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Health Technology Clinical Committee Public Meeting

March 22, 2013

Josh Morse: ...state healthcare dollars are safe and proven to work. The program provides a resource for the state agencies that purchase healthcare. We develop these scientific evidence-based reports on the medical devices and tests that are selected, and we facilitate this committee to help them make their decisions. Our objectives, overall, are better health for Washington citizens through the use of proven healthcare. We strive for transparency, to minimize bias, and for consistency. We have the ability to re-review and update our reports as we need to, and we do this through a cyclic process. This is a very high level overview of our process. The topics that go through this program are selected by the director of the Healthcare Authority. They are nominated by our agency medical directors primarily, but anybody may nominate topics for review. We contract with evidence-based vendors to write the evidence reports. We develop key questions. We publish drafts of all of our work products. We collect comments, then this committee we bring the report and comments to the committee for a determination. The agencies then implement. The focus of our questions are, is it safe, is it effective, and does it provide value? Again, we use transparent methods. We seek the best evidence for our reports, and we seek independent decisions from this committee.

The clinical committee decisions must give the greatest weight to the most valid and reliable evidence, objective factors for evidence consideration include the nature and the source of the evidence, the empirical characteristics of the studies, and the consistency of the outcomes. Additional factors they will consider include the recency, relevance, and any bias.

These are the current topics that we have scheduled for this year. Today, again, we will have hyperbaric oxygen and cervical level fusion. On May 17th, the 2 topics will be ablation procedures for supraventricular tachycardia and cochlear implants. On September 20th, we will have carotid artery stenting and cardiac

nuclear imaging, and in November we currently have scheduled 2 updates, one for hyaluronic acid and one for hip resurfacing. We have a number of documents out for public comment right now, including draft key questions for cardiac nuclear imaging and hyaluronic acid, and we have draft reports out right now for the 2 May topics.

And how can you view those draft documents? They're available on our website, which is shown here on the slide. You can join our stakeholder list and receive e-mail updates on what the program is doing and when we publish draft documents or final documents and you can comment or attend these meetings. Thank you.

Craig Blackmore: So, I would just add, excuse me. It's Craig Blackmore. I'm the chair of the committee, and I would just add a technical comment. It's important for the committee members to remind you that we need to speak into the microphone and identify ourselves. The meeting is being recorded, and the transcript is publicly available so it just helps with recordkeeping. It is an open public meeting and we have designated time periods throughout the day when we will be soliciting comments from the public, but those are the only intervals that we really have for the meeting to other input.

The next item on the agenda is HTA previous meeting business, and the first part of that is approval of the minutes from the last meeting and the minutes have been posted on the web and are available to the committee members in your notebooks if I can find them. So, I would solicit a motion to approve the minutes or any comments or corrections that the committee members would see in the minutes.

Carson Odegard: Carson Odegard, I move to approve the minutes.

Craig Blackmore: Do we have a second?

Seth Schwartz: Seth Schwartz, I second.

Craig Blackmore: Any further comments on the minutes? Okay, so we will vote to approve the minutes from the last meeting. This is separate from approval of the decisions made at the last meeting. So, in favor of

approving the minutes, just raise your hands please. Opposed to meeting approval, or?

Josh Morse: Okay, all approved.

Craig Blackmore: We have 8. Okay, next item is we look at the decisions that we made in the previous meeting, which was relating to stereotactic radiation surgery and relating to vitamin D screening and at that meeting we rendered a preliminary decision and then we charged the program staff with taking that decision and formatting it and documenting it and then we have the opportunity at this meeting to make the final approval of that decision. So, the first of those is stereotactic radiosurgery and again, this has been posted, made publicly available, and is contained within the booklet for the committee members. So, I will either entertain comments on the draft findings and decisions document for stereotactic radiosurgery and stereotactic body radiation therapy or I would entertain a motion to approve. Any comments? A motion to approve, or a motion to not approve.

Marie Brown: I would like to motion to approve, Marie-Annette Brown.

Craig Blackmore: Alright, we have a motion. Is there a second?

Chris Standaert: Second from Dr. Standaert.

Craig Blackmore: Second from Dr. Standaert, and all in favor of approval of the draft findings and decision on stereotactic radiation surgery and stereotactic body radiation therapy, please raise your hands. And that is everyone.

Josh Morse: Approved.

Craig Blackmore: Next item on the agenda is the draft findings and decisions around vitamin D screening and testing and again, this is publicly available and has been provided to the committee members in their packets. Any comments on this document from the committee. Alright, can I have a motion to approve, any of the committee members?

Kevin Walsh: Kevin Walsh, I'll make a motion to approve.

Craig Blackmore: And second?

- Carson Odegard: Second.
- Craig Blackmore: From Dr. Odegard. All in favor, please raise your hands.
- Josh Morse: All approved.
- Craig Blackmore: Alright, and so that decision is finalized. The next item on the agenda is hyperbaric oxygen treatment for tissue damage including wound care and treatment of central nervous system conditions. We are slightly ahead of schedule, but I would – do we have scheduled comments?
- Josh Morse: We do.
- Craig Blackmore: Okay, so we will proceed with the public comments starting with the people who have told us in advance. If there is anybody here who wishes to address the committee and you haven't told us in advance, there is a signup sheet out in the hall. Just put your name down, and then we will give you the opportunity to do so.
- Josh Morse: We have one person signed up in advance, Dr. Karen Crotty. You do not have slides, is that correct?
- Karen Crotty: I do not have slides.
- Josh Morse: Okay.
- Craig Blackmore: I will ask anyone who addresses the committee, if you could please identify yourself and tell us if you are speaking as an individual, if you are representing a group, and if you have any financial conflicts of interest, including if somebody has paid to have you come to the meeting. Thank you.
- Karen Crotty: Thank you. Thank you for giving me the opportunity to address the committee. My name is Dr. Karen Crotty. I am an MB, PhD., in exercise physiology is my Ph.D. I am a physiatrist in Spokane, Washington. I am medical director of Spokane Hyperbaric Chamber. They did not pay me to come here. I came of my own free will, and I just wanted to start by addressing the Hayes Draft Report for January 4, 2013. In my opinion, it does not correctly convey the start of hyperbarics in regard to the treatment of central nervous system conditions or wound care.

In the Hayes Report, the quality of each review was rated using the assessment of multiple systemic reviews plus internal checklists. This made it very difficult for me to really understand the report, as this is not the typical way that scientific articles are evaluated. It appeared that perhaps reviews were assessed, but individual research papers were ignored.

Also, I did not find that the material reviewed was very current. They cited 227 references and over one-half of them were greater than 8 years old. The article by Morgani H. in the Journal of Neurosurgery, he dated back to 1969. Even though they stated that no foreign studies were allowed, I found 3 studies that were referenced in foreign journals. Also, the references they cited did not include articles by some of the top research that is being done now in the United States. That would include Dr. Paul Harch from Louisiana State University, Dr. Newbauer who has currently passed on who basically was the father of hyperbarics from Florida, as well as Dr. James from Scotland. Why was their research not included in the Hayes report?

When we look at the cost of certain medications, such as TPA and MS drugs, the costs are astronomical running between \$3000 to \$6000 per month per patient and this occurs month after month. The cost of hyperbaric treatment at a privately-owned hyperbaric center is around \$5600 for 40 treatments. What would happen if a hyperbaric treatment was added to the medical recommendations? My guess is that they would no longer need to be on expensive medications for the rest of their life. We must change the way we think about hyperbarics. Oftentimes, the injury, whether it be arterial insufficiency, deep wounds, or brain injury are quite advanced before they are allowed to get into hyperbarics, and the reason is because insurance does not pay for these. They have to go through fundraising and the whole 9 yards before they receive their hyperbaric treatments.

I feel that we need to start treating all wounds that are grade 2 and above, not just diabetic wounds, but those caused from pressure sores, as well. Many of my spinal cord injured patients are months in bed, because they cannot get hyperbarics. Currently, the law reads that Medicare only pays for grade 3 diabetic wounds and not pressure sores.

Dr. Paul Harch has repeatedly shown that improvements with hyperbarics in brain injured patients using SPECT scans. SPECT scans, in themselves, are very controversial because unless you do them exactly the same way, oftentimes they can give you false results. Yet, when we request insurance companies to pay for hyperbarics we are told it is off label and experimental, yet many antipsychotic drugs are used off label and are experimental in treating the same hyperbaric patients, especially when they become agitated.

My last request is should the committee decide against HBOT, at the very least please approve the coverage to occur at centers who are actively participating in IRB-approved trials. Thank you.

Craig Blackmore: Thank you. That's the only speaker we have signed up. Was there anybody else here that did not have an opportunity to sign up that wished to address the committee, and then if we could check the phone and see if there is anybody who has called in.

Is there anyone who has called in who wishes to address the committee regarding hyperbaric oxygen treatment? Okay, then, let's put the phones back on mute, and we will move on. Next on the agenda is the agency utilization and outcomes.

Kerilyn Nobuhara: Good morning. I'm Kerilyn Nobuhara. I'm the senior medical consultant for Washington Medicaid, and on behalf of the agency medical directors, we would like to thank you for the consideration of this morning's topic, which is hyperbaric oxygen therapy for tissue damage, including wound care and treatment of central nervous system conditions.

Hyperbaric oxygen therapy is systemic treatment with 100% oxygen delivered at greater than 1 atmospheric pressure. These situations are delivered in either single or multiple patient chambers. The AMDG workgroup does understand that hyperbaric oxygen therapy can be truly life-saving in certain situations, and these acute conditions were very specifically excluded from this topic assessment, and those conditions include decompressive illness, carbon monoxide intoxication, cyanide poisoning, gas embolism, gas gangrene, and progressive necrotizing infections. Next slide.

There are 2 codes, which identify the use of hyperbaric oxygen treatment in the outpatient setting. Those are CPT 99183, which is the physician or other qualified personnel in attendance of the patient during the treatment, and HCPCS C 1300, which is the facility fee for hyperbaric oxygen therapy, and this is based on a 30-minute interval of time. Next slide.

The chambers themselves are under FDA 510(k) approval, and they are considered class II prescriptive medical devices meaning that they can be physician owned and they do require a provider with prescriptive authority to actually order the treatment. Hyperbaric oxygen therapy is delivered either in the hospital base or in a freestanding independent facility. Medicare will only reimburse in the setting of an inpatient or outpatient hospital. The joint commission does recognize the Undersea and Hyperbaric Medicine Society, which does provide many safety, as well as clinical guidelines for the use of hyperbaric treatment. This is a voluntary participation, and there are 2 accredited facilities in this state, which are Virginia Mason and Southwest Hospital.

There are a number of hyperbaric chambers in the state of Washington. There are 3 military chambers. The majority of the chambers are hospital based. There are a handful of freestanding hyperbaric facilities in the Puget Sound.

So, why did the agency medical directors select this topic? There is an increasing amount of direct too-consumer advertising for hyperbaric treatment, and when you see statements like this, such as 'do you need a medical condition to benefit from hyperbaric therapy, no.' We are always concerned that there may be some misuse of the technology. Next slide.

The other cause for concern was the variation in practice patterns that we see across the state of Washington, so this is from the Medicaid data. It is paid claims per client per year for ICD-9 250, which is the diabetic wound, and we itemized this based on county and you can just see that there is a tremendous variation in paid claims per client per year for this same diagnosis across Washington State. Next slide.

You can see the same thing happening for ICD-9 990, which are radiation therapy-associated wounds where by county, again, this

is Medicaid paid claims per client per year. You can see a tremendous variation in the number of claims, which are submitted for the same diagnosis. Next slide.

There is a Medicare national coverage determination in place for hyperbaric oxygen therapy. This has been in place, since approximately 2006. There are a number of covered diagnoses, which were excluded from the assessment, and I referred to those earlier. Next slide.

And there are a number of covered diagnoses, which are included in this morning's assessment, and those include the preparation and preservation of compromised skin grafts, treatment of chronic refractory osteomyelitis, crush injuries, and suturing of severed limbs. These are conditions which, again, are all covered based on the Medicare national coverage determination. Next slide.

Also included in this morning's assessment are osteoradionecrosis, soft tissue radionecrosis, and the treatment of diabetic wounds with some very specific clinical criteria, again, Wagner grade III or higher for diabetic wounds, as well as having tried and failed a course of standard wound therapy. Next slide.

Current state policy for L&I, DOC, and Medicaid prior authorization is required for all diagnoses for hyperbaric oxygen treatment. Regence, which again manages the PEBB plan has very specific clinical criteria, for which hyperbaric oxygen is considered medically necessary. They do have concurrent review for some of these diagnoses with treatment review thresholds set between 30 and 40. Next slide.

You also have very specific criteria around coverage for diabetic wounds. Again, they are saying Wagner grade III or higher with other clinical criteria, mainly revolving around the care of the underlying disease, which is, of course, diabetes. Next slide.

The AMDG workgroup established the following criteria ranking for hyperbaric oxygen treatment. For safety, it was felt to be a medium concern, efficacy high, and cost high.

For safety, primarily the concerns revolved around reported adverse events known for hyperbaric oxygen treatment and those

include otic and pulmonary barotrauma, oxygen toxicity, visual changes, as well as changes in seizure thresholds.

For effectiveness, which is also felt to be of a high concern from the agency medical director workgroup. Not only in terms of which diagnoses would best benefit from treatment with hyperbaric oxygen therapy but also there are concerns about what would be the optimal frequency, dose, and duration of the treatment for each of these diagnoses, and the workgroup did intentionally include this as key question 1A in order to get some guidance from the committee for these specific concerns. Next slide.

Cost was also of a high concern. This is a volume-based code in terms of the facility fee and so, what are the cost implications of HBOT compared to other alternative treatments. For the agency utilization data, could you click a couple times? You can see that over the past 4 years, from 2008 to 2011, there has been a slow increase in both the patient counts, as well as the treatment day counts in both the PEBB and Medicaid population. L&I has a very varied population in terms of HBOT therapy. Most of those clients are actually receiving related to some industrial accident. Can you click again? The average treatment numbers per patient are between 23 and 29 in the Medicaid and PEBB populations with the average minutes per patient ranging from 2100 to 2200. Next slide, and can you click a couple times?

