiology.

Craig Haug: OK. I guess we didn't have you on our list of subject matter experts. But if you could send us a disclosure form then you know to tell us…

(Lance Reinsmith): Yes, I sent that to -- it was sent to, I think it got through to (Virginia) by (Alicia Blakely) was.

Craig Haug: All right. Why don't you introduce yourself and tell us any conflict of interest you have.

(Lance Reinsmith): Yes. So I'm (Lance Reinsmith), I'm an intervention radiologist of muscular skeletal in San Antonio, Texas. I work in private practice. I have no conflicts of interest. I perform these procedures almost daily.

And so the question was about the time course, and when I read the literature whether for studies that have a primary outcome favorable to (vertebral) vertebroplasty or vertebral augmentation you can look at Vertos reflection criteria of less than -- Vertos II is less than six weeks. (Inaudible) showed benefit at one month or selection criteria less than eight weeks. The (Farooqi) trial was some patients were at four weeks, the VAPOUR trial less than six weeks and then the 2018 study by (Yang) published in (Spine) that was less than three weeks.

All of them showed primarily outcomes favorable to vertebroplasty. So and then there was a comment before about the RAND/UCLA. If you look at, if you look into what their seven different appropriateness variables their duration of pain their recommendation is based upon the four categories less than one week, one to three, three to six or greater than six weeks, the recommendations are almost exactly the same throughout the entire spectrum of those.

So there was no, they're basically showing that there was no benefit in or no consideration. So I think literature's saying that certainly less than six weeks is supported for treating these patients. And in my practice I follow the RAND/UCLA paper and I was pretty much following that beforehand. But for my patients I have I will treat patients in less than six weeks if they come to me and they have functional impairment and other criteria the seven clinical variables from that trial or from that paper.

But one other thing I wanted to talk about, oh I'm sorry do you have a question?

Craig Haug: So the more severe the symptoms and severe the disability, the sooner you'll do it and the less time you'll give to. It's kind of sliding scale in other words?

(Lance Reinsmith): Correct I mean, right. And every patient has to have advanced imaging findings positive and then for pain level. And then someone had mentioned that the previous studies didn't treat patients with (mild pamper). I thought the inclusion criteria for at least the Buchbinder trial was for pain level greater than three which to me if someone had less greater than three pain I would very -- be very cautious to treat them in fact I wouldn't.

Joshua Hirsch: Thank you. I don't think that's correct (Lance). I think you're mixing that up with the revised criteria for the INVEST not the Buchbinder trial.

(Lance Reinsmith): Oh the (INVEST), OK.

Joshua Hirsch: So.

(Lance Reinsmith): Well yes, that's right. The (INVEST) I have in front of me is pain greater than or equal to three and it was up to one year for their inclusion criteria so.

Craig Haug: I think in general most of them are moderate to severe. But anyway, did you have any other points because we probably have to move on? We have four more questions and we want to have time so.

(Lance Reinsmith): Well just a quick because I was having some trouble getting in earlier when we were talking about the first thing. I know we seem like we're beating a dead horse talking about this, but when I read these questions in the CAC it says over non-surgical management. And to me non-surgical management at least in my practice if I'm running a trial based upon what I can and cannot offer a patient, non-surgical management for me means doing nothing.

So the results of Vertos II, (Farooqi) and the (Papa Nastacio Anderson) meta-analysis are more relevant to me than the 2009 papers which offer an alternative to vertebral augmentation I cannot offer them. So from non-

surgical management, my definition then I guess differs from what was actually tested in those 2009 papers.

Craig Haug: Meaning the periosteal injection, is that what you're talking about?

(Lance Reinsmith): Correct, because that is not a service I offer for the treatment of vertebral fractures.

Craig Haug: Right, and that was part of VERTOS IV also. So do you think that should be offered prior to augmentation?

(Lance Reinsmith): I haven't really thought about that. I think that it's…

Craig Haug: And that's what the VERTOS IV authors suggest.

(Lance Reinsmith): Right. I mean and some of it I have not thought about as offering in my practices. I mean it's not.

Craig Haug: OK.

(Lance Reinsmith): It's not how I was trained.

Craig Haug: OK, all right. Let's move on. Operator Dr. Beall is on again. Dr. Beall time is getting short, do you have a specific comment on the length of non-surgical management?

Douglas Beall: Yes, I do have a specific comment Dr. Haug. So again the RAND/UCLA criteria we have extra recommendations, right. It's about the duration, pain, (inaudible) the seven things that were mentioned. And they report in there the experts recommend that duration of time is not important.

I think what we deal with six to eight weeks of non-surgical management is just a mean that's been reported over and over again. There's no evidence for this. The evidence that does exist are by (Kim and Bailey) for bracing. So Dr. (Kim) at (JBJS) says when compared no brace operates hard brace for 12 weeks there's no difference in pain reduction.

Dr. (Bailey) in (Durham Neurosurgery) recommends a test of the brace or no brace for eight weeks and hyper acute fractures meaning less than 72 hours.

Again no difference in pain reduction. (Rasluska) did a meta-analysis in EUROSPINE five studies that showed low quality evidence for opioids (inside) your spinal braces.

So there's any conclusion or insufficient data to recommend optimal conservative management for vertebral compression fractures. And this is the actual data including meta-analysis that we have. One other comment Dr. Haug about your periosteal injection of bupivacaine, I mean I guess it can be offered as a treatment but this was offered and tested in the VAPOUR trial, so in the VAPOUR trial specifically fractures less than six weeks not three weeks but six weeks.

And I do have another comment that I won't make because of the timing, but for paraspinal injection of bupivacaine the two adverse events and the augmentation for the VAPOUR trial was one that was related to anesthesia, another one was non-spine related.

The two adverse events in the paraspinal injection of bupivacaine one was turned out paraplegic because of fracture crack from anteroposterior or compressed (inaudible) and the other one required surgical decompression. So if we're going to inject the paraspinal bupivacaine we have a lot more on paper that shows we need to be following these patients along and presumably they were. One was paraplegic and the other one was required decompression.

So this doesn't do anything to deal with the lack of structural integrity of the bone which as pointed out is a primary principle of this. So if we do recommend something like this, we better be very cautious about doing that is doing something to protect the structural integrity of the bone.

Craig Haug: Right, thank you Dr. Beall. I don't think we have anybody else in the queue. I think we've covered this question fairly well so why don't we go onto the next one?

The next set of questions is for skeptics and advocates alike. So the first one is what significant evidence gaps exist regarding the clinical criteria of individuals who should receive vertebral augmentation? A few people have I

think raised the question of whether future studies comparing to a true sham let's say are even ethical. Dr. Hirsch, you want to kick that one off?

Joshua Hirsch: So just could you repeat the question whether or not it's ethical to do a sham trial?

Craig Haug: Right, I think it's been questioned whether that's even feasible, whether ethical or practical if the patients are unwilling type of thing.

Joshua Hirsch: And that is a point that we hear commonly. I would say that I differ with many in my community so again setting my own personal bias. There is no question that it would be difficult to randomize those who are in pain.

And as our colleague from endocrine spoke about earlier, there clearly is a selection bias for people who are in pain and have the opportunity to opt out. In VAPOUR they did not because essentially Medicare in Australia whatever the Medicare equivalent is called closed down access to vertebroplasty in the wake of the 2009 trials. I've argued for sham trials and have done that in writing and in many presentations because I believe that there are obviously skeptics based on those trials that are out there.

And Dr. Haug actually was citing some work we did when he talked about the decline of the Medicare population in the wake of the trials being treated from 24 to 14 percent. While that has since risen, as a believer in augmentation, as a believer in the mortality benefit, it really bothers me that 80 percent of patients some of them clearly having fractures that would potentially benefit from these procedures are not being treated.

And I think the way to get at that is to get past this issue of community equipoise. Now there isn't really that much equipoise in the sense that people are debating internally whether they believe the procedure works, people generally are supporters or are not supporters. But in the community think of it as a dumbbell type equipoise something my friend, Dave Kallmes, talks about, we have proponents and people that are against the procedure.

So, for me the -- notwithstanding the challenges of doing the sham trials and notwithstanding the challenges of recruiting for those trials, I believe the way

to actually increase the number of patients we're helping and therefore the mortality gains associated with the procedure is by proving the procedure against sham. I recognize that this is a difficult proposition but in my mind it is therefore not unethical.

I would now open it up to other subject matter experts who I'm certain will disagree.

Craig Haug: Operator, can we get the next commenter?

Operator: Next question from the line of Dr. John Barr.

John Barr: Thank you. Actually I've been waiting quite a while so part of what I wanted to answer was probably almost an hour ago there was an issue about new fractures. In fact among the 15 reported trials, 11 did report on new fractures and of those, two showed a statistically significant difference.

The (Farooqi) trials said fractures were more common in the control group and the (Blasco) trials said they were more common in the treatment arm. So I think we can conclude from this that there probably is no difference in the fracture rate certainly in a negative fashion from vertebral augmentation either with vertebroplasty or kyphoplasty.

Craig Haug: Do you have any comments with regard to the current question as far as evidence gaps -- evidence gaps that exist?

John Barr: I'm not convinced we have any significant evidence gaps.

I also wanted to comment on the last question which was the waiting period and I'll be very quick with this. Clearly we have evidence that this doesn't cause fractures. We've had fracture fixation is clearly the standard of care for weight bearing bones, we have an excellent safety profile for augmentation, we have an unquestionable survival benefit, we have the benefit to decreased deformity and height maintenance with augmentation.

Whether or not this truly has a durable result for pain, I think we have multiple factors that strongly argue for treatment based on the patients' symptoms without some arbitrary waiting period. And in fact the whole idea of the

waiting period first entered the literature in the original long expired now FDA guidance document which has no listed authors. And there is not any reference prior to that in any medical literature that suggests that there is a reasonable rationale for a waiting period prior to intervention.

Craig Haug: Dr. Barr, wasn't there I think in the Vertos II study didn't they do an extended length outcome where they found that most patients got better on their own and so they made a case for waiting six weeks?

John Barr: I think that may be correct but that was long beyond the time when the procedure started to be popularized in North America and decades beyond its application within Europe.

Craig Haug: OK. And what about the question about evidence gaps?

John Barr: I'm not convinced we have serious evidence gaps. I think rather we have a very compelling body of evidence that there are numerous benefits to augmentation that are unquestionable. The only argument that may still be on the table is exactly what the role is in pain relief, the level of pain relief, the durability. But I think that's really a secondary issue to all the other evidence we have that's compelling that this is a highly beneficial procedure.

Craig Haug: OK, thank you. Operator, next commenter?

Operator: You're next from the line of Dr. Deborah Tracy.

Deborah Tracy: Yes, thank you, sir. I already introduced myself so I won't do that again.

I'm not sure I'm understanding the question, what significant evidence gaps. Do you mean in collecting data and patient selection? Is that what you're getting at in the clinical criteria?

Craig Haug: Well that's the question, I mean there's a lot of different aspects.

Deborah Tracy: OK. So I personally think looking at all this literature it's almost impossible to not have gaps. In patient selection we have issues with time, with the architecture of the spine and the fracture, with the age of the patient, with the

coexisting diseases, with the degree of osteoporosis. In imaging we have in the original studies there were MRIs, there were x-rays, there were CT scans.

There's different doctors choose different things, some patients can't have an MRI because they have a pacemaker or a stimulator or some other cochlea implant or metal object. In the technique I think that the dural puncture in the (Kallmes) study was significant in that I think we watched the medial cortex of that procedure like a hawk and anybody who would get a dural tear would be considered either inexperienced, rushed or maybe negligent.

So the technique also matters and if there is extravasation of cement is it causing other painful conditions and the evaluation of that? The statistical methods would be almost impossible for a medical doctor without a PhD and statistics to evaluate just from reading a paper because we don't get all the data in the paper of the patient selection and different things that happen in the process.

And in terms of survival, I would like to point you towards the documentation by Edidin who did a claims based study and some dramatic difference between conservative therapy and cement augmentation, and (Zampini) who also found a dramatic difference between those who went home early and stayed and mortality and other things including cost.

I would also like to say that in my opinion it is absolutely unethical to not provide this procedure. I mean and in terms of time, I see people in the hospital who are one day after a fall they can't move, they're flat on their back, they have a bed pan underneath them, they have a full e-catheter in place, they're tachycardic, they're hypertensive and there's no way even one day after the fall that I would say no, conservative therapy would be the way to go and they can't tell the (inaudible) brace.