In terms of amount paid for the agencies over the past 4 years for hyperbaric oxygen therapy, amount paid from Medicaid \$816,000, 1.9 million for PEB with the per patient averages being between \$5,000 and \$16,000. Next slide.

As you can see on this slide, the type of client which will usually receive hyperbaric oxygen treatment is the older client. So, generally 50 years and older for both the PEB and Medicaid populations. Next slide.

In terms of allowed amounts for payment, the main thing to note is that Medicare does have a relatively high facility reimbursement fee, and you can note that –can you click again – right there where the facility reimbursement for the Medicare population is about 40,000 as opposed to the other pairs. Next slide, and can you click a couple times?

So, for the PEB population, these are the allowed amounts broken down by diagnosis, and you can see that the highest expense in the PEB population from 2008 to 2011 were for any radiation treatment associated wound, as well as for a diabetic wound. Next slide.

For the Medicaid population, we show a very similar trend, in terms of spend, according to diagnosis, where again radiation associated wounds and diabetic wounds represented the highest expense from the Medicaid agency. Next slide.

Again, we were concerned about the variation and practice pattern, so this is the treatment ranges based on days broken down by diagnosis, and you can see that for radiation associated wounds and diabetic wounds there is a range from 3 days to over 100 for a specific client, and click again, and the number of minutes, which are associated with those treatment days, also range widely between 90 minutes and over 12,000. We see the same kind of wide variation in terms of practice pattern and treatment days in the Medicaid population with treatment days ranging from 1 to 93, and click again please, and the treatment minutes ranging from 30 to over 8,000.

So, what are some of the risks, which were a concern for the AMDG workgroup? There is a small concern about a lack of regulatory oversight for the freestanding HBOT facilities. There is not a true designated third party to oversee the actual facility functioning and safety recommendations. The second is that this technology assessment was very challenged by a lack of definition of clinically meaningful outcomes, and it was also challenged by the tremendous variation in practice patterns. Part of the reason for that challenge is that there are no clear endpoints for treatment and a very basic example of that would be what is the definition of a healed wound. Because of the lack of clear endpoint for treatment, cost effectiveness studies are very, very difficult to conduct. The other risk is that reimbursement, much like any other technology, which is assessed here, is based on utilization rather than on episodes of care. What are the benefits for hyperbaric oxygen therapy? Of course, promotion of wound healing, reduced risks of major amputations, and potential for limb and/or functional salvage for the patient.

Other agency considerations, the most frequently utilized indications for HBOT, as I just showed you, are actually supported by a moderate quality of evidence, which you will hear from our vendor, and those diagnoses are the diabetic foot ulcers, the late effects of radiation injury, as well as osteoradionecrosis. You will also see that the quality of evidence is low for certain commonly used diagnoses for HBOT treatment, and those include refractory osteomyelitis. We would actually note that some of the quality of evidence was probably adversely impacted by the wide array of available treatment options for refractory osteomyelitis, so keep this in mind as you are going through your deliberation of this technology. The other caveat would be that there are frequently overlaps of indications for HBOT treatment and an example would be that complex diabetic and radiation injury associated wounds are frequently treated with skin grafts or flaps and therefore, the quality of evidence was probably also adversely impacted. You will also hear from the vendor that there is a paucity of evidence supporting the duration, frequency, and dose of HBOT for specific diagnoses. The AMDG recommendations to the committee would be to cover with conditions in the inpatient or outpatient hospital setting only for the treatment of diabetic foot wounds. We would maintain that the Wagner grade III or higher would be important to keep in your consideration of this technology. We would also recommend that HBOT be covered as an adjuvant treatment for refractory osteomyelitis, late radiation induced tissue and bone damage and for the prevention of osteoradionecrosis following tooth extraction. We would also recommend the HBOT be covered for the prevention of loss of function or for limb salvage for those patients who have compromised flaps or skin grafts.

We would recommend that HBOT not be covered for thermal burns; venous, arterial, and pressure ulcers; migraine or cluster headaches; multiple sclerosis; acute and chronic sensorineural hearing loss; cerebral palsy; and traumatic and chronic brain injuries. Any questions?

Craig Blackmore: Thank you. At this point, are there any questions from the committee members specific to the agency report?

Michelle Simon: Hi, this is Michelle Simon. I have a question. I am wondering if you looked at the treatment patterns in hospital-based clinics versus freestanding clinics and noticed if there was any difference

in the scatter versus time for treatment or days of treatment in hospital versus private?

Kerilyn Nobuhara: We did not look at the freestanding facilities, because we do not reimburse the freestanding facilities. They do not have core provider agreements with Washington Medicaid.

Craig Blackmore: I just wanted to clarify a couple of slides. Your slide #7, can we bring that back up please? And while she is bringing that up, you talked about on your slide #24, HBOT treatment course variation by diagnosis and you pointed out that there is a tremendous range in the number of treatments that people get for radiation for example and for diabetic wounds and you gave us the average and you gave us the range, and I wonder if you had information on the mode or what the most common number of treatments is or the distribution? Because my problem is, you know, somebody only got 1 treatment. Well, that doesn't mean they got better or something could have happened to them, and somebody got 100 treatments, and that could be an extreme outlier that affects the average. But, if I know that most of the people got 20 treatments or less and then the rest are outliers, that's useful. So, I don't know if that's something you have access to right now, but if you did it would be useful.

Kerilyn Nobuhara: So, first question, the denominator is small for both of these, especially when they're broken down by county. So, let's say that this is really just a visual representation. I wouldn't really include any kind of statistical analysis of that, if that's what you were trying to drive at.

Craig Blackmore: Well, so this is a number of treatments when you say paid?

Kerilyn Nobuhara: They are paid claims per client, and a claim can range in the number of units or number of minutes that are associated with them.

Craig Blackmore: Okay.

Kerilyn Nobuhara: I did not include that, but the number of units or number of minutes associated with each claim will vary between 1 and probably 8.

- Craig Blackmore: Okay, and then should those bars go all the way to the bottom of the graph?
- Kerilyn Nobuhara: To zero? No.
- Chris Standaert: I think the bottom line is the minimum treatments for that thing and the top line is a maximum. Am I reading correctly? The bottom one...
- Craig Blackmore: Yeah, minimum and maximum, okay. I'm glad I asked, because I was confused. Thank you.
- Kerilyn Nobuhara: And then in terms of your second question, I'm not sure if Margaret has that data or not.
- Craig Blackmore: Yeah, I don't know if, while we're going through other things, we could get that. If we can, great, but otherwise, any other questions?
- Carson Odegard: I have one. Carson Odegard, in respect to the range of treatments, I see that the necrosis and the osteomyelitis ranges are narrower; however, the beginning of the treatment starts at 14 or 15, it doesn't start at that but goes up to 14/15 days, which is quite a stretch from the other conditions that are 1 to 3 days. What's the nature of the disease or the wound that jumps it up? Maybe the clinical expert would know? Does that make any sense?
- Craig Blackmore: Why don't you hold that question until we get through more of the scientific background, but in terms of this report? Okay, so thank you and the committee will have more opportunities to ask other questions as they come up. I just want to sort of respond to Carson a little bit. We always have a clinical expert in the room when we discuss the technologies and that is to make sure that there is not some clinical aspect of the care that is not apparent to the committee that is affecting the decision making such that we're not acting on the best evidence. So, if I could please introduce Dr. Neil Hampson and if you could just give us a sort of – first of all, thank you for being here, and if you could give us a 1-minute introduction to introduce yourself to the group, that would be great.

Neil Hampson: I am a former hyperbaric practicing physician. I retired in 2010 after 22 years of practicing at Virginia Mason. I am board certified in 4 specialties, internal medicine, pulmonary disease, critical care medicine, and undersea hyperbaric medicine. I have been the president of the Undersea Hyperbaric Medical Society, which is the premier scientific medical society for hyperbaric medicine in the world. I have been the chairman of the hyperbaric oxygen therapy committee that puts out the report every 4 years of recommended diagnoses for treatment that is used by the FDA to determine what hyperbaric chambers can be marketed for. I have been involved with government level hyperbaric decisions for 15 years. I am most interested in carbon monoxide poisoning, which is not on your list, as you deem it already proven. Any questions about my background?

Craig Blackmore: So, again, thank you for being here. The way we work this is that the committee is charged with making their decision based on the best available evidence and the evidence vendor, Hayes in this case, is charged with reviewing the literature and summarizing evidence, and presenting it to the committee. We rely on the clinical expert to make sure that we are evaluating the evidence in the proper clinical context, because none of us are experts, and definitely not all of us experts in this field. So, your role really is to be sort of on call and we will, throughout the morning, have a lot of questions for you and we will let you know when we need your input.

Neil Hampson: Okay, I have answers to almost all of the questions that have been asked so far, so.

Craig Blackmore: We're off to a good start. Okay, thank you. Now, looking at my watch, it is – where are we?

Josh Morse: We are about 30 minutes ahead of schedule.

Craig Blackmore: Yeah, so we're still ahead of schedule. I want to just – because we moved quickly through the open public comments, I just want to make sure there isn't anybody here who came late but was expecting to be in the open public comment period and make sure that if there is anybody who showed up late that they still have an opportunity to address the committee. So, is that the case? Is there anybody here who had hoped to address the committee and has just arrived? Okay, I just wanted to double

check. So, we will move on and the next item is the evidence report from the Hayes group.

Female: I just wanted to tell you briefly, we had the trouble with the slide [inaudible] arrived back.

Craig Blackmore: Okay, thank you.

Karen Crotty: Hi. My name is Karen Crotty. I am the director for health services research at Hayes. Before joining Hayes, I was the assistant director at one of the country's evidence-based practice center at the University of North Carolina at Chapel Hill, so that should either give you more confidence or less confidence in my ability to do the review. My objective today is to efficiently but hopefully with enough detail walk you through this report. It is a very large report, so the biggest challenge, I think, getting through all of this in the time that I know Josh and Christina are going to make me stick through. So, if it seems that we are moving from indication to indication rather quickly, that's because we probably likely are, but I am very happy to answer questions, probably better to get through the report, but I am here to facilitate you and your needs to make a decision. So, let's see how that goes.

The key questions, there were 5 key questions, as were outlined by Kerilyn that we wanted to look at. The majority of this presentation, the majority of the report, in fact, concentrates on the first key question, which is the question of effectiveness, because that's where most of the data was. We were hoping to see some data on optimal frequency dose and duration. There is very little out there. We have some data on harms. We want to address any evidence that is out there on differential effectiveness, so we tried to look at that again, not a lot of data, and the cost data will also be briefly discussed. So, we examined a comprehensive list of evidence when we looked at this from all of the usual sources, though we won't spend time going through this. We also looked at guidelines. We looked at the national guideline clearinghouse for guidelines that might be relevant here.

So, I am going to spend no more than about 5 minutes walking you through the methodology, but I am very happy to come back to the methodology and discuss any and all of the issues, including those that came up during public comments, but briefly

to select the evidence, we conducted a title and abstract review. When we scoped this topic, it became obvious that it is a very large topic, and Washington State wanted to cover all of these 9 indications, so we made a decision to essentially select systematic reviews and to supplement the systematic reviews with primary data that was published since. Now, in doing that, it is a limitation to the report, the systematic reviews that we looked at, plus the primary data. They cover 156 primary data studies to have looked at all 156 individually would have been a much longer report. We are, however, confident that where the systematic reviews did not give us enough detail on being able to adequately rate the quality of each individual study, we pulled that individual study, and we rated the quality of that, and we did that for quite a number of these studies. Our methodology, as you will see, for rating the quality of the evidence is aligned with that of grade, of Cochran, and of the agency for healthcare research and quality. So, Hayes has a criteria checklist that aligns with all of those. So, this line basically is hard for you to see, but it's an indication of how we selected the systematic reviews and the primary data studies that we looked at. In all, we selected 21 covering 156 approximately studies.

I've spoken briefly about the quality. We rated the quality of systematic reviews, then we rated the quality of the individual studies using the information within the systematic reviews and pulling it where necessary, and then we graded the body of the evidence. Now, I am going to pause for a second to discuss briefly the grading of the body of the evidence. So, after rating the quality of each individual study we then looked at that. We looked at individual study quality. We looked at the applicability to the population interventions, the comparators, and the outcomes of interest. We looked at precision and the quantity of data around the estimate of effect. We looked at the consistency of the studies in the direction that they went, and we tried to look at publication bias. So, it's these 5 domains that drive the final decision of whether an indication was given a high, moderate, low, or very low grade. So, this is what you already know. If something is given a high quality grade, it basically means we have high confidence in the results and future studies are unlikely to change the estimate and the direction of affect. If something is low or very low, then we have very little confidence, and future studies are very likely to change, both the estimate and direction of affect.

So, if everybody is comfortable with that, we will move directly into the evidence and make an attempt to get through it. So, the first key question, as I said, is going to – the majority of the presentation we will focus on this. Because of the number of studies evolved here, I am going to present the data according to the level of evidence found, because I think that makes most sense for the committee. So, for example, we are going to discuss the indications for which we found moderate quality evidence of the effectiveness of HBOT followed by those indications for which we found low quality evidence of effectiveness. We will then look at the indications for which we found moderate quality evidence of no effectiveness and finally we will briefly discuss those indications for which there was simply insufficient evidence, either because of a lack of data or because the results were quite mixed.