Craig Haug: So are you in the further studies would be unethical camp?

Deborah Tracy: Yes.

Craig Haug: OK. OK thank you.

Deborah Tracy: Thank you.

Craig Haug: Operator, next commenter.

Operator: Your next question from the line of Dr. (Christopher Myer).

(Christopher Meyer): Yes hi, I'm (Chris Meyer) I'm a CAC representative for the Wisconsin Radiology Society and I have no conflict.

And I just wanted to make a comment sort of to tie in to the last person's comments with regard to the reduction in mortality as probably being a stronger argument for vertebroplasty and vertebral augmentation versus conservative therapy. I'm a chest radiologist so I'm more familiar with screening studies and LST, and certainly when we look at randomized control trials we're concerned about mortality reductions.

And it's my understanding that there's at least four good studies out there too by (Edmond) and one by (Lang) and one by (Lin) looking at mortality reduction. And I'm happy to then listen to other people's comments, thank you.

Craig Haug: So if I could just ask which camp are you in; further studies are needed or would be contraindicated?

(Christopher Meyer): I don't honestly I don't know that I have an opinion about that. I think that from what I've seen so far or from what I've heard so far, I don't think that we need to do additional studies.

Joshua Hirsch: Dr. Haug, this is Josh I'd just like to make a quick comment. The largest publication demonstrating the mortality advantage is one where I served as the senior author. I'm very proud of that effort. So I just want to repeat why I think it is ethical in that context and I understand that I am subject to criticism for this belief.

But why I believe that it is ethical to do these types of trials, because I don't think there is any chance that we will convince a sizable group of referring clinicians about the benefit Dr. Tracy, yourself and many others have described absent demonstrating that on sham based trials.

And so if we in my opinion if we think about the mortality advantage across a population versus on that individual patient which is a very difficult argument to make, the greater benefit will be derived from proving to those skeptics that what we believe to be the case is true. I'll just make my comment end at that point, I know there are other people lined up too to speak.

Craig Haug: Yes, and let me just ask the question because this is coming up in my mind more and more when landmark studies come up, not just in this area but other areas. If it goes against, especially if a procedure's already out there and widespread, it seems like it's impossible for the study to ever be good enough to not to be criticized and basically ignored. So that would be the other argument, besides the ethics and the practicality, whether a study could ever be good enough to withstand the slings and arrows of entrenched belief. Dr. Hirsch?

Joshua Hirsch: Oh you're posing that to me? Well I mean I think the challenge is that it's not just belief though it's characterized as belief in the sense that the proponents of the trial are either the patients, the patient advocates or the providers that have done the procedures and seen the remarkable benefit associated with it.

And versus other sort of more general question of if you have a trial that demonstrates for example a medication doesn't work that is already in common usage. This wouldn't occur but I'm trying to get away from a procedure, so in this imagined state where there are reasonable or meaningful alternatives one could imagine a practice change. What we saw in 2009 was that the patients that were not referred in after the trials came in six months later more debilitated.

And so I think that the proponents of the procedure are basing their opinions not just on belief for this type of anecdotal approach but from the I would call it real world evidence of what the conservative therapy cohort does -- and conservative therapy is a real therapy it was characterized earlier as doing nothing, that's not correct -- the adverse consequences of conservative therapy versus augmentation. And I do believe these are some of the reasons we saw the mortality benefit.

It's clear that the trials are an uphill battle both to get done but also to have widespread belief in them. But again, I do think really as far back as our introductory comments, in this particular situation there's really compelling data on that different people can take different things from, and therefore whether you're arguing for the procedure or against it there really is strong data on both sides.

The preponderance of the data is supportive of the procedure the vast predominance, but the few sham trials have obviously really thrown a chink in that armor. Again for me and this may be a largely theoretical comment, I'm disturbed by the 80 percent of patients that are not treated. And I think a lot of that is coming from the fact that there is this really bifurcated belief system in the value and reasonability of offering these procedures.

And if we ever really want to get at that group that in my opinion is suffering unnecessarily, we're going to need to convince the referring community the members that don't believe in the procedure right now. I'm confident that if we were to see that there would be that type of reaction.

Craig Haug: Thank you. Operator, if we could have the next commenter.

Operator: Your next question from the line of Dr. (Melissa Chambers).

Craig Haug: Go ahead doctor.

Rene Chambers: Yes this is -- right thanks. This is Rene Chambers again. I have just a quick comment about this very fact and Dr. Hirsch began by discussing equipoise.

Josh, I'll take your theoretical comment and trump with a philosophical comment. The state of genuine uncertainty on the part of clinical investigators would make clinical trials difficult from a practical standpoint. However, even though there will be questions about the ethics, I think it would be ethical to go forward with clinical trials, I think they're feasible.

I think the fact that emotions often times overshadow facts can be overcome with clinical trials. And there was a publication probably 30 years ago in the New England Journal about clinical equipoise, and that stated that the requirement of equipoise is satisfied when there is a genuine uncertainty

within the expert medical community not just on the part of the individual investigators.

So for that reason, I think there is clinical equipoise. So clinical trials are appropriate if they would not preclude ongoing care to those select patients in need of vertebral augmentation in order to reduce their morbidity and risk of mortality. That's all I have.

Craig Haug: Thank you, thank you. Operator, next commenter.

Operator: Your next question from the line of Dr. John Barr.

Craig Haug: Go ahead Dr. Barr.

John Barr: Yes, actually many of my comments have been made by others already. But my feeling is that it would be of questionable ethics given the very well demonstrated repeatedly survival benefit to augmentation to run further trials on that point alone.

Craig Haug: Thank you. Operator, next commenter.

Operator: Your next question comes from the line of Dr. Douglas Beall.

Douglas Beall: Hey there, Doug Beall again. A comment about the ethical nature of this, I'm going to respectfully with a qualified disagreement disagree with Dr. Hirsch. So I think this is unethical to do this, the (provize) on that is only in a very ethical way and let me tell you why.

This is a (nod out) to our endocrine rheumatology and internal medicine docs, the treatment ferocity versus an underlying disorder and meta-analysis by (Moland) 2011 for (inaudible) said that you have a mortality reduction of 11 percent. So one of the reasons we don't do comparative placebo controlled trials in anti-osteoporotic medications in the United States primarily is because of that.