So, moving to the indications for which there is moderate quality evidence of effectiveness, we will look at the diabetic nonhealing wounds, late radiation tissue injury, and traumatic brain injury, as well. So, for diabetes, we found moderate quality evidence suggesting that the addition of hyperbaric oxygen therapy to standard wound care promotes wound healing and obviously we won't discuss all of the studies for all of the indications, and we will concentrate on the main results, and one of the key systematic reviews here pooled data from randomized controlled trials and found that HBOT was effective in complete wound healing, and as that was pointed out, the definition isn't always clear of what complete wound healing is, but over a 6-week period, patients that received hyperbaric oxygen therapy were more likely to have complete wound healing than those who are not, and the finding was found to be clinically meaningful in that just 8 patients needed to be treated for 1 patient to have complete healing with the absolute risk difference between the hyperbaric oxygen group and the control groups of being around 12%. That was at 6 weeks. The 12-month data for this did not reach significance, but there was a large amount of heterogeneity, as you can see by the I-squared between those studies, so we decided to look at those 3 individual studies. One of those studies was a poor quality study, so we weren't able to draw any reasonable conclusion from that. The other 2 both showed quite a significant benefit in favor of HBOT for complete healing. In addition to those trials, there were observational studies from

other systematic reviews that also showed benefit. Primarily, I think there was 1 study, which was a cohort study, that showed no difference between the 2, but for the most part, the observational study supports the data from the trial data. So, that was for the instance of complete healing.

With regard to diabetes, we also looked at amputation as one of the major outcomes of interest. So, there was pooled data from 5 studies, also found that hyperbaric oxygen therapy was effective in preventing or reducing the risk of amputation and therefore improving limb salvage. This, again, the relative risk for this in the pooled data did not reach significance, but one of the studies excluded patients that were at very high risk for amputation, and when that study is removed, the data becomes significant at that point. In addition to that, there are some observational studies that also showed benefit to hyperbaric oxygen therapy for patients, 14% versus 31% in favor for one study and there were a number of case series, which obviously are not presented, but the data for the risk for amputation generally points to a benefit for the use of hyperbaric oxygen therapy.

So, with that, we will move to late radiation tissue injury and we can certainly come back to any questions on all of the indications as we go. So, a complicating factor in the study of late radiation tissue injury is the difficulty in comparing results across the anatomical areas. There was a Cochran review, which did make this attempt to look across all anatomical areas, and data was pooled from across studies and for 4 trials, there was a 36% versus 28% in favor of hyperbaric oxygen therapy found, but once again, and mainly due to the fact of the variation across anatomical areas, there was high heterogeneity and so the authors of that report, of which Dr. Hampson was actually one, did not provide an overall estimate of effect, but they did in that review go through the various anatomical areas to give the results, and there was a strong indication from those studies that there is a benefit to hyperbaric oxygen therapy, particularly for patients that had head/neck cancers, as well as cancers of the rectum and other cancers in those areas.

So, there have been a few recent studies. Also on this, one of the studies that is listed up there is a 2012 study that is the study on hemorrhagic cystitis and while that study actually compared hyperbaric oxygen therapy with intravesical hyaluronic acid

installation, and it did not see a difference between the two. They were both beneficial for improving. This outcome is on the resolution of tissue damage, or necrosis, and 6 months and 12 months and 18 months there was significant improvement with both treatments. So, hyperbaric oxygen therapy was not found to be better.

In addition to that, there are several case series, which show anywhere from a 50-100% complete or partial healing with the use of hyperbaric oxygen therapy. So, we always look at the data that supports the trial data. The other outcomes of interest for late radiation tissue injury prevention of osteoradionecrosis after tooth extraction in an area that has been radiated also shows benefit to hyperbaric oxygen therapy. In fact, there was data from 9 pooled observational studies showing that the instance rate was 4% versus 7%, overall in favor of hyperbaric oxygen therapy. In addition to that, there is evidence to suggest that complete mucosal cover and establishment of bony continuity for osteoradionecrosis also benefits from the adjunct treatment of hyperbaric oxygen therapy. So, the evidence for the use of hyperbaric oxygen therapy in relation to osteoradionecrosis is fairly moderate. One of the more controversial indications, I believe, is the indication of traumatic brain injury because there was a good quality Cochran systematic review, which looked carefully at this just a number of years ago. It was either last year or 2011, and they pooled data from studies, and they found that hyperbaric oxygen therapy significantly reduced the likelihood of death amongst patients with traumatic brain injury with a number needed to treat of just 7 to prevent 1 death. However, for those patients that survived, there was no evidence of a functional benefit. When the authors looked at the likelihood of an unfavorable functional outcome, which was defined as anything from severe disability, vegetative state, or death there was no benefit to hyperbaric oxygen therapy. So, this is one of those indications where the evidence is moderate that patients may have a higher likelihood of surviving, but the benefit after that is largely unknown. The data is imprecise and inconsistent. So, that is something for the committee to keep in mind.

So, those were the indications where there was any level of moderate quality evidence. Moving to some indications where there is evidence of benefit, but the quality of the data is low. So, for these, we look at other nonhealing wounds. We look at

refractory osteomyelitis, and we look at the acute phase of sensorineural hearing loss. So, for the nondiabetic wounds, we see that there does appear to be some short term benefit to the use of hyperbaric oxygen therapy, but the data is sparse. It is generally of low quality, and because a lot of the studies looked at ulcers but looked maybe specifically at venous ulcers or looked at pressure ulcers, the data when aggregated is not very strong. There is some data on compromised grafts and flaps also, which does show benefit for hyperbaric oxygen therapy, but again, the seven studies that are involved here, the quality of the data was unknown for one, not unknown because we pulled it from a systematic review but because the authors of the study provided so little data that it was not possible to adequately rate the quality of that study. There were other poor and very poor studies. Now, they all showed benefit, so there was consistency in the direction of the result, but we have fairly low confidence in the methodological rigor of these studies, which is why compromised grafts and flaps and crush injuries both get a low quality of evidence but showing benefit.

So, refractory osteomyelitis, as was pointed out, this is an indication that is currently covered and the problem with refractory osteomyelitis is that the data comes from very poor quality studies. Regardless of where you look and how you look, most of the studies on this are case series. They all show an extreme benefit for hyperbaric oxygen therapy but as you well know, relying on case series is a difficult thing to do. There is one poor-quality nonrandomized control trial, which is the trial that is quoted the most. That trial did not show a benefit, but again, I would have very low confidence in the methodological rigor involved in that study, too. So, there is a lot of evidence out there, all showing benefit for hyperbaric oxygen therapy for refractory osteomyelitis, but the quality of the evidence is not strong, which is why it is sitting here in the low quality evidence segment. There is some new and increasing evidence to suggest that while the evidence for complete resolution of refractory osteomyelitis is not there, evidence for a reduction in the risk of relapse does perhaps suggest that there may be a benefit. It is showing mixed results here, because there are two studies, but one of them was a poor nonrandomized trial. The actual fair quality nonrandomized trial, which is the first one, is a very recent study. I think it was in late 2012, and although it's just a trial of 32 people, so this doesn't get to move the indication into moderate

quality evidence for this outcome. It did show that 0% versus 33% in favor of hyperbaric oxygen therapy for prevention of relapse rate. So, I think the jury is probably still out is the takeaway message from that.

So, migraine was one of the indications that the director regroup was interested in looking at, and we have placed migraines in the category demonstrating benefit, because there was pooled data from three fair quality trial suggesting a significant benefit in favor of hyperbaric oxygen therapy for the resolution or significant relief of migraine. In fact, the numbers needed to treat for patients to have resolution or significant relief was just two. So, with a relative risk of 5.97, so the estimate of effect here is very high, but they are three very small studies. The total sample size is still only 43 for these studies, and so while there was a strong benefit in these, this still was graded as low quality evidence, because there simply was not a big enough sample size to warrant giving this a moderate quality level of evidence. In addition to that for all the other outcomes that we would be interested in, in relation to migraine, things like pain intensity, frequency of migraines, the need for rescue medication, and there are really only two studies that are of interest here. There was no evidence that hyperbaric oxygen therapy was beneficial in reducing the risk of those or improving symptoms.

So, sensorineural hearing loss has probably gained the most traction, I would think, in recent years for hyperbaric oxygen therapy as a treatment, and I think the takeaway message from this report looking across the evidence is that it is still mixed. There is some evidence in the acute phase for patients that present within two weeks of sudden hearing loss that hyperbaric oxygen therapy may be beneficial in recovery, but what the evidence showed was that patients were significantly more likely to have a 25% return of hearing but not a 50% return of hearing, and the clinical meaningfulness of a 25% return of hearing is difficult and probably largely depends on the severity of hearing loss when the patient presents. The problem with the data is that there was no standard severity scale for entry into these studies, so the patients varied quite greatly in how severe their hearing loss was. Now, of these studies that are here, there were two studies, which did stratify the patients according to severity of hearing loss, and they actually both found contradictory results. One found that the more severe the hearing loss the more benefit

that was achieved from hyperbaric oxygen therapy. The other found no difference based on severity. So, again, the evidence is mixed there. If I had to weigh one way or the other, there is some evidence to suggest that for patients that present early, there may be some benefit, but the quality of the evidence would be low.

So, moving on to those indications for which we feel there is moderate quality of evidence of no effectiveness, we are going to look at the chronic phase of sensorineural hearing loss and multiple sclerosis. During the public comment section, there was a comment to say that a lot of the studies are old, and that actually is quite true, particularly in relation to multiple sclerosis and that is not because we did not look for recent studies. It's in relation to multiple sclerosis. There has not been a randomized control trial done since the very early 1990s. So, there seems to be a lack of interest in the scientific community, because I think people feel that this question has been answered. The studies that were found in that early evidence really found no meaningful benefit for the use of hyperbaric oxygen therapy for multiple sclerosis and there likely has been observational data since, but there has not been a clinical trial. The same is also true for both of the outcomes that we looked at for multiple sclerosis. Similarly, for chronic sensorineural hearing loss, there does not appear to be a benefit to hyperbaric oxygen therapy for those patients that have chronic hearing loss. Now, of the two studies, two fair quality trials that are in here, one of them defined chronic as anything beyond two weeks. The other one defined chronic as anything after six months. So, even within the available data, there is not consensus but both showed that there was really no benefit beyond that time. Then there are those indications for which we wanted to look for answers, and we really didn't find an awful lot. So, for those that there is insufficient evidence, we include crush injuries, thermal burns, nontraumatic brain injuries, cerebral palsy, and headaches. So, we won't go into detail on all of these, because there is little point when the evidence was really that there was maybe one or two studies and where there were more than two studies, there were mixed results. For example, if you see there cerebral palsy had three fair quality studies. One was a randomized control trial and that also had four studies, but basically the results were mixed. Some showed that there was benefit. Some showed that there weren't, and we basically would have low confidence due to the high risk of bias

associated with those poor quality studies and then the inconsistency in the results.

The same is true for thermal burns. There were just two fair quality RCTs. One showed a benefit and one did not. Surgical reconstruction and grafts and flaps and crush injuries is interesting because those again are indications for which many people do cover, and it's difficult to find good quality studies from those, and the evidence for both shows a benefit, but we just didn't find enough of the evidence for it to get a grade other than insufficient for the purpose of the report.

So, we then looked at, at least we tried to look at, the optimal frequency dose and duration for the treatment, and several of the systematic reviews that we selected planned to look at these indications but found a paucity of data. People did not look carefully at this. There were three systematic reviews that looked at frequency and dose, but the evidence from those was insufficient, mixed, and it mainly came from studies that had a high risk of bias. So, unfortunately, the question of the optimal frequency dose and duration remains largely unanswered.

Fifteen of the systematic reviews and four of the primary data studies that we looked at provided data on safety. I think the overall data on safety is that with hyperbaric oxygen therapy, the harms are generally mild and self-limiting. They usually end with the end of treatment. The most common harms that we see are barotrauma, visual disturbance, claustrophobia, and on rare occasions there have been cases of oxygen toxicity, which obviously is not a mild harm.

Notable indication-specific harms from the literature, I will not go through everything on this slide, because it basically just reiterates the harms that I just discussed, but for the indications that we did find some harms for, it included those harms that were mainly ear problems, temporary visual disturbance.

The third question was an attempt to look at the differential effectiveness and safety of HBOT. We found no evidence looking at sex, race, ethnicity, disability, wound duration, or treatment setting. The data simply was not there. We did find some data on age and severity of hearing loss, but the data was mixed, and I do have a slide coming up on both of those. We found some low-

quality evidence to suggest that the radiation dose that a patient had been exposed to may be a factor in late radiation tissue injury and there is also some evidence to suggest that measuring transcutaneous oxygen measurements may be an indicator for patient's ability to respond to hyperbaric oxygen therapy. So, on that, there was a randomized control trial and a poor quality, as they all are, case series looking at the area of age and sensorineural hearing loss, but the study found that there were no significant differences between patients younger than 50 and older than 50. The other report, the case series, found that patients greater than 50 were more likely to benefit but that was a case series. So, overall, there is insufficient evidence as to whether or not age is a factor. Similarly, for the degree of hearing loss, we discussed this when we were looking at the data on sensorineural hearing loss. There is basically insufficient data, because it is mixed. Some studies are saying that the more severe patients are more likely to benefit, but that is not consistent in the results. With regard to the radiation dose. It appears that patients that were exposed to greater than 60 Gy of radiation dose may benefit more from hyperbaric oxygen therapy and its ability to prevent osteoradionecrosis. So, that is something we have to consider.

With regard to transcutaneous oxygen measurements, there is evidence to suggest that if TCOM is measured under hyperbaric conditions, then it is a fairly good indicator of a patient's response to hyperbaric oxygen therapy. There are also a number of studies, which look at measuring transcutaneous oxygen measurement in normobaric conditions. So, having a patient breathe 100% oxygen but outside of the hyperbaric chamber, and then there were some studies, which also looked just at breathing some elevated oxygen, but the results on those are mixed, as to whether or not they are an indicator of how well a patient may respond to hyperbaric oxygen therapy.