That was followed by a debate in the New England Journal between (Stein) and (Ray) that said if we know something is effective we shouldn't be using a placebo, and they cited the Helsinki document that reinforces long standing

prohibition against offering placebo instead of something that's known to be effective. So I buy that and I sign off on that.

And the most recent articles referred to previously published just last year (inaudible) and Josh is on the last author in that, I was the second author in that trial and instead of an 11 percent reduction in mortality we reported that vertebroplasty had a 24 percent reduction in mortality and kyphoplasty had a 55 percent reduction in mortality.

So, kind of my definition that may be unethical but to solve if there's significant controversy in the physician population whether or not this is effective or not, the qualified portion of that would be that this could be ethical under certain circumstances for example short term crossover. A very controlled trial with a small number of sites participating with very supervised conservative management so that that -- but in general because of these because of the Helsinki document and the presence of something that has been shown to be effective, I think this is unethical.

And in regard to something that's good enough to withstand entrenched beliefs, we could talk about randomized control trials, placebo control trials et cetera, but we do have a registry that's 1,096 pages total of which 732 patients have six months follow up data that I referenced earlier as dramatic pain reduction, 6.7 point reduction pain and a Rowland-Morris disability that went from severely disabled to mild from a 21 to a seven.

So I think in the absence of something that's beyond criticism, real world data would have to supplant that.

Craig Haug: Thanks Dr. Beall. Let's move on, we have three more questions and about 45 minutes. Now though I think as we go on, some these questions will have already been partially answered, so I would just ask people to not bring up things that we've already hashed before.

Getting to the next question, and it relates to what we were just talking about, what types of information are there? There's not just randomized control trials. And actually one of the voting questions related to what other types of information would be warranted blinded randomized trials, non-blinded,

observational, propensity adjusted claims based data, systematic reviews, and registries as was mentioned.

But this next question relates to the claims based data, which is another way to go about trying to answer the question that sidesteps I think the ethics and practicality issue we were just talking about. So the question is how important do you consider the claims based data which suggests that kyphoplasty and vertebroplasty have a mortality advantage over non-surgical management?

I mentioned in my intro that that Dr. Hirsch's is a senior author on this paper, they found a four percent increase in propensity adjusted mortality risk associated with the drop in utilization after the 2009 study. Dr. Hirsch, you want to lead that one off since it's your baby so to speak?

Joshua Hirsch: Sure. Well my elderly osteoporotic baby. I think that Dr. Haug cites a point we made in the paper.

I would cite a different one which is actually something Dr. Beall just mentioned, using this analysis at multiple time points in fact at every time point, there were very substantial mortality benefits of augmentation over non-surgical management. And this was looking at 2 million patients with osteoporotic vertebral compression fractures over 10 years from the fee for service Medicare database.

What I would say to me the striking point was that at one year the mortality difference was 55 percent between kyphoplasty and non-surgical management which was the most dramatic finding. This corroborates almost every claims based study from multiple databases and actually multiple countries.

There's a single study done in the United States actually friends of mine or at least the senior author is a friend of mine where they found the same finding but applied propensity score matching, and on that basis excluded the data. However, I would without getting into a critique of that technique suggest that to argue that there isn't a signal from the multiple, multiple other papers including papers that looked at morbidity and mortality, including papers that had propensity score matching would be disingenuous. In the same way I

argue that one should try to glean important findings from trials where maybe one doesn't agree with the findings.

So to me that mortality benefit has been very meaningful and it has impacted my specific procedural choice, and I believe that it is at this point having looked at such a large dataset and I think this has been seen on this call well established as part of the discussion. I would say that there are two theoretical reasons that I think this mortality relationship exists.

The first is conservative management is not risk free management. And while we can talk about paralysis and other things that occur with worsening compression fractures, in general patients who are getting conservative management are put at less activity, are put on opioids frequently actually. And there's little question in my mind that these interventions are not necessarily as good as mobilizing someone quickly.

The second thing I would say and this was alluded to by different speakers, there are now two studies Vertos IV and VAPOUR that looked at patients' longer term and did serial x-rays. And I would correct an earlier statement that there is no loss of height after augmentation, I would say there is a far less substantial loss of height in augmented patients.

And when we think about the natural history of this disease and how people get multiple (VCS), it's pretty clear I think that as you add up fracture after fracture, height loss after height loss from untreated vertebrae this could also contribute to the mortality findings that we saw. So Dr. Haug was kind to let me speak about something I feel strongly about, I admit I'm biased, but I consider this claims based data to be very important and it guides my thinking on a lot of the questions here.

I think we should open up to other subject matter experts.

Craig Haug: Thank you. Operator, next commenter.

Operator: Your next question from the line of Dr. Deborah Tracy.

Deborah Tracy: Thank you again, thank you for tolerating me here. I'm so grateful that you've opened this up nationally. I don't think I've ever -- it's ever been done before.

But for those of us on the call who don't have a lot of background in this, I would like to point to Edidin who is one of the authors in the domain of literature we were provided who in 2013 did a study called the Life Expectancy Following Diagnosis of Vertebral Compression Fractures in the Osteoporosis International Journal. He to 858,978 claims, he found that cement augmentation -- he studied cement augmentation to conservative treatment.

The kyphoplasties in the study were 119,000 and the vertebroplasties were 63,000, and the adjusted life expectancy was 85 percent greater for those that received the cement augmentation than those that did not. The kyphoplasty in the study had a 34 percent greater adjusted life expectancy than the vertebroplasty.

Now (Zampini's) claims based study and we're talking about claims based is not in the domain of this literature but (Zampini) let me get that here did a study of a 5,766 patients in February of 2010. He found discharge to home in the operative group was 38 percent and discharge to home in the non-operative group was 21 percent.

He found discharge to skilled nursing in the operative group was 26 percent and in the non-operative it was 34 percent. Discharge to facility was 35 percent in the operative group and 47 percent. Mortality in the operative group was 0.3 percent and in the other group was 1.6 percent. And the cost was greater of course for the kyphoplasty group of $37,000 compared to the in hospital cost of the non-treated patients of $20,000.