So, finally, we wanted to look at cost from the point of view of value and unfortunately, there are a lot of studies out there from two very good quality systematic reviews. There were 11 studies, which overall provide low quality data suggesting that hyperbaric oxygen therapy is cost effective, but the data is severely limited by first of all the sparse amount of data on cost and the varied amount of data on cost, and also the unreliable efficacy estimates that we have just been discussing. So, of the 11 studies that were

included, there was just one model, which was found to be robust during sensitivity analysis. So, overall, the current data is simply insufficient to determine the most cost effective uses for hyperbaric oxygen therapy. That one study that was robust was a Canadian study in 2007. It was looking at diabetes, and it found that adjunctive hyperbaric oxygen therapy was dominant over standard care for patients with patients the quality adjusted life years were 3.64 versus 3. For the controls, the 12-year patient costs were just over \$40,400 US dollars, those are 2012 adjusted dollars, versus the almost \$50,000 for the controls. That really is the only study that was found to be robust, so evidence generally not strong.

We looked at practice guidelines to give a reference to the data that we have found and also just to look across agencies to see what others have found, and we looked at 27 reviews. We included 14 of them. They covered a range of the indications, as you see here. Two of the guidelines were cross-cutting. In other words, they looked at more than one indication. The European Committee for Hyperbaric Medicine recommended hyperbaric oxygen therapy for nonhealing wounds where standard care had not been effective. This is in line with what we have found when it comes to diabetic foot ulcers. A 2006 report by the wound-healing society in the US recommended hyperbaric oxygen therapy for diabetic foot ulcers. Interestingly, NICE in the UK did not recommend the use of HBOT for inpatients with diabetic foot ulcers, even though they did cite the fact that there is moderate quality evidence of effectiveness. Looking at pressure ulcers, three of the four guidelines that we looked at agreed that hyperbaric oxygen therapy should not be routinely recommended and in line also with what we found, the DOD and the VA do recommend hyperbaric oxygen therapy for the prevention of amputations.

Other guidelines that were of interest, the guidelines on late radiation tissue injuries tend to agree in favor of hyperbaric oxygen therapy for prevention of osteoradionecrosis and treatment of late radiation tissue injury. The most recent guideline of interest, I think, is that from the American Academy of Otolaryngology, which went ahead and recommended hyperbaric oxygen therapy as an option for patients who present within 3 months of the onset of sensorineural hearing loss. Now, the panel did look at the evidence, and they noticed that the

evidence was modest and imprecise, but they decided that it was sufficient to promote greater awareness off the therapy.

Very briefly, we looked at the payer policies, and this was discussed just before my presentation, and we basically, for those indications that we found moderate quality of evidence, those were indications that generally have been covered by the payers we looked at. There was one notable exception and that is refractory osteomyelitis, so we found low quality evidence, again based on the rigors of the studies, all four agencies that we looked at cover refractory osteomyelitis for hyperbaric oxygen therapy and again, the probably reason is because it is particularly difficult to have a trial that is of good quality for this particular group of patients. For the issue of sensorineural hearing loss, one of the payers is actually now covering it. So, you will see for those indications that we found low or insufficient evidence, the payers are generally split on whether they cover it or not.

So, just a quick recap. Moderate quality evidence for indications that we looked at were the diabetic foot ulcers, late radiation tissue, osteoradionecrosis. There was that moderate quality evidence for the reduced risk of dying but remember there was no improved functional outcome for TBI. The low quality evidence of effectiveness for some of the other nondiabetic, nonhealing wounds, refractory osteomyelitis, the acute migraine relief, but not for the other outcomes for migraine and then the acute phase of sensorineural hearing loss has mixed evidence leaning toward possible effectiveness. No effectiveness for multiple sclerosis and the chronic phase of sensorineural hearing loss, and then those indications for which the evidence was insufficient are noted on the last slide.

So, it would be remiss not to point out the gaps in the evidence. Clearly, there is still a need for methodologically rigorous studies. We were not able, for example, to answer the question on subpopulations, differential effectiveness. We were not really able to answer the question on the adequate frequency, duration, and dose, and we really do need more robust models on cost effectiveness, but of course they require more effective data on estimates to include. So, I do have some additional slides if we need them, but I think I will hand it over to all of you for questions at this point, and I will call on Dr. Hampson, if needed. So, thank you.

Craig Blackmore: Thank you. So, at this point I would like to ask the committee members if they have questions specific to the report. Generally, the way that we do this is, we focus on you for a period of time and then we have an open discussion amongst the committee where we would still almost certainly have further questions, but at this point, are there any questions specifically relating to the report we just heard?

Seth Schwartz: This is Seth Schwartz. I have one question on slide 21. I was looking at the amputation rates and when you share the pooled data, it said it was ineffective, but when they excluded the study of high risk patients, then it became effective, and I'm just curious about one, what did that study of high risk patients look like? Did it show no effectiveness at all? And is that – I guess is that something that was handled in any other studies, this classification of high risk patients? Is that a standard classification or was that – did they do something unique in that paper?

Karen Crotty: The answer to your question on whether or not they found effectiveness is they did not find that with patients – when they excluded patients for high risk of amputation, there was not a benefit to hyperbaric oxygen therapy in that one study. So, I think you can – it's hard to know what to read from that, because it was one particular study, and it was not a particularly large study. So, I think the review of authors from, this was also a Cochran review, they did note that when you conduct a meta-analysis and you have the five studies in there, it came very close to showing effectiveness. If you look at the risk, it was quite close to showing effectiveness and with removal of that one study, it did become effective, so.

Seth Schwartz: I guess one of the questions would be in followup, did the other four studies exclude those high risk patients, or were those patients just mixed into the general population in the other studies?

Karen Crotty: They were mixed in from the point of view of they were not excluded. These studies don't always give you a lot of information on who the patients were and what their risk for major amputation was. This was a quirk of that one study where they simply excluded patients that were at high risk, and it may have

been for IRB reasons potentially. So, but yes, they had a mixed population.

Michael Souter: This is Mike Souter. I just had a question about the sensorineural hearing loss. Looking through the evidence tables, the longest followup period I could see far back evidence of acute benefit was six months. Is there anything that you know to contradict that?

Karen Crotty: I'm sorry. Can you repeat the question?

Michael Souter: I'm talking about sensorineural hearing loss and the evidence of acute benefit. The longest followup period I could see was six months.

Karen Crotty: Yes.

Michael Souter: Okay.

Karen Crotty: No, there are no studies that I know of, I think, that go beyond looking at six months, and in fact some of them immediately post-treatment and within weeks, six months is probably the longest, and there may only have been a couple of studies that looked that far even.

Chris Standaert: Alright, I have a couple of questions. One, thank you for the report. There's a lot of stuff. I recognize the scope of the topic. I personally always find it troubling when we get reports that are reviews of systematic reviews. I think we lose granularity every time this is done, which always gets troublesome for me, but there's a lot of data here. Specific questions, one, so the studies on TBI, I'm confused by your language. One, TBI is a ginormous range. You can have a very mild concussion to a very severe catastrophic head injury, and they're all TBI. So, you didn't mention at all what kind of patients we're talking about. Then, this issue of you reduce the risk of death but you don't improve function, but on a functional scale, just being alive has to be better than being dead, right? So, that doesn't inherently make any sense. So, if the issue is that there are studies that look at outcome being, do people survive the injury or not survive the injury and then you find lower rates of death, and then there are separate studies that look at equivalent levels of injury that get treated, and there is no functional improvement noted, those are two totally different types of studies, and that is where I'm getting

confused. I'm not sure what we're talking about here, again, in even the type of patients we're talking about with head injury.

Karen Crotty: Sure, yeah.

Michael Souter: Can I just offer a quick observation, just because neuro-critical care is my area there, and she is separating out death and poor functional outcome is a very common scenario in looking at treatment of traumatic brain injury. Your question about the range. As to how it pertains, I think that is appropriate, but it is not unusual to divide death and pure functional outcome, because for many people looking at persistent vegetative state can be analogous or even thought sometimes to be worse than death.

Chris Standaert: Oh no, that's where my question comes from, because there's a judgment here that's sort of, you know, yeah – that goes back to the whole nature of the studies and why I'm a bit confused, because if you take patients who have a severe injury and you treat them and what you're measuring is sort of – if the only two outcomes are going to be death or persistent vegetative state, again, one could make a judgment call that depending on the individual views of the family, the patient, and the whole thing, but I'm unsure who the studies were designed and what the outcomes were and whether they are binary in that manner or whether there is a subpopulation of people who survived who actually had some degree of true function performance and cognitive performance that was just equivalent to those in that same cohort who survived and weren't treated. So, the way it's phrased, and again this is where the granularity issues comes when you look at systematic reviews. I'm not – I'm not sure what you're talking about.

Karen Crotty: Sure.

Chris Standaert: Does that make sense?

Karen Crotty: It does make sense, and I agree with you on both items. I think we absolutely lose granularity when we have to look at systematic reviews, and it's difficult to decide what to do with your resources. Do you try to cover as many indications as you can, or do you take two and look at them in great detail? Specifically for this, I can tell you that the patients in all of these studies, it was

not consistent as to who was enrolled. It was consistent that they all had severe closed-head trauma, and the Glasgow coma score ranged from 3 to 12 across these studies, and I know that is huge.

Chris Standaert: That's huge. I mean, that's – 3 to 12, I mean you're going from essentially nonresponsive to alert and somewhat communicative.

Karen Crotty: Yes, and of those four pooled studies, two of them the patients were comatose and two of them had inclusion criteria that simply said the patient had to have somewhere between a GCS score of 3 and 12. So, you're absolutely correct. The variation here in the type of patient, the severity of the disease, was quite great. Now, interestingly, the heterogeneity was 0% when you look at those four pooled studies. So, despite the fact that there was this potential variation in the trauma, it did not seem to affect the outcome that was being measured. I'm not sure that's helpful other than from a methodological point of view. It seemed that it was okay to combine these particular four studies. I mean, that's basically all that tells us is that it was okay to combine these four studies. If we were looking at an 85% I-squared up there, then you'd say they should never have combined these four studies. We should only look at them individually. But even within those studies, when you're talking about enrolling patients that have very mild TBI to comatose patients, it's an enormous range, so as with everything else, we'd like better data for sure.

Chris Standaert: And where are some of those studies on patients where mortality wasn't the primary endpoint? Where they took people who survived their brain injury and looked at their outcomes, and was that washed out in the results of everything else, or were there no studies like that? I'm just – I'm still trying to wrap my head around what you're saying.

Karen Crotty: Sure, yeah. Well, the four – those particular pooled studies that are up there looked at both. They looked at mortality and then they looked at those patients who survived, but I – we could go back to look at the data to see if there were studies that only looked at functional outcome. When I look at the followup period here, you can see it ranges from 10 days to one year, so clearly here were patients that they looked farther out. So, whether they were patients that were in a persistent state of vegetation or whether they were patients with functional

outcomes. You're right. A limitation of this is that we didn't get to delve into that.

Chris Standaert: Right. It's a little tricky for us, because when we look at significant outcomes, obviously survival is a significant outcome, and we are going to have data that says they survive, but it's fuzzy. So, my other question is.

Craig Blackmore: Actually, can I?

Chris Standaert: Oh, sorry. Go ahead. You want to say something?

Craig Blackmore: Yeah, I want to just drill down on this a little more. So, I'm trying to understand this, and what I'm seeing is that there are four fair quality randomized clinical trials, 387 patients, and they show a mortality benefit with the number needed to treat of seven, which is huge. I mean, there is basically nothing in medicine that gives you a mortality benefit in a number needed to treat of seven. But at the same time, I am seeing on here that there is a followup timeframe somewhere between 10 days and one year. So, I don't understand how they're generating a simple risk ratio. Is this survival analysis? How are they coming up with this? I don't understand the inclusion criteria, except that it seems to me that the mortality rate, overall, is between 30 and 40%, which would imply that these are not Glasgow coma scale 3 people, unless they are dying of other causes. So, I'm sort of, I'm trying to understand how this all fits together. If these people have a Glasgow coma scale of 3 and they're dying, they're not dying from their head injuries, but yet they're dying, and yet we're seeing this huge mortality benefit. So, and then the third piece is why are these fair trials? Why aren't they good? What's wrong with them, because the data that I'm seeing here, again I'm not buying it without more information. So, I don't know if you have access to the trials themselves that we could get more information on, but I think we will need to understand. There's a little bit of a disconnect that we need to understand.

Karen Crotty: Sure, yeah, and I'm more than happy to share the particular review. That comes from – one thing that I do know is that the studies did not provide detail, as to the end cause of mortality in these studies, and so your suggestion as to if they had a GCS of 3 they didn't die from their TBI, what did they die of is an extremely valid question. So, we can either – I can either spend some time

now trying to pull out some of the individual study data or I can provide it.

Craig Blackmore: We'll take a little break, and we'll all get coffee and if you're working through the coffee break, sorry, but that would be very useful.

Chris Standaert: It would be useful.

Kevin Walsh: Just as a followup to that, I think one other thing that would be useful is that you mentioned that the inclusion criteria was GCS 3 to 12, but I'd be interested to know what the range of patients actually enrolled was.

Karen Crotty: Okay.

Chris Standaert: Yeah, the whole who are we talking about question. Who we're talking about really matters.

Craig Blackmore: And were the things they died from actually equally distributed among the groups, you know? If they're...

Chris Standaert: If they died from chest trauma with their head injury, then it doesn't matter.

Craig Blackmore: Right.

Chris Standaert: Mike's shaking his head over here. I have one more question. If you want to stay on this issue, you can...

Michael Souter: Well, no. I think Craig has suggested coffee, and maybe that's best.

Craig Blackmore: Well, I was suggesting that when we get to the coffee, but we could do that.

Michael Souter: I'd just make a comment. I mean, this is an area that I worked in all the time. Trying to tease out – we're generally talking about small studies. We're talking about studies - we've already outlined a significant range of pathology that comes in, and even GCS, itself, can seem as a very arbitrary classification for what are very different pathologies that present. The main observation I would make, and this is just my observation as a practitioner in

this area is that anytime you are looking at followup studies of 10 days, that's worthless in terms of, you know...

Chris Standaert: Unless that's when they die.

Michael Souter: Well, again, looking at people who die early, again, there is great heterogeneity for why people die. Some people will die from their injuries, late complications. Some people will die because their families decide when a sufficient time has elapsed for it to be a reasonably detailed level of prognostication that they will decide that they no longer want to pursue care in those circumstances, and there may be advanced directives operating. So, there is a high frequency of withdrawal of care in those circumstances, even though somebody may actually be surviving from their pathological injury. That happens all the way through that kind of continuum of care, so it makes an incredibly thing to tease out.

Craig Blackmore: And it – and it also means that you cannot assign a simple risk ratio to mortality when you've got variable timeframes for your endpoint, and that's what I don't understand here.

Chris Standaert: I'm with you. So, my other question is, you talked about healing of nondiabetic wounds, and you talked about studies that looked at the use of HBOT and wounds that did not show effective healing. What is effective healing of a normal wound? How do we define that? Do you know?

Karen Crotty: Well, I know that each of the authors did a fairly poor job of defining it. They simply defined it as complete healing. Some of the studies looked both at complete healing and also in reduction in wound size.

Chris Standaert: They talk about applying it to patients who are not showing effective healing. So, that is – I guess my question would be whom that is exactly, and if you leave it open to the – so if we say language like that at some point, it gets very tricky for us, again.

Neil Hampson: There's typically no reduction in wound size with standard wound care over a predetermined amount of time of a month or six weeks.

Chris Standaert: Okay, thank you.

Kevin Walsh: One more question about the migraine data. It seems pretty clear that for most of the other outcomes, there was no benefit, but I am trying to understand the one where there was benefit. Was that using hyperbaric oxygen to stop an active migraine attack, like a single attack? And if that's the case, was that single treatment or was that multiple treatments?

Karen Crotty: It was usually a single treatment of 45 minutes.

Craig Blackmore: So, how can you have resolution or significant relief but not have resolution or significant relief in the pain, the nausea, the vomiting, the frequency, or the need for rescue medication?

Karen Crotty: Well, I think they basically followed patients for the week afterwards and so they would have measured resolution of pain immediately afterwards and then they looked, it was usually over a week or 10 days. So, their definition of complete resolution was likely immediately post treatment, whereas when they looked at need for rescue medication, etc., the data basically suggested that either the migraines returned or how they look at those outcomes is just somewhat different.

Craig Blackmore: Yeah, and so when we say there were three fair randomized clinical trials that there was relief in migraine, you know, again I get back to the question of why were they fair. They were very small, so that would be one limitation. I mean, was there a sham comparison or was there some sort of blinded assessment of outcomes, because obviously that would be a huge factor here.

Karen Crotty: Yeah, I mean, for a study to be rated as fair, it would have to have first of all no fatal flaw in the study that would render it. For example, if it was a randomized control trial and randomization was somehow broken, clearly that would go in there. We would have looked at blinding. We would have looked at allocation concealment. We would have looked at study power doesn't get taken into consideration when you're assessing the internal validity of a study. So, it's looked at separately. So, while a study might be very small, when you're looking at the internal validity and the methodological rigor, you're assessing things like selection and blinding and whether or not the groups were comparable. So, there was nothing about these studies that would have rendered them to be poor from a methodological

perspective, but taken together and looking at that sample size, I think you would have to take that into consideration, because while the internal validity might have been fair. The applicability to the general population of patients with migraines is obviously very small.

Craig Blackmore: Right, but I'm still asking the question why they were fair instead of good. I mean they had problems.

Karen Crotty: Oh yeah, exactly.

Craig Blackmore: Do we know what the problems were for these that you could...

Karen Crotty: For the – I would have to look at each of the three, but for the most part it was always a lack of reporting as to the method of blinding or to the method of randomization. Those were usually the two things that – because for something to be given a rating of good, everything would have had to have been reported well. There would have to have been evidence of centralized randomization. There would have to have been evidence that the groups were allocated using concealed envelopes or whatever, and for the most – it's usually not that they didn't do it. It's usually that they didn't report how they did it.

Craig Blackmore: Okay, thank you.

Seth Schwartz: This is Seth Schwartz. One comment and one question about that. The question would be, do we know how the controls were treated for those trials?

Karen Crotty: I will have to look at it.

Seth Schwartz: Okay.

Karen Crotty: For those particular three studies, I am not sure if – my memory is that there was no treatment. It was hyperbaric oxygen therapy versus no treatment, but let me double check for you in case there was a sham treatment for any of those three.

Seth Schwartz: I think that's interesting to know, because we know there are a number of medical treatments and other things that might be as effective as this, so that would be useful to know. The second is just a comment, which is that if we have three randomized trials

with a total of 43 patients, many of those trials might have had five patients in each group. So, it's interesting to know what the statistics look like for those papers, because it is hard to believe that for the studies that it said they showed.

Karen Crotty: Yeah.

Chris Standaert: And again, I assume – you know, this migraine thing they're talking about as an abortive treatment for a single episode of migraine is, I assume, what they're talking about, right?

Karen Crotty: Sorry.

Chris Standaert: They're talking about the hyperbaric oxygen therapy as an abortive treatment for a single episode of migraine.

Karen Crotty: Yeah.

Chris Standaert: These questions of rescue medication almost become irrelevant to that individual event, because you're talking about as an abortive treatment for one event, not trying to change the long-term – if you're doing it every single time, you could alter the medication. That's the whole study-designed question. How many patients? Is it a one-shot deal and how do you get people with an acute migraine to get to a hyperbaric oxygen therapy chamber quickly to abort them?

Karen Crotty: Yeah.

Chris Standaert: I mean, it – I'm thinking the same thing Seth is thinking that if we can look in the weeds a bit, we may find it doesn't show exactly what it says it shows.

Michelle Simon: Yeah, it might be nice to know if these were done in the Emergency Room or in private settings, also, or who funded them. I'm just curious about that.

Chris Standaert: Yeah.

Neil Hampson: I was just saying [inaudible] hospital-based facilities.

Craig Blackmore: So, I have another question, another can of worms, here. I'm looking at slide 20, which is the diabetic nonhealing wounds.

There are a number of studies here demonstrating some benefit, but I wondered, we had a lot of discussion about the grade of the wound and you say you've got a lot of variability in terms of the grade for the entry criteria for the studies, but I wondered if among the three or four randomized clinical trials if we can tease out the effect size among different grades, or if they all included a mixture or sort of what that case mix looks like.

Karen Crotty: Yeah, sure, and I do actually have that in front of me. So, unfortunately, it's probably not going to be what you want.

Craig Blackmore: Probably not.

Karen Crotty: But, the inclusion criteria, it did vary in those trials. So, one of the trials, which was a trial by Doctor in 1992, that's actually his last name. He wasn't just the doctor. It included any person with diabetes with a chronic foot lesion, and the time was not specified. Faglia in 1996 included people with diabetes and Wagner grades II, III, or IV. Lynn in 2001 and Kessler both enrolled people with early diabetic foot with Wagner grades 0, I, or II, and Dugan 2008 and two other trials simply included patients with diabetes whose lesions had been present for more than four weeks, six weeks, and three months respectively. So, that's all we have. That's all we know from these studies.

Craig Blackmore: But do we understand – I mean, those are different populations. Do we have information on the effect size and the different – I mean, we've got one statement 0 to one, and how did that one do? And we have one study on longer-standing ulcers. We need to try to tease that out.

Karen Crotty: Well, if you notice, all of them seem to include a range like that. Not one of these studies only enrolled patients with Wagner III and IV, and the ones that included patients with a range did not stratify their results, so we don't know. We simply know that they lumped them all in together and this is what they found.

Craig Blackmore: Okay.

Seth Schwartz: Do we know the basis for the Regence decision or other decisions to use a level of Wagner III for coverage?

Kerilyn Nobuhara: It's from the Medicare NCD.

Craig Blackmore: Did the Medicare NCD provide justification for their decision.

Neil Hampson: Yeah, I could go through that. Is that okay?

Craig Blackmore: Yeah, please.

Neil Hampson: Well, in a grade 0 is a wound that you can't see, so it's easy to heal that one. A Wagner grade I is a superficial wound that is easy to heal no matter what you do. So, if you randomized them to crunchy granola, it will prove effective, as effective as standard wound care. A Wagner grade III is an exposed bone or a deep abscess, and in actuality I was surprised to see in your utilization data that there are that many patients that are getting hyperbaric treatment in this state for diabetic foot wounds, because it is very hard to qualify someone for hyperbaric treatment by the Medicare criteria. You have to have a Wagner grade III wound that has failed to improve with a month of standard therapy and there aren't too many patients that don't get amputated before a month is over if they're not improving with antibiotic and local wound care therapy, but that is the level of wound which you need to have to show a difference in outcome between hyperbaric and no hyperbaric and most of that comes from the Faglia study, which was done in Italy, and they had a variety of – they had II, III, and IV I think. They had moved them all to the hospital for three months and had one randomized to standard wound care, dressing changes, antibiotics, leg elevation, all the usual, and the other got the same thing plus hyperbaric, and grade II's had no difference and grade III's and IV's did have a difference in major amputation, and that's where CMS got that from.

Craig Blackmore: So, that was one of the trials that you had listed on slide 20 here? Is that right? Yeah, okay.

Chris Standaert: So, they did stratify on that study, then? He just said that they did stratify on that study.

Karen Crotty: I was looking at the TBI data.

Craig Blackmore: We're giving you too many things to do at once here. Do you have access to the Faglia study that we could confirm if there is stratification published on the different categories? Because that

may be important to the committee. Why don't we – it's just about 10 of 10. Why don't we take a coffee break. We have inundated our team with questions and work, so why don't we take about 15 minutes and start up again at 10:05.

Alright, I'm going to call the meeting back to order. It's five after. Alright, I'm going to ask the committee members to resume their seats. We will get back in action here. So, how are we doing on that lengthy list of questions and further work?

Karen Crotty: [inaudible]. So, I believe one of the questions was what [inaudible]...

Craig Blackmore: I'm sorry. I think you need to be just a little closer to the mic.

Karen Crotty: Alright, is that better?

Craig Blackmore: No, worse.

Karen Crotty: Oh, how about now?

Craig Blackmore: There, yes.

Karen Crotty: Okay, sorry. Excuse me. So, one of the questions was what were the controls? Were there sham treatments, and so, the sham treatments varied, of course, from just breathing air at a normobaric conditions, air at a pressure of 280A, 10% oxygen between 2 to 2.5, and one of the shams was actually 100% oxygen but at normobaric rather than hyperbaric conditions. I think just one of the studies also had patients on a medication. Was that what we saw? They all looked at termination of the acute attack within one to two hours of the treatment, and so those other outcomes – so the question was if only two patients needed to be treated for complete resolution, then why are we looking at things like rescue medication, pain, etc. So, they looked at things like nausea and vomiting, which, of course, are common symptoms of migraines. They look at the week post treatment to see whether or not there was an increase that benefited those, and it didn't. So, I guess, and I would need the clinical expertise on this, if a patient has a migraine, and they have resolution of the pain from the migraine, is it still possible that they can have the nausea and vomiting associated with the migraine without that pain. I don't know the answer, but that's what they looked at and

found that hyperbaric oxygen therapy did not improve those symptoms.

Chris Standaert: But they're very small studies, yes?

Karen Crotty: They're very small. They're very small studies.

Chris Standaert: We have the type 2 error issue if after acute migraine, nausea, and vomiting isn't that common – it's common enough but it's not everybody and you only have 10 people and then you have to try to find the difference between the groups of five on something that occurs in one out of 10 or 20.

Karen Crotty: Yeah, they wouldn't have empowered to find that.

Chris Standaert: You don't get it.

Karen Crotty: So, that's what I came up with for the migraines. Does that help?

Carson Odegard: Yeah, it helps.

Karen Crotty: So, the TBI – I am still in the throws of looking at that, but some answers, I think, to the questions – I think the main issue, the main question you had was what did – who were these patients, and it does vary across the studies. What would be nice actually would be to be able to pull up the types of meta-analysis. I know you can't see this. I'm holding it up more for my effect. When they do these meta analyses, they obviously have the estimate of affect for each of the studies and showing the confidence interval, and this might be helpful to look at. There isn't an enormous amount of detail in here about who they looked up. I can go through each of the studies to tell you whether or not they looked at both death and a nonfavorable outcome, if that's helpful.

Chris Standaert: If you can tell us about the studies – I guess as I keep thinking about it, what – if you're looking at mortalities in outcome in particular, that would be useful. I don't know if the studies exist or if you looked at this, but if you get an improved short-term mortality in the first month or so, then that would be significant. But if it's all jumbled together and they just don't tell us that sort of thing, then they just don't tell us that sort of that thing, so I'm just curious about what the details of the studies were.

- Karen Crotty: Yeah, it is a little jumbled, and there probably isn't exactly...
- Chris Standaert: The answer.
- Karen Crotty: ...the answer. The answers may or may not be in the details of each of the studies, because sometimes they don't say – they do say, you know, what their followup point was for each of the individual studies. One of the studies reported that all patients reach the final followup point of 10 days. So, that would have been – that was their measure of where they looked and whether or not the patient died, for example. So, that study wouldn't give us details as to what happened post 10 days.
- Chris Standaert: I mean, can you give us some of the details of the individual studies?
- Karen Crotty: Yeah.
- Chris Standaert: So we can see what we were talking about again?
- Karen Crotty: For sure. So, the study by Arturo. So, these are, some of these are quite old studies. There was no blinding, obviously, for most of these. The patients had closed head trauma. They did stratify their patients, but then they did not present those results by stratification.
- Chris Standaert: How many patients did they have?
- Karen Crotty: Sorry, they had 60 patients, 31 in the HBOT group, 29 in the control, and it was one hour for 10 days. They followed by four days rest and repeat if not responding. The standard care, so the control was hyperventilation and furosemide and they looked at death, unfavorable outcomes, and adverse events, and their measure was the jaded score. The actual Arturo and Rockswold at 12 months – I'm sorry. I'm trying to see if I can actually pull out individual study data from each of these. The problem is when Cochran do the systematic review and they pool the data, they don't then give you the individual study results for each of those, except as here. For example, I can actually pull it from here, I guess, if I do it that way. Arturo found a risk ratio of 0.88. That was not significant because the confidence interval...
- Chris Standaert: Are you talking for death or risk ratio for what?