So I personally am very impressed by the claims based literature, and to provide this type of study costs tens of thousands, hundreds of thousands in servers and requiring the claims, the Medicare claims based data. Also the National Institute of Health Care Excellence in the United Kingdom did their own claims based study and found that cement augmentation was an appropriate intervention with -- for people with unhealed osteoporotic compression fractures and whom pain is severe and ongoing.

And you can see the compression fracture definitely causes architectural changes in the spine, we know that. So, further pain could also be caused by muscle -- reflex muscle spasm or other conditions that I stated earlier and thank you very much.

Craig Haug: Thank you. Operator, next commenter please.

Operator: Next question from the line of Dr. Douglas Beall.

Douglas Beall: Thank you. So in regard to the claims based analysis there is overwhelming data. (Edmond) had two papers 858,000 which was mentioned, the other one was over a million was 1,038,000.

For (Summit two) the article that was written referred to previously by Dr. Hirsch is that it examined the downward trend in treatment after the 2009 New England Journal articles. And the upshot of that was it put 75,000 people at increased risk of life lost and statistically at least demonstrably at least 6,800 people lost their lives because of the downward trend in treatment. So this is incredibly important.

I would also somebody referenced the (McCall) article previously, I would also caution a broad interpretation of this without actually reading the paper. They did propensity score matching and they did it at short term and long term about a month and a year and found out of three out of the four time points measured there was a statistically significant reduction in mortality. The only one that wasn't statistically significant was the patients at one year they were treated with vertebroplasty but the P value was 0.18.

And if you take all the patients and they called out 71 percent of the patients, if you take all the patients in that dataset you do a propensity score matching as was done in the (Ong) paper with the propensity score match, you get a huge reduction in mortality. So you have to really qualify that before you say there's no reduction in mortality whenever three out of your time points state that there was a significant reduction.

The fourth one is 0.18 and all of the rest (Zampini), (Chan), (Edmond's) both papers, there's papers from (Arthur Lang), there's (Casper) has paper, there's

papers from Hong Kong, from China, from all over the world as was previously. So the claims based analysis at the very basis is consistent and I think certainly cannot be ignored.

Craig Haug: Dr. Beall, how would you compare or think of the registry information versus claims based data?

Douglas Beall: Well registry, so claims based analysis you'd Kaplan-Meier for survival cost regression for mortality. The way that the registry was done is not claims based. In fact the way that this registry was done in the United States registry, it was done according to the Noridian criteria because this was originally the inception of this, this was done as a request from the Noridian region for Medicare.

And so what was done is specifically the LCD the inclusion, exclusion criteria for treating patients with vertebral augmentation the LCD for Noridian was used for this. So this is not only real world data, this is done with Medicare patients, this is done under Medicare criteria using the specific LCD.

So I would confess that dramatically I mean this is as real world as real world gets for the U.S. registry sponsored by society by the way, and just contrast that between the claims based analysis that specifically studied morbidity -- not only mortality but statistically significant reductions in morbidity as well for most of these patients, most of these papers.

Craig Haug: Thank you. OK, let's move onto the next question. I don't think anybody else is in the queue. And again this may be one that we touched on in prior discussions, is vertebral augmentation indicated for patients requiring hospitalization for pain management? Operator, can you see if there's any comments on that question.

Operator: At this time if you would like to ask a question, please press star then the number 1 on your telephone keypad. Again that's star then the number 1 to ask a question. We'll pause for just a moment to compile the Q&A roster.

Joshua Hirsch: Because pausing causes me pain, let me go ahead and make a quick comment here. I think that the hospitalized patient does represent a different

population in the sense that one can argue that they are already potentially far along the pathway of failing conservative therapy.

So, in my outpatient practice I have more extensive discussions about conservative therapy than inpatients that have already been admitted to the hospital with pain. I think that's likely true across much of the country. And this is I think consistent with Medicare efforts and multiple efforts to try to move patients out of inpatient high acuity areas as quickly as is medically safe and reasonably possible.

Craig Haug: And also the decreasing the use of opioids.

Joshua Hirsch: Yes.

Craig Haug: Thank you. Operator, can we have the first commenter?

Operator: Your first question comes from the line of Dr. (Jeffrey Coe).

Craig Haug: Dr. (Coe). Dr. (Coe), your line is open if you can hear us. Are you on mute perhaps? If not operator…

(Jeffrey Coe): OK, I'm sorry I was on mute. I'm sorry I'm here now. Can you hear me?

Craig Haug: OK. Yes we can hear you.

(Jeffrey Coe): I'm sorry.

Craig Haug: It's a common thing.

(Jeffrey Coe): I'm sorry. Orthopedic surgeon California CAC. This subset of patient represents the patients who will benefit from the most from this is equivalent to the unstable hip fractures that require medical stabilization.

And (inaudible) it's actually in many ways a more expeditious and simple procedure to perform, these patients I think probably if you would extract these patients out of Dr. Beall's registry or the other trials that show the increased mortalities are probably the single subgroup that have the greatest advantage. And so, not perhaps not without any exception but as a rule with

rare exception that these patients most likely would benefit from vertebral augmentation assuming the diagnosis is correct.

The issue is as many of these patients get admitted for treatment of back pain and unfortunately the hospitalists perhaps don't make the appropriate diagnoses and delay getting the MRI, radiographs and the like. So it's a question of education and perhaps convincing those that this is a real benefit to these patients. And I'm going to also speak back to the ethics of if you don't mind the ethics of performing a randomized control trial again despite recognizing there's a mortality benefit.

Even if you could ethically perform such a trial and you thought that having a few patients die would benefit the larger patients that would die because you haven't convinced the referral base, you still have to counsel the patients and their families that if you enroll in this trial that there is prevailing evidence that there is a higher mortality if you have randomized the control group. And if you do that you're not going to have good patient selection so it's a catch-22.

That kind of trial would be impossible to perform ethically. I'm done, thank you.

Craig Haug: Dr. Hirsch, it sounds like you're being hoisted on your own petard.

Joshua Hirsch: Yes, I mean I acknowledge that people will disagree with my point of view on this, and certainly I do believe that there are serious questions about mortality benefit of the patient in front of you versus societal. I stand by my comments and I understand that they're subject to criticism.

I will say that trials could consider as was mentioned by other speakers short durations with crossover that would mitigate the mortality concerns. But we don't know when that mortality risk begins and I'm prepared for different people of good intentions and faith to simply disagree on this point.

Craig Haug: Operator, the next commenter please.

Operator: Next question from the line of Dr. Douglas Beall.

Craig Haug: Dr. Beall.

Douglas Beall: Just a short comment on this. The concept about treating acute or hospitalized patients this was studied of course in (Yang) and (Wilcox) VAPOUR trial. The VAPOUR study said if they older had a high intensity pain score higher than the rest of the other sham trials and that they were they had been hospitalized before.

And it reported a greater amount of outcome and improvement of course because the higher the pain score the greater the improvement after the patient's improved. But this has been documented in fact not only the VAPOUR trial but also (Yang) the vertebroplasty versus non-surgical management randomized control trial published just recently.

Craig Haug: Thank you. Operator, do we have any other questions?

Operator: Again if you would like to ask a question, please press star then the number 1 on your telephone keypad. Again that's star then the number 1 to ask a question. And your next question from the line of Dr. John Jordan.

John Jordan: Yes, Dr. John Jordan from Los Angeles area representing Providence Little Company of Mary Medical Center in Torrance and also the chair of the standards and guidelines committee for the American Society on Neuroradiology.

Yes just a brief comment on hospitalization, I agree with Josh at this and others that this is a special group of patients that we're talking about. I think in terms of the clinical management the benefits are somewhat evident, but also the very significant economic benefits. And I think we've all seen cases where patients have been not treated and let go only to return to the emergency room and be re-hospitalized again.

Obviously you get into a significant diminishing returns from a financial point of view in not treating these patients sooner than later. I think also the evidence that was pointed out earlier in terms of the mortality benefits speak strongly to treating these patients while they're admitted.

And then finally the other issue is hospital acquired pneumonias and et cetera, other things that occur when patients are hospitalized for a long period of time would also be mitigated by treatment.

That's all I have.

Craig Haug: Thank you. OK, I don't see anybody else in queue so let's move to the final question.

Are more trials on exercise or rehabilitation interventions needed and will they be done? Operator, can you see if anybody wants to comment on that question?

Operator: At this time if you would like to ask a question, please press star then the number 1 on your telephone.

Your next question from the line of Dr. Douglas Beall.

Douglas Beall: No, I agree with the other speakers that this is all the non-surgical management trials, rehab trials these are repeat literature. I mean 250 articles a year, there's (last man) analysis, there's 1,587 articles in English language and many of these use this as a comparator.

So I don't really think that this needs to be examined any further. We do know the relevant rate of mortality of somebody that has a spine fracture is 8.6 times age match (controls). That comes from a (Colispit) trial. So this is something that's known, people have a known increased morbidity, mortality. We know that by treating them we reduce their morbidity and mortality.

In terms of optimal non-surgical management, I just gave you articles by (Bailey) and (Kim) and (Rasluska) that says there's really no benefit to doing this. I think the only literature gap there potentially may be optimal non-surgical management for patients that have low to moderate pain that are getting better. Non-surgical management is very appropriately applied to patients and this is based on the appropriateness criteria RAND/UCLA appropriateness paper.

If people have a low to moderate pain or the symptoms are getting better, if they have moderate to severe pain or their symptoms are getting worse, one of the seven things were mentioned previously they should go onto treatment regardless of time. So I think the data's replete in this regard and the only potential improvement would be in the refinements of the patients that could tolerate non-surgical management.

Craig Haug: Thank you. Operator next commenter.

Operator: Your next question from the line of Dr. Deborah Tracy.

Deborah Tracy: Thank you again. I would have to compliment Dr. (Jordan), I was to a lecture given by the Providence group and they have very high mix scores, they focus intently on quality. And for Dr. (Jordan) to say that this is a cost and a quality issue I think had great impact.

I would also like to say the question prior to this about hospitalization, when a patient requires hospitalization for a fracture, if their pain is from the fracture they often have other comorbidities like CHF, renal failure, severe osteoporosis from their autoimmune diseases lymphoma, myeloma, and multiple myeloma. And so they should absolutely be considered candidates for kyphoplasty, vertebroplasty.

In terms of exercise, I personally and this has nothing to do with the literature find it a contradiction in terms to ask someone who has a fracture to exercise. And I've seen many patients from acute care rehab hospitals fail that modality and return to the hospital as one of the other doctors suggested as a readmission which is a no-no in this day and age for treatment of their bone fracture. Thank you.

Craig Haug: Thank you. Dr. Hirsch, do you have anything to add here? I don't think anybody else is in the queue right now.

Joshua Hirsch: You know I can just add my experience because I don't consider myself an expert in rehab. What I have clinically employed is physical therapy after the patient returns from for their follow up visit when I think that would be helpful. In my experience the physical therapy that people are able to participate in

when they're acutely suffering from a fracture is really quite limited, and it has more to do with range of motion et cetera.

That doesn't mean it shouldn't be studied because I think any time we can optimize ancillary or alternative therapies that is worth doing. So I think there are probably opportunities there but I would defer to people who are more expert than me on what they are.

Craig Haug: Thank you. We don't have anybody else in the queue so I'm going to reach out actually to my fellow CMDs, I asked them to hold back to allow the maximum time for the experts to weigh in. But since we have a few minutes here at the end I'm just going to ask them if are there any that want to ask a question or make a comment? (Eileen), are you out there?

(Eileen): I am out here. So one of the thoughts that occurred to me is an after listening…

Craig Haug: And you're a medical director for Noridian and you're a…

(Eileen Moynihan): Oh I'm sorry. And my background is one of those rheumatologists. So one of the things I experienced in practice was a very difficult time getting medication for some of these folks in terms of drugs like FORTEO it's almost impossible. How much do you think the difficulty in getting some of those things for this group plays into the fact that treating them surgically becomes more of an issue?

Joshua Hirsch: I'll start that off but I know we have other endocrine and rheumatology type folks on the phone. I didn't catch your name so I'll just call carrier medical director (at the moment).

Craig Haug: Dr. (Moynihan).

Joshua Hirsch: Thank you Dr. Moynihan and thank you Dr. Haug. Dr. Moynihan, I think that there is no question that there's a terrible scourge of osteoporosis and the access to expensive medications isn't the only issue. My own mother took herself off bisphosphonates without telling me and she's a slight Caucasian woman. Really, she is a set up for fracture because she kept hearing about avascular necrosis of the jaw on TV.