- Karen Crotty: This is for death. So, the risk of death with hyperbaric oxygen therapy. So, patients that received hyperbaric oxygen therapy was 0.88 times less likely to die than a patient that did not, but the confidence interval went over 1.
- Craig Blackmore: That's at – at what interval was death? We don't know?
- Karen Crotty: As in how – at what time did they?
- Craig Blackmore: Yeah.
- Karen Crotty: I don't know the answer.
- Chris Standaert: Yeah, and this is the issue with reviewing systematic reviews, that we don't get the data that – to find it for us.
- Craig Blackmore: [inaudible] an issue.
- Chris Standaert: Oh, it's certainly an issue with how they did the study, but we just don't know that.
- Karen Crotty: And so the...
- Marie Brown: They had random assignment you said? All those had random assignments?
- Karen Crotty: So, these were – these were all randomized control trials, but they were not blinded clearly. It's – the assessors were blinded in some cases, but clearly the patients can't be blinded. So, I'm sorry that wasn't perhaps as helpful as you need it to be. I think you did have one other question that we looked at, which was – we were talking about the diabetic foot ulcers.
- Craig Blackmore: Stratification of ulcers.
- Karen Crotty: Actually those, so the diabetic, the slide 20, the three pooled studies, Faglia – actually I was incorrect. Faglia was not one of those. The Faglia study was related to the amputation. So those, the incidents of healing for three other studies where there was no stratification for those three. The Faglia study that Dr. Hampson was referred to, Dr. Hampson says that the CMS used it primarily for their decision, but it was not in – they didn't look at

incidents of healing, so it is not included in those three. It is included in the study on amputations.

Craig Blackmore: And which – do we know where that is in here?

Karen Crotty: Yes, sorry, just let me...

Craig Blackmore: Anybody find what slide we're on?

Karen Crotty: So, here we go. So four of the amputations...

Chris Standaert: Slide 21.

Karen Crotty: ...for the pulled data, the five studies were Dr. Faglia, Abidia, and Lundale. So, there was a total of 309 patients. They showed a trend toward benefit from HBOT in the rate of major amputation, which, I just had the definition of that, was with no statistical significance between the groups. So, the study that had the high risk of amputation was the Lundale study, so that's the discussion we had when that study was removed. I am trying to find the details for Faglia here. HBOT provided no additional benefit for minor amputations.

Let me tell you a little bit more about those four studies to see if that helps. So, the Abidia Study – again that was a small study, 18 people with diabetes, just two groups. They showed no – they included patients that showed no sign of healing at six weeks.

Craig Blackmore: Why don't we do this. I think it's going to be important to the committee to understand whatever evidence there is around differences between Wagner II and Wagner III that was identified in some of the other coverage decisions. So, if you could try and track down that particular study and report back to us in a little while, and I think we've got – we're gonna have to break up this topic into a bunch of different segments, so I think we can start working on some of the other pieces of it and give you a chance to get your thoughts together and drill down. So, that being said, what I'd like to do then is sort of organize our discussion for the rest of the morning. We've got a whole bunch of different potential indications for hyperbaric oxygen therapy. There are some that are outside of our scope that we've heard about where it's being used, and we need to focus down on the specific ones that are in the key questions, and I just want to make sure that I

get to the key questions so we get this correct. Somewhere we must have the key questions. Yeah, I'm looking for the key questions. Okay, page two of the Hayes slides.

Key questions, okay, so here looking at slide four, there are a whole bunch of specific clinical indications and, I think we could either...

Marie Brown: What page are you on?

Craig Blackmore: I'm on page #2 of the Hayes presentation, slide #4 of the Hayes presentation. So, I think we've got our three options, right? We can approve, we cannot approve, or we can approve with limitations. So, I think what I would propose is if we go with approve with conditions that the conditions be defining the specific clinical scenarios where the coverage would occur, if that makes sense. Then, we would go through each of these areas where we were asked to make a decision and decide whether or not that was one of the conditions. Then we would have one vote at the end. The other way to do it would be to go have a separate decision for each of these and I just think it's simpler to do it the way I described. So, I am going to start us in the place where we are headed towards approval with conditions. If we go through all of these and we want to approve them all, then when we get to the vote we would just vote for no conditions, and if don't approve them all and we get to the vote we would just vote for no coverage. But, in the meantime, I think we can sort of chug our way through here and figure it out.

So, I think to start, we're not going to do the diabetic yet, because we're working on that. Why don't we start – I'm going to stay away from soft tissue injury that might – why don't we start at the bottom? We'll start at the bottom. Sensorineural hearing loss. So, I'm going to ask the committee, I'm going to ask a committee, I'm going to ask a committee member, a volunteer, to summarize where they think we are in terms of sensorineural hearing loss as a way of initiating the discussion. Does anybody want to take a stab at it? Dr. Hampson?

Neil Hampson: Can I make a few comments about the process and maybe ground it a little bit?

Craig Blackmore: Sure.

Neil Hampson: Assigning this topic to the Hayes group was an enormous task. It's like you're asking them to do a review of a specialty of internal medicine. It's like saying what is chemotherapy good for? And they had probably I don't know 3,000 or 4,000 articles that relate to these topics, and I agree that reviewing systematic reviews is not always as satisfying as you would like, but the amount of literature behind this is overwhelming. The Undersea has a great medical society has a committee size of yours that meets and reviews the literature and these are specialists in hyperbaric medicine from across the country and around the world where that's their job, and we have a hard time keeping up with it. So, the fact that she doesn't know the answer to all these questions is not surprising, because nobody on our committee knows all the answers to all those questions either. It's a lot of information. I practiced hyperbaric medicine for 22 years, and I can tell you that just because something has evidence of efficacy from a positive randomized controlled trial does not mean that we endorse treatment of it. An example would be the migraine issue. Those are old studies. Oxygen is a potent vasoconstrictor, and that's what you want in migraines, so people tried some experiments to see if it worked in migraines, and it did, but none of us treat migraines. I think that would be cost ineffective, because there are such effective medications nowadays to do that in the Emergency Room. When I look at your list, at Virginia Mason we do 4,000 to 5,000 hyperbaric treatment a year. So, I don't know what that means I've treated in 20 years, but I never treated a patient with acute traumatic brain injury, chronic brain injury, cerebral palsy, any kind of headache, multiple sclerosis, or sensorineural hearing loss. UHMS has a list of indications that they believe are supported by evidence that supports efficacy and a cost –benefit ratio that is favorable, and none of those things are on their list. Actually, sensorineural hearing loss was just added, but people that are very familiar with this field have done the work that you're trying to do right now, I think, and I'm trying to think of a kind way to say this, but you're reinventing the wheel a little bit. I'd be happy to go through each one of these indications when you get to them and tell you what the standard of care is in the United States.

Craig Blackmore: Thank you for your comments. There are a lot of organizations that do work that might be similar to this one, and they do it from different perspectives and they do it in different ways, and we do

it based on the best evidence, as dictated by the legislation in a transparent way before the public. The recommendations of various other organizations are included in the information we have and continue to review, but it's also our responsibility to make the best decisions based on the best evidence. So that being said, let's start with sensorineural hearing loss. Again, I would ask one of the committee members to give us a starting point. Alright, let's start over there with Dr. Elmore. Where do you think we are? Start us off. I intentionally didn't call on Dr. Schwartz.

Seth Schwartz: I know that. I kind of want to stand down. So, maybe I will stand up.

Joann Elmore: Well, and I have a bigger picture question, too, that I am holding back.

Craig Blackmore: What's the bigger picture question?

Joann Elmore: I think I agree with, by the way, how you are organizing us as a committee, and it's always a pleasure sitting on this committee watching how you move us forward. I – and I also agree that we need to sort of take off quickly some of these ones in which there is low quality, inadequate data to just hone in on a few conditions. When we get to those conditions, my question has to do with the variability in the dose, frequency, and duration in that there are these studies that we're hearing that are moderate quality that show efficacy and yet when we asked our 1A question of, what's the optimal frequency, we hear that there is inadequate data. I know that starting us off, you asked a good question, which is the agency has data showing the range, can they provide us information, and why does a patient need 80+ treatment per claimant, and shouldn't we set a threshold there in our conditions, and then I would like to hear the clinical advisors comments on at what point is it appropriate to stop hyperbaric oxygen therapy? And then, even though the response from the Hayes to question 1A of our committee was that there's no data on adequate or appropriate frequency of treatment per condition, there are the primary studies that were done that had specified numbers of treatment, and I can't imagine all of them went up to 80. So, when we get to the specific conditions, I would appreciate if we could get back to the frequency and duration.

- Craig Blackmore: I think that's a very good point. So, sensorineural hearing loss?
- Joann Elmore: Inadequate data.
- Craig Blackmore: Okay.
- Michelle Simon: I would say in chronic sensorineural hearing loss, there is definitely data showing that it is not effective, but there is some mixed data in the acute cases of sensorineural hearing loss, apparently. I'll say that.
- Craig Blackmore: Which slide are we on?
- Chris Standaert: 29.
- Michelle Simon: Slide 29 has acute.
- Craig Blackmore: Thank you.
- Michelle Simon: Slide 32 has chronic.
- Seth Schwartz: Yeah, this is Seth Schwartz. I think what Michelle says is accurate in my mind, which is that there's no data to support its use in chronic hearing loss. I think the definition of chronic is variable. Actually, looking deeper at some of those trials, I think there was some poor evidence for that 2-month/3-month window, which is part of why the American Academy of Otolaryngology guidelines brought in the window, although there was not enough data to say it was a recommendation. In that guideline, it was left as an option, because there was so much uncertainty about it. I think the other thing that comes out is this question of functional improvement. So, there's this – which is true in every intervention we look at – there's the difference between what is statistically significant and what is clinically significant, and I think this is one of those conditions where that is very true. If you have someone who is profoundly deaf and you give them 25% improvement in hearing, they're still profoundly deaf, they just might be aware of an explosion going off next to them, and that's not meaningful improvement, whereas if they have moderate hearing loss and you give them a 25% improvement, that might get them up to a more mild range where suddenly hearing becomes effective, and that is meaningful improvement. So, I think a lot of those trials struggle with that, and there's not

enough granularity in any of those trials to sort out the answer to that question. So, I think there is some evidence that there is improvement based on fair quality randomized trials in the acute period, but I think it's uncertain whether that improvement is clinically significant or not, and that's kind of where I fall at.

Craig Blackmore: So, I guess the question for the committee would be, is this enough evidence that we want to support it or do we wait for more? Other comments on sensorineural hearing loss.

Michael Souter: One of the questions for me always again is the comparator here and I just, in looking at what the report says about the Cochran review that was undertaken for the acute care in these patients, I think it's worthy to note that it didn't show any benefit for the hyperbaric treatment plus steroids versus steroids alone, and I think that steroids would seem to me to be not that unusual a treatment for acute loss. Am I right, Seth?

Seth Schwartz: You're correct. I think the challenge in looking at sensorineural hearing loss in general is that the natural history of the disease is that a significant percent of the patients will get better even if you do nothing. So, somewhere between – a significant percent of the patients, about 50% of patients will get better, even if you do nothing. It doesn't mean they will get 100% better, but they will show improvement that would meet the criteria for improvement based on this study. So, it's actually pretty hard to show improvement in treatments for sensorineural hearing loss, and in these trials the comparative group was typically oral steroids, and that had historically been considered the gold standard although the guideline that I just referred to sort of downgraded that to an option, because the data is actually so mixed on whether or not there is a benefit to for oral steroids. Based on the same problems they had in showing a benefit with hyperbaric oxygen therapy.

Michael Souter: And again, one of the things that is coloring my thinking about this or any possible benefit in the acute is that their followup period is only six months, and I think it's difficult to know whether that is really adequate to demonstrate a sustained benefit and improvement versus just something that's artifactual because it could be viewed as placebo.

Seth Schwartz: So, Mike, I would make one comment about that. In sensorineural hearing loss in general, the studies, both in terms of the natural history studies and the treatment studies are pretty clear that if people are going to experience a benefit, the benefit tends to be early, and if you look at the natural history studies or the treatment trials, the benefit tends to occur within the first three months, and then people show stability after that. So, something on the order of 97% of patients are going to improve will have improved by that period of time and there's usually not a whole lot of improvement beyond that, but the results are pretty stable for long term. So, most of the trials don't go much beyond that, because we know that it tends not to change a lot after the three to six-month period.

Michael Souter: So, I get the early improvement. So then you're saying that if you're improved by six months, you're saying that's going to stay sustained?

Seth Schwartz: Correct.

Michael Souter: Okay, alright. In summary, though, I'm still not necessarily convinced by the acute data either. I'm not swayed just given the mix of it.

Craig Blackmore: Are there thoughts on sensorineural hearing loss?

Chris Standaert: I guess, so if you throw everything into, you know, cost-benefit risk, all that sort of stuff, they're talking about some benefit in acute phase within two weeks of hyperacute, really, not three months, not 10 weeks, but within two weeks. It's a small window you have. I mean, are there other effective treatments for these people? So, if you don't do this, you do what? You give them – and it goes back to the comparator issue also, but – so you have a treatment that has some evidence it provides some improvement in people when given hyper-acutely. Are there other acute treatment choices that have effectiveness in a similar range, or is this really you don't do any of it? There is no effective treatment, you just sort of watch them and half of them get better and half of them don't?

Craig Blackmore: So, the typical treatments are oral steroids is really the most common treatment and the data is somewhat mixed on it, but it is still probably the most common treatment in the acute phase.