I think we have a terrible public health crisis related to osteoporosis, I mean absolutely terrible. And I think that when I talk to patients about vertebral augmentation, I will not talk to them about it without being in context of osteoporosis medication. And what I always say is that I'm a cheerleader, I don't manage osteoporosis.

But I've worked very hard to develop collaborative practices in various institutions with endocrine, and in our institution now also rheumatology to optimize management because what I say to the patients is vertebral augmentation is the battle but the war is osteoporosis. And in a perfect world if people were getting the proper medication for these fractures, I think we would conceivably have less requirement for treating these painful VCFs.

But I feel like we're probably a long way from that. I will say that osteoporotic patients with a fracture are likely to be suffering from pretty dramatic osteoporosis and they should qualify for aggressive therapy with osteoporosis medication.

(Eileen Moynihan): Agreed, easy to agree but difficult to execute. Thanks.

Craig Haug: Any -- yes Dr. (Clark).

(Larry Clark): Yes (Larry Clark) NGS Internal medicine and co-worker with Dr. Haug who did a great job putting this panel together and thanks thank you to everybody. I found Dr. Tracy very compelling, she really recalled my time working as a medical consultant on a rehab unit in her stratification and portrayal of the patients with the comorbidities onto bisphosphonate taking opiates.

And really I need to walk away from this reviewing the mortality data in light of her comments. One of the things that I would like to do I've heard Dr. Beall go back to about three or four papers (Edmond), (Hong), the Buchbinder study that's the Australian study and review some of these implications again. And I think what I want to do is look at some of the findings particularly the mortality findings in light of Dr. Tracy's comments and the comorbidities that contributed to that patient data. Sorry but thank you everybody.

Craig Haug: Thanks Dr. (Clark). Any of the other CMDs out there want to make a comment or ask a question of our experts?

(Steve Boren): Yes I do. Craig, (Steve Boren) here.

Craig Haug: Hi (Steve Boren), yes. Why don't you introduce yourself?

(Steve Boren): Oh yes. My name is (Steve Boren), I'm one of the (NGS) medical directors who work with Dr. Haug and Dr. (Clark). The point I want to bring up is a number of people have mentioned the various costs. It's illegal for Medicare to use cost in making coverage decisions.

Craig Haug: Thank you.

(Steve Boren): You're welcome.

Craig Haug: Any other comments from CMDs? Dr. (Lurvey), introduce yourself.

(Art Lurvey): OK. I'm (Art Lurvey), I'm a contractor medical director in the west coast with Noridian and I want to thank the subject experts.

We are all aware that the literature per se is mixed and we appreciate those who've worked on the studies and those who are deeply involved and understanding the statistics to be able to help us understand which of the studies seem to be better than the other studies and understand some of the problems with the studies. So, I really want to thank the subject matter experts.

Craig Haug: Yes, and did you mention your specialty?

(Art Lurvey): Oh I'm sorry, I'm a board certified endocrinologist.

Craig Haug: Thank you. And there was somebody else who chimed in there along with Dr. (Lurvey).

(Sydney Hayes): Yes, Craig this is (Sydney Hayes) from (Novitas) and I'm a pulmonologist, and I would agree that all patients are not alike and that sometimes time is of the essence. When you are pushing steroids and other drugs for fibrosis and so forth and the collapse starts it usually is more than just one vertebrae and

often once they go to bed and you cannot get them up to cough, clear their secretions it is a death spiral.

So I'm not sure that waiting six weeks would ever be appropriate for those patients, and I do appreciate all the subject matter experts and their input today. Thank you.

Craig Haug: Thank you. Anybody else from the CMD side?

Joshua Hirsch: Craig, could I just make a comment to one of the -- your colleagues that I really appreciate the point made about Medicare not relying on or not being allowed to utilize cost effectiveness data. I would make the following two points.

I believe in alternative payment models of the future, vertebral augmentation is going to actually be widely utilized because I do believe that when one compares it to the expenses that incur directly as well as the indirect expenses of the people becoming much less active across networks and across alternative payment models we'll see an appreciation of the benefits of the early mobilization, diminishing the medication, not needing braces et cetera.

The second point I wanted to make is that the NICE of the NHS is not limited in the way PCORI or Medicare is. They are as part of their protocol thinking about cost effectiveness. And I don't remember for sure but I think it was Dr. Tracy from Florida who earlier referenced the NICE guidance which their first page of guidance is that an appropriate patient's vertebral augmentation should be offered.

And again I'm only making this point because they absolutely consider cost effectiveness in their recommendations.

Craig Haug: Thank you. Any of the (CMDs) want to either ask a question of our experts while we have them or make a comment? If not operator I think Dr. Beall wants to weigh in again.

Operator: Dr. Beall, your line is open.

Douglas Beall: Thanks. Just one comment about the treatment of osteoporosis, so I've treated vertebral compression fractures and I do lots of large vertebral fractures. I also treat patient's underlying disorder and I'll just read just a little bit what the contractor medical director of (Novitas) and I think she'll appreciate this agreement that I don't quite think it's that hard to get approval for anabolics thankfully.

I usually start off with those for people that are the typical patients that have severe osteoporosis and followed by and resort to the therapy and see them throughout their whole course. I mean and the treatment for vertebral compression fractures is no substantive for treatment of the underlying disorders. And for my colleagues that don't treat the underlying disorder, I would encourage you to do so.

We have (inaudible) the treatment gap that's there. The treatment of with vertebral augmentation does not mean the treatment for the underlying disorder that caused that fracture shouldn't be pursued. And so it's a little bit an editorial comment but I do find that it's effective, that it's not that difficult that, provides good, sustainable and many times a whole life duration treatment effect on people that treat their underlying disorder even after you've treated them with augmentation.

Craig Haug: Thank you. Operator if you could open the next commenter but I want to ask them a question before.

Operator: Your next question from the line of Dr. (David Epstein).

Craig Haug: Dr. (Epstein), I don't have you on my …

(David Epstein): Yes (inaudible).

Craig Haug: Yes, I don't have you on my list though. Are you a CAC member?

(David Epstein): Yes, Florida CAC 20 years and no financial (disclose). Did someone else want to make a comment first?

Craig Haug: No. But if you could send us your disclosure form after the meeting I'd appreciate it but go ahead.

(David Epstein): Actually it was already sent and they received it.

Craig Haug: OK.

(David Epstein): So actually I'm an interventional radiologist in the Fort Lauderdale area. I've been initially vertebroplasty then kyphoplasty for 15, 20 years. The vast majority of our practice is inpatient, we get a small number maybe 10 percent are the most that comes to our clinical office. But most of these are patients who have come through the ED typically.

And I have always been very much in favor of the rapid treatment side. I see what happens when these patients sit in the bed and particularly the ones who we have (to be consulting on) after four or five days in the hospital. So my sense of treatment failure, conservative treatment failure is an 80 year old who's got (in bed) no movement facility and has got (one Percocet). I consider that a treatment failure even if it's the first day.

As far as the pain level cut off, I don't do the scale. I just look at someone (inaudible) happens even on the inpatient side someone an 80 year old, 100 year old, we've done 105 year olds if they can get out of their bed faster than I can then I don't think they need the procedure. But I do have a question Beall I would be interested to see.

Now this may already exists I haven't seen it, maybe Dr. Beall has is that we do see on occasions sometimes we have some hair trigger docs in the ER or the hospitalists and we'll get a patient who has a fall of a variable severity has some pain, they get a scan and we see on MR only a (P2) signal in the vertebral body indicating an acute fracture but there's no compression. And let's say that their pain is not severe so therefore we really don't have great criteria to treat that.

But I would be interested if there is or could be obtained the data that shows what the natural course of these fractures that are only visible on MR so we don't have 50 years' worth on data on these what the natural course of untreated non-compressed vertebral fractures particularly in the lumbar spine.

Craig Haug: Dr. Hirsch, do you want to address that?

Joshua Hirsch: Yes, it sounded like Dr. (Epstein) was specifically asking Dr. Beall. I would just say this is straight forward, if a person has limited symptoms I think that independent of the MRI I would recommend managing them conservatively and see how they're doing.

And I think our general guidance that one would get on most fronts including the much referenced RAND/UCLA study that included the multiple different people, I think the amount of height loss is not significant relative to the degree of pain the patient's in. But the situation that you described where the person is getting a scan because the person is trigger happy there's a finding I would absolutely not advocate treating that patient.

(David Epstein): Well these are patients who actually probably do have pain who may have had pain relevant to the fracture. But and again I'm not, we're not currently treating these if they have insufficient pain let's say no pain. But the question was really just going forward is anyone because I get asked this by the referring docs well if you don't treat it…

Craig Haug: Dr. (Epstein).

(David Epstein): Yes.

Craig Haug: Dr. (Epstein), Dr. Beall is back in the queue so it sounded like you were asking him.

(David Epstein): OK.

Craig Haug: And we're coming up really to the four o'clock mark so we got two people in the queue if both could keep their comments pretty short.

(David Epstein): OK.

Craig Haug: Operator, can you open Dr. Beall's line.

Operator: Dr. Beall.

Douglas Beall: Yes thank you. This has been described before. There's a good article by (Wysop) that I can send you that goes along where somebody has an increased star signal or a (flute) sensitive signal but does not hurt, there's exactly the opposite has been described in the same article.

There is another provisional set of data that says if the patient has severe pain but the fracture's not seen hyper-acutely but is seeing acutely meaning more than week. So the synthesis of this is based on what we know, based on what's been described is treat it symptomatically and it's these can be seen. Whenever we think we know everything there is to know about vertebral fractures I mean these are some of the outliers.

But this it has been described before and the treatment is short term follow up meaning two weeks and observation if they don't have very much pain.

Craig Haug: Thank you. Operator, next commenter. And again Dr. Tracy, go ahead.

Operator: Dr. Tracy.

Deborah Tracy: Thank you. I wanted to thank the medical director who stated who complimented me number one. And I wanted to state that when he does go back, I did comment on the Buchbinder study but I didn't comment on the (Cowmi) study that when he does go back to that study to focus on the fact that 1,813 patients were screened and the enrollment was 131 took four years less than half of what their target was which they abandoned after the four years.

And that for 80 percent power each group should have had 133 participants and not 60 plus as they did have, that they accrued patients that were 27 to 52 weeks out from their fracture and that their imaging was inconsistent in other words what Dr. Beall and other physicians have pointed out about edema in the marrow. If you do an x-ray you have no idea what the age of the fracture is and they had x-rays, CT scans and MRIs.

And that the sham procedure finally (RCS) injection is not -- is considered a treatment actually and that's what they used against the cement augmentation. Thank you.

Craig Haug: Thank you. All right, well it looks like we're coming up to the four o'clock mark, I don't see anybody else in the queue. The CMDs any other last minute comments or questions? OK.

Dr. Hirsch, any concluding thoughts?

Joshua Hirsch: Yes, you know Craig I really appreciate the opportunity to co-moderate. And I just want to thank given the very strong feelings people have on both sides of this topic their thoughtfulness and sensitivity of the comments we received and the really high level civilized nature of the discussion. So I just want to nod appreciation to all those that were brave enough to make comments and thank the carrier medical directors and in particular you Dr. Haug for making this discussion possible.

Craig Haug: Thank you and special thanks to you as well for co-moderating and acting the honest broker. I know it couldn't have been easy, so thanks very much for that; I think it added a lot. And so just before closing I'd like to say that the meeting transcript and audio recording will be published on each MACs website in probably about a week I think and the voting results probably the week after.

Remember, only the aggregate, not individual scores, will be published. To have your votes count please return them, I'm going to say by one week, March 27th. I would urge people to use the Excel spreadsheet; that will make things a lot easier for us and probably more accurate. Again if we have to transcribe from some written document, especially if it's sent in, that will delay things and also make it probably less accurate.

So from a variety of standpoints I would really strongly urge people to use that Excel spreadsheet to vote. Again it wasn't meant to put responses to the discussion questions, it was purely meant to log your vote and that will go a long way to speeding things up and making it more accurate. I'm sure I speak for all the MACs and the CMDs in appreciation for everyone's participation in today's CAC. It provided invaluable perspectives and information that will surely inform our future policy.

And again, a special thanks to Dr. Hirsch for acting the honest broker. Otherwise thanks again to everybody and have a good evening.

Joshua Hirsch: Thanks a lot Craig.

Operator: This concludes today's conference call. You may now disconnect at this time.