There is also – steroids have also been delivered via intratympanic routes. They actually inject steroids into the ear, and that is usually used for salvage, so for patients that don't get better either spontaneously or with oral steroids, transtympanic steroids are offered and there are no great but actually stronger evidence in support of that treatment. Beyond that, there's really nothing else that's been shown to be effective.

Joann Elmore: Can I ask a question of the reviewers? When you said that there is a large, systematic review suggesting that HBOT is beneficial among patients who present within two weeks of the onset of the disease. What was your evaluation of that systematic review if you just evaluated that document? What quality was...

Karen Crotty: [inaudible].

Joann Elmore: Yes.

Karen Crotty: Was rated good quality.

Joann Elmore: Good quality?

Karen Crotty: Yes, that means [inaudible].

Joann Elmore: And how many studies were in that systematic review? I know that you had it here. Let's see.

Craig Blackmore: There eight studies. This was the Bennett Study, right?

Karen Crotty: It was the Bennett Study.

Chris Standaert: Page 27 of the report.

Karen Crotty: [inaudible]. It had seven [inaudible]. So we had seven studies from the good quality review plus the one study [inaudible].

Joann Elmore: And was there some similarity in the treatments that they offered? Yes. Okay.

Craig Blackmore: So, can you drill down a little more for me on slide 29. Maybe I just don't understand. There were eight studies, and then we have three columns here, pooled data from two RCTs, pooled data from two RCTs, and then pooled data from two other RCTs.

So, these different poolings are because of heterogeneity? Is that right? And why didn't we pool all eight? We pooled them because these are the ones we could pool.

Karen Crotty: No, we didn't pool.

Craig Blackmore: Cochran?

Karen Crotty: Yeah, Cochran pooled.

Craig Blackmore: Okay, so when Cochran did that, if they had pooled these particular two that looked at 25% there seemed to be a benefit, and when you looked at the particular pool, the two that looked at 50%, there was no benefit, and then this other group in the middle...

Karen Crotty: That middle study, the [inaudible]...

Craig Blackmore: The middle two...

Karen Crotty: ...with seven participants, that is actually the separate study, the sequence study that was in 2010. So, they looked at recovery and instead of looking at percentage they looked at greater than 50 decibels or between 10 and 50 decibels. So, they looked at a slightly different outcome and they did not see a benefit when looking at that, but how that compares to a 25% recovery versus 50% recovery, I don't know.

Craig Blackmore: Okay, so, if one looks at this, one would say that there is a slightly increased probability of getting 25% recovery, but there is no significant difference in getting 50% recovery, and there is maybe an increased probability of getting 15 decibels. Is that right?

Karen Crotty: [inaudible]. There did not seem to be an increase in the [inaudible]. So, the pooled data from the two suggest yes, greater than 25%, then they also – the difficulty with this indication, too, is the outcome that they looked at. So, you had mean improvement looking at the mean difference. So, yes, if we're looking at a mean difference of 15 decibels, [inaudible]. So, again, that is slightly different to looking at it [inaudible].

Joann Elmore: The increase of decibels would be then like a clinical indicator. That would be something more...

Seth Schwartz: I think what you're looking at is a matter of degree. So, it's a question of how do you set – what outcome are you looking at, and really you're looking at degrees of outcome. So, decibels are basically just the scale of measurement for hearing loss. The bottom one where it says no benefit, that's pure tone average, so you're averaging the decibel improvement over four different frequencies typically. So, the way I look at this is that if you have a lower criteria for outcome, so in other words, if you will accept a smaller benefit then it is successful, or there's the suggestion that it's successful. If you set a higher criterion for improvement, then it's not. So, I think the way I would read this is, there's fair evidence that it will give you a small improvement and no evidence that it is going to give you more than that.

Kevin Walsh: But also because you had mentioned before, it doesn't specify what your hearing level is when you present. To get a certain percentage of improvement does not translate into function at all.

Seth Schwartz: Correct.

Kevin Walsh: So, I feel like we're being teased here like yeah, maybe, but we really aren't told if.

Seth Schwartz: Yeah, I think that's a totally valid point. I think that's the same thing that the guideline committee struggled with, which is that you don't have the data to know whether it's going to be clinically significant or not, because in some patients a 15 decibel improvement is the difference between whether they can use a hearing aid or whether they're deaf. In other patients it's small functional improvement. In other patients, it's totally insignificant.

Kevin Walsh: The kernel of truth in what you just said was that there's no evidence.

Seth Schwartz: I don't think that's entirely true. I think that there is evidence that you get better. The question is how much better is it. I think the equivalent would be, if you look at a blood pressure medication, you may show that a blood pressure medication lowers your systolic blood pressure by 10 percentage points, or by 10 points on the scale. Well, that's real. That may be a real difference, but the question is, does it matter for the patient, and I think what we

know is – I think there's some evidence that hyperbaric oxygen therapy improves the outcome, or it improves the number, but is that of significance. So, I think it works. The question is, does it work for everyone, does it work enough to make a difference, and I think that's what we don't know.

Craig Blackmore: So, I guess that's what we have to grapple with. Further discussion? Richard? It looked like you were getting ready to say something.

Richard Phillips: No, I just don't think there's much benefit that's been demonstrated across the board. You know, I think, Seth said it very well. He knows the stuff. Not much to contribute.

Craig Blackmore: Okay, well then I think I, at this point, should take a straw vote in our draft list of conditions if this would be one that we would wish to include for coverage if we go that way. So, this is not a vote with the cards. This is a straw vote, and I would like to see a show of hands for committee members who would include this on a list of conditions for coverage. Hands please. Maybe I'll start with the hands of the ones who would not include this on a list of conditions for coverage. Okay. So, let's move on down our list, or up our list. Somebody remind me what page we were on. Page two of the Hayes I think it was. Let's mark that page.

Joann Elmore: Slide four of the Hayes. Why don't you put it up?

Chris Standaert: Headache and migraine.

Kevin Walsh: You wanted to work backwards from the bottom.

Craig Blackmore: So, we're going up, right? I just have to find the right page. So, that takes care of sensorineural hearing loss. Headache and migraine. Who wants to start us off on this one?

Chris Standaert: There seems to be insufficient evidence. We have very small studies of what we don't know a lot of details of and it doesn't seem as though there is sufficient evidence to recommend this as a routine treatment.

Craig Blackmore: Okay, so where's slide...

Chris Standaert: And that it's going to change any significant health outcomes for the benefit of the patients.

Craig Blackmore: We're at about slide 28 at this point.

Michael Souter: I agree with Chris that it's – largely its comparators are shams, and I think there are many other modalities of therapy and we're hearing from a clinical expert that people aren't using it anyway, so I'd see no reason to cover it.

Craig Blackmore: I would add that the benefit, if there is one, is only looked at in 43 patients.

Richard Phillips: I would say the same thing.

Chris Standaert: In the midst of three separate studies accounting for 43 patients.

Craig Blackmore: And it's a common condition. It's not like there's only 43 cases in the state or something.

Chris Standaert: And the comparator would be significant, as Michael pointed out, the number of medications and approaches for migraines has expanded over 20 years greatly.

Craig Blackmore: Any other comments on that.

Richard Phillips: In that sense, it is almost as if we have insufficient evidence to really assess, because really what we should be comparing for migraine is available modes of treatment, and basically we weren't given that, and it seems silly to even make a decision on it based on, at least from my perspective, because we just don't have it.

Craig Blackmore: Well, there is certainly no evidence...

Richard Phillips: The problem wasn't even addressed.

Craig Blackmore: ...no evidence that it's better than other current treatments.

Richard Phillips: Saline might be better.

Craig Blackmore: Okay, any other discussion on that? Alright, how about a show of hands for those who would not include this on a list of conditions

for coverage. Okay, so we're all, I think, kind of in the same place on that. I will now find my bookmark again. Multiple sclerosis.

Joann Elmore: We would not include it.

Richard Phillips: I don't think multiple sclerosis was included on that.

Michelle Simon: Go straight to voting.

Richard Phillips: Yeah, I think we...

Chris Standaert: Yeah, we've seen the evidence that actually says it doesn't work.

Michelle Simon: Right.

Chris Standaert: Not just there's no evidence, but the evidence is that it doesn't work.

Craig Blackmore: Alright, non-inclusion of MS? Cerebral palsy?

Michelle Simon: Similar.

Craig Blackmore: Okay, so again, I just want to get on the record we're looking at the fact that there's not really good evidence and what evidence there is, is really not suggesting a benefit anyway. Brain injury. Let's start with traumatic brain injury.

Michael Souter: So, I think this – there's no really good evidence for this. This field is deeply flawed. It requires considerably more research. I think it's worthwhile actually pointing out that there's actually a substantive body of thought, which is that actually oxygen in excess is actually bad for you in acute brain injury. So, I think in that kind of context the only possible resolution from here is no coverage pending. People can go and do the research that they need to do.

Craig Blackmore: Okay, so potential theoretical benefit but potential theoretical risk and data that is I would say significantly flawed by a lot of what we've discussed.

Seth Schwartz: Craig, one other thing I think I remember reading but don't remember hearing today was when we looked at the harms and most of the harms were pretty benign overall, but it seemed to

me, I remember it being that in the TBI patients there were some actually more significant risks.

Michael Souter: The lung injury.

Chris Standaert: Actually, even when you look at their data on functional outcomes among TBI patients in their studies, the trend is down. It's unfavorable functional outcome at final assessment. So, even if you follow the trend of the data, it goes the wrong way. They give the relative risk of 0.51, so the risk of a good outcome goes down, not significantly, but.

Seth Schwartz: The only question I would have about that is, are you including the patients that survive that might have otherwise died? Is that dragging down the functional? Again, I don't know [inaudible].

Chris Standaert: But this is the whole thing about details, right? Yeah, we don't have the level of detail we would like to really answer the questions we would like to get at. The population, do you think, really would benefit – when theoretically even considering this, we don't have it.

Craig Blackmore: It's also worth mentioning the risk, I mean, this is a heavy trauma, particularly if we're dealing with severe head injury. These are severe trauma patients with severe head injuries and wheeling them to the hyperbaric chamber away from monitoring on a routine basis poses risks.

Chris Standaert: Pulmonary issues and intracranial pressure issues and all sorts of stuff that could theoretically be affected.

Richard Phillips: Do you have a question from the expert?

Craig Blackmore: Dr. Hampson?

Neil Hampson: I just have a comment. We reviewed this in the Hyperbaric Medical Society a couple of years ago and turned it down as an indication based on the fact that we did not believe the functional outcomes were worth the risk of hyperbaric treatment. These are 4+ sick patients, and many of them have bolts in their heads and taking them sometimes down the hall to the hyperbaric chamber might be dangerous but taking them across town in an ambulance is even more dangerous. One of our members called Dr.

Rockswold who did one of the four studies, one of the larger ones, and he recommended that this not be opted as a routine therapy but be continued as an experimental therapy.

Craig Blackmore: Well, I want to – well, other comments from the committee? Okay, then I want to move on, and I want to include – do we need to talk about other brain injuries where there is even less data?

Group: No.

Craig Blackmore: Okay, so non-inclusion of brain injury. The three of you over there did not give me an indication.

Group: No.

Craig Blackmore: Thank you. Okay, late radiation tissue injury. Anybody know what page you're on.

Joann Elmore: Slide 22.

Craig Blackmore: We haven't talked a lot about this. There are different categories. There is the mandible, the osteonecrosis. Does anybody want to start us off?

Chris Standaert: We do have some data. It's a large field, as there are a number of different conditions that are falling within this, but we're getting into the moderate quality evidence at this point, that there is some benefit in correcting tissue damage in necrosis of late effect of radiation treatment, and I reference the Cochran review from 2012, in particular.

Joann Elmore: And they have...

Chris Standaert: In some ways, this is getting us into the other categories, which is where we start seeing some benefit being documented, which are really high risk wounds.

Craig Blackmore: I'm going to let the committee do its thing here for awhile, but who wants to start us off with the data here?

Seth Schwartz: I'd like to make a comment. This is Seth Schwartz. I think that it's a little challenging, because there is quite a bit of heterogeneity in terms of the conditions that were treated, but I think the

directionality of the effect was positive in virtually every study that was looked at from the randomized control trials down to the observational trials. I think when you look at the conditions that were looked at with observational rather than randomized trials, part of that has to do with, I think, frequency of those conditions. So, osteoradionecrosis, the mandibles are highly uncommon and I think would be difficult to study in a randomized trial and maybe that's why there wasn't more data, but it seems that at least all the trials that were there did show a benefit for those patients. I guess the one other comment would be, it wasn't clear to me that there was a good alternative for those patients either.

Craig Blackmore: Other thoughts?

Carson Odegard: I have one comment, or actually one question. You know, the benefits were pointed out in the Cochran review. In the Fritz Study where basically they had insufficient evidence, can you talk about the Fritz Study at all? Do you have any information about that?

Karen Crotty: I do, but I think [inaudible].

Carson Odegard: Yes, the other systematic review.

Karen Crotty: There were two other systematic reviews.

Carson Odegard: Right, Fritz and who was the other one?

Karen Crotty: So, yeah there was actually – just give me one minute so that I have it exactly in front of me.

Carson Odegard: Sure.

Seth Schwartz: While we're taking this minute, can I ask Dr. Hampson a question?

Craig Blackmore: Sure.

Seth Schwartz: You know, one of the questions that has come up is about the differential duration of treatments and settings for the chamber and those sorts of things. I'm just curious, are there recommendations from the Hyperbaric Society about what recommendations for treatment for a lot of these conditions?

Neil Hampson: We have utilization review requirements for every condition that is approved. For example, sensorineural hearing loss, we just approved that last year. It has to be acute, it has to be within 14 days, you can get 20 treatments. If you're not improved you have to a utilization review done by a physician who is board certified at another facility to justify continuing treatment for radiation tissue injury. There is a maximum of 60 treatments allowed before you have to do the same kind of utilization review. We have those for every indication, and it alarms me to see the variability that was shown in the early data, not just the high end but the low end too because we know in radiation tissue injury that the outcome of soft tissue radiation necrosis, radiation cystitis is different whether you get below the threshold of 30 treatments or above it, and some people are getting 15 treatments on average. I think that somebody needs to look at the diagnoses by facility and see whose doing these low number, or high number of treatments, because there are guidelines, and when I work with different insurance companies to establish a hyperbaric coverage policy, I strongly encourage them to put lower and upper limits in.

Craig Blackmore: So, for the committee's benefit, the data that we were shown demonstrates a range. The reason I was concerned about it is because the minimum and the maximum may be extreme outliers that are not relevant for consideration. I mean, you might have only gotten five treatment because you died. So, what we need for that sort of information is the mode and the distribution so that we can see –I mean, who cares if somebody got 100 if everybody else got between 40 and 60. So, I think we need to be careful in interpreting that specific piece of data.

Chris Standaert: Yeah, all we have is the range.

Craig Blackmore: All we have is the range, which is really...

Chris Standaert: Not helpful.

Craig Blackmore: ...that's not what we need.

Neil Hampson: You do have a mean.

Joann Elmore: We do have the more detailed evidence table, and it says the direction of the findings and almost all of them with one exception show benefit.

Craig Blackmore: So, what – which slide are you on?

Joann Elmore: I'm on the big long attachment. It's the section on radiation.

Seth Schwartz: Well, the Cochran showed benefit for certain conditions, but the study that Carson referred to, Fritz, the analysis here is that there's insufficient evidence.

Carson Odegard: Yeah, I found the answer to that to, going back in the appendix that it's insufficient, I think, due to high bias.

Seth Schwartz: Right, the study itself was graded as fair because of bias, but the conclusion, even of the authors, was that four irradiated patients requiring tooth extraction that it was insufficient evidence.

Carson Odegard: Right, is that what you found, too?

Karen Crotty: Exactly. Well, so there were the two reviews and the difference between those and the Cochran review was they included the observational studies, and I just wanted to check the percentage, and it was the 7%, so both reviews looked at both the trials and the observational studies. They included slightly different observational studies, which is why they both got into the report. They both came up with the same instance rate, 7% versus 4%, but interestingly, they drew slightly different conclusions. One suggested that there was low quality evidence that hyperbaric oxygen therapy was effective in preventing osteoradionecrosis. The other one said it was insufficient with the same incidence rate, and they all code the same. There was only one trial on this, and I think it's a nonrandomized control trial. That's the one that was included in the Cochran review, which is a lot of the evidence and the approval for this indication – it was pretty large. It was 5.4% versus the 29.9%, but that is the study with the unclear - it's the trial, but it had the unclear risk of bias, because they gave very little detail on the study.

Carson Odegard: Right, okay, good. Thank you. I appreciate it.

- Chris Standaert: And that's a particular – we're talking about a particular category within soft – within LRTI at this point. You're talking about the bone thing, the osteoradionecrosis of the bone with a dental extraction.
- Carson Odegard: Yeah.
- Chris Standaert: As opposed to all the mucosal things and other soft tissue disease.
- Joann Elmore: But they also say that evidence suggests that radiation-induced tissue and bone damage to the head, neck, anus, and rectum showed consistent clinical improvement with HOT.
- Craig Blackmore: You're reading the Cochran, or?
- Joann Elmore: No, I'm reading...
- Carson Odegard: Fritz?
- Chris Standaert: That's the report.
- Joann Elmore: The full report.
- Craig Blackmore: You're reading Hayes.
- Seth Schwartz: Well, it's actually from Bennett, which includes Cochran.
- Carson Odegard: Right.
- Seth Schwartz: It's page 147 of the appendix.
- Chris Standaert: What are we pondering at the moment?
- Chris Standaert: Alright, so we're supposed to be pondering radiation tissue necrosis, and I'm probably going to have to break it down a little more, as we seem to have at least a distinct group of the osteonecrosis of the jaw in patients who have been irradiated, and that's a little different from soft tissue.
- Chris Standaert: Right.
- Craig Blackmore: So, why don't we start with the jaw. We're looking at basically slide 23 at this point, prevention of osteoradionecrosis after tooth

extraction in patients who have been irradiated and we've got at least data from Cochran.

Seth Schwartz: It looks like they break this into three categories, unless I'm not seeing this correctly, that there is bone and soft tissue of the head and neck. There is tooth extraction in irradiated field, and then there's radiation proctitis.

Craig Blackmore: And hemorrhagic cystitis.

Seth Schwartz: And hemorrhagic cystitis.

Craig Blackmore: So, I mean I would like to start with the tooth extraction piece. There are trials pertaining to that specific indication. They are not randomized trials. The vendor describes them as moderate, although one fair observational trial is not overwhelming, certainly, in terms of strength of evidence. Comments from the committee on that subset? Does anybody want to? We're drilling down, and the data is thin is the bottom line, so.

Seth Schwartz: I guess I just have a question about the way it's reported there. So, there are the nine pooled studies, which shows a 4 versus 7%, and then there's the incidence rate at 6 months, which is much more dramatic. It is 5% versus basically 30%. What's the difference between that right there that we're looking at? Why are those 2 paragraphs separated?

Joann Elmore: Different ends. Different sample size.

Neil Hampson: The reason that there are a small number of studies is that the first study that came out in 1985 was the Mark Study, and it was a randomized control trial that was positive. So, not a lot of people invested their effort to go on and study it again. It's the study that showed a 5% incidence of ORN in the hyperbaric group and the 30% incidence in the penicillin-control group.

Craig Blackmore: So, if I could ask our vendor, so – I mean, I just want to get back to Seth's question, and looking at slide 23, there are two different, under prevention of osteoradionecrosis after tooth extraction, there are two different sort of clusters here. There are the observational studies, and then there's one that says incidence rate, and they seem to be very different. Can you help us understand the difference?

- Karen Crotty: Sure. Christine, can we pull up number – it's 22 is up there. Can we have 23 up there for a second?
- Craig Blackmore: It's just the next slide. Yeah. So up top there, we've got pooled observational studies, which show 4% incidence and then we've got this, and I presume this is the one randomized trial that Dr. Hampson was talking about on the bottom there?
- Karen Crotty: Yeah, and the only reason that is pulled out is because it was the only trial like Dr. Hampson just said, but they were both looking at the same outcome, so they should be considered together.
- Craig Blackmore: Okay. So, there's one randomized clinical trial. We don't know how good it is.
- Karen Crotty: We don't know how good it is.
- Craig Blackmore: We haven't heard a lot of detail, and then there's some observational trials, and in the randomized trial, if anything looks better than the observational trials, but both groups show some benefit.
- Karen Crotty: Exactly.
- Craig Blackmore: Okay. Okay. Okay, committee members have other comments on this?
- Kevin Walsh: Well, am I right, Seth, that this a situation where there's not an alternative treatment, is there?
- Seth Schwartz: Well, I think – I think if you look at what the current standard of care is, that's correct. I mean, I think HBOT is the – for osteoradionecrosis of the mandible, HBOT is the treatment, and there isn't anything else.
- Kevin Walsh: I'm comparing it to migraine where there's lot of alternative treatments that are readily available. The evidence isn't good, forget it. In this situation, there is no alternative.
- Seth Schwartz: I think they're looking at incidence. So, these are patients that don't have ORN but have had radiation of the mandible. You pull a tooth and then the question is do they get ORN or not? And

based on that randomized trial, there is a dramatic difference between whether you get it or not. The significance here is that if you get it, the only treatment for it is hyperbaric oxygen and if it doesn't get better, you end up having to have massive surgery to resect a huge portion of your jaw and the functional impairment is dramatic. So, you're looking at huge consequences.

Kevin Walsh: Right. So, my point was trying to get toward- this is one of those situations where it's better than nothing, basically, because that's the alternative.

Chris Standaert: Any other choice is nothing, right.

Kevin Walsh: Or better than worse.

Joann Elmore: But it does have some data.

Chris Standaert: It does.

Craig Blackmore: Okay, so let's have a show of hands, and I have been doing not in favors, so I will do not in favor again in the interest of consistency. So, raise your hand if you do not think this would be a covered condition.

Michelle Simon: Just doing ORN or the entire?

Craig Blackmore: Just the jaw. Okay, so if you do think this should be on a list of conditions for coverage. So, that is certainly most of us. Alright, now we have to look at the other aspects of late tissue necrosis.

Chris Standaert: Do we break them all down to multiple things or do we consider them as soft tissue, since we're talking about – I mean, this could be anywhere in the body that we're talking about, mucosa, skin, and all sorts of stuff.

Craig Blackmore: Well, what do you think?

Chris Standaert: I think consider them as soft tissues. Personally, as we go through this, we have an NCD we have to deal with one way or another. We have to say whether we agree or disagree with the NCD, and we are coming along very similar with what the NCD shows, and if we just follow that same line, we may find a reasonable way to approach coverage.

Craig Blackmore: Yeah, but I don't have any problem with being different from the NCD [inaudible].

Chris Standaert: Oh, I don't either, but I don't have a rationale to pull them all out as separate soft tissue either, frankly.

Craig Blackmore: I think that is making a point.

Joann Elmore: Well, the summary was that there's moderate quality evidence from three pooled studies, 246 participants, one fair, two unclear quality due to poor reporting reported significant benefit from HBOT in achieving complete mucosal cover among patients.

Seth Schwartz: I'm not sure that there's a lot of dissent amongst the group. It may make sense to take a straw poll before we dig any deeper on this one.

Craig Blackmore: Okay, I've been going non-inclusion as a covered condition first, so the non-inclusion people please raise your hand, and the inclusion people please raise your hand. Thank you, Seth. Okay, so that means we've looked at basically the whole category of late radiation necrosis and we thought we would keep that on our list. Now, we're moving up to refractory osteomyelitis.

Michael Souter: Sorry, can I just ask one late question that's occurred to me. Do we need to define what is late, or can we just leave that up to the clinicians involved?

Craig Blackmore: I would leave it up to them.

Michael Souter: Yeah, okay.

Craig Blackmore: Personally, I don't know what – I would suspect it's already been well defined. Okay, back to osteomyelitis and does anybody know what slide that is. Here it is, slide 27.

Chris Standaert: Our issue with osteomyelitis is the quality of our studies and the level of our study. There are no RCTs and they talk about there are 21 case series and refractory osteomyelitis is not overly common. So, you run into – you can certainly find studies but we have no RCTs and we have lots of other stuff, lower level data.

Seth Schwartz: I actually would have a question for our clinical expert on this one, just trying to understand this process. Reading this, it looks like they are defining the point at which to use hyperbaric oxygen therapy was something like six months of antibiotic therapy and the infection was still present, and then they elected to treat those patients and it looked like then some people got better and some people didn't.

Neil Hampson: Refractory osteomyelitis is very rare. Osteomyelitis is easy to cure with an appropriate course of antibiotics. Chronic refractory osteomyelitis is defined as osteomyelitis that has failed appropriate antibiotics after bone biopsy demonstrated organism was shown and sensitivities were appropriate with the course of antibiotics given. The mechanism theorized for use of hyperbaric oxygen therapy is two-fold. One is that the milieu of chronic osteomyelitis is hypoxic and neutrophils need oxygen for their oxygenated burst to kill bacteria. So you allow oxygenated neutrophils to do their job. The other thing is that hyperbaric oxygen therapy stimulates osteoclasts, which go along like the pac-man character and munch up dead necrotic bone, but it's not a common problem. That's the reason, I think, there are no big trials and no big randomized trials.

Craig Blackmore: Thoughts from the group? I guess my thinking would be, if we were careful about how we define chronic osteomyelitis as that very small group that had failed all these other interventions that...

Chris Standaert: I suppose if you get down to it, you can go to the alternative question. You're talking either resection or amputation usually. So, if you can't kill the infection with something, sooner or later you have to cut it out. So, depending on the limb and where that is and how bad that is, and you've already failed, again, known identified theoretically-attractive treatment options that don't work for six months and those are your other choices. There's some evidence that suggests it may work and it's troubled by the low incidence of the disease and the difficulty studying, probably matching people out and making a true RCT would be difficult is what would be your comparator. More of the same, I suppose.

Carson Odegard: I also had a question, this is Carson Odegard, about that followup period, too. I mean, if you have 80 – if you're taking them at six months in chronic state, failed conventional treatment, you follow

them up for 84 months after that. I mean, something would have been done. I mean, I don't know what the natural history of that type of disease is, but seven years...

Chris Standaert: They probably don't have that data either, I bet. The natural history of untreated osteomyelitis, unsuccessfully treated osteomyelitis after six months. They don't know what the natural history would be.

Craig Blackmore: But the other treatments are invasive.

Chris Standaert: Yeah, but...

Craig Blackmore: They might be revascularization or whatever, but they're not...

Chris Standaert: Yeah.

Craig Blackmore: Okay, other thoughts?

Karen Crotty: Sorry, I'm interrupting only to answer a question that was asked during the break, and we did look at those studies to pull out the ones that looked at that 84-month period. So, there were at least two of those studies that were both case series, however, that looked at five years and six-and-a-half years, and in both of those cases, the overwhelming majority of patients that had undergone HBOT had no symptoms, as they were defined in that study.

Carson Odegard: Okay, thank you. Thank you for looking that up. I really appreciate it.

Craig Blackmore: Okay, so, anybody else? So, again, we'll vote first for non-inclusion of refractory osteomyelitis. So, non-inclusion hands. So, inclusion hands. Okay. We're making progress. It's good to start with the easy ones. Other nonhealing wounds, including ulcers, flaps and grafts, thermal burns, and surgical wounds. So, that's a big group. The slide is 54? 34, sorry.

Okay, so our vendor has broken this down into crush injuries, thermal burns, and surgical reconstruction flaps.

Chris Standaert: And ulcers.

Craig Blackmore: And ulcers, is it somewhere else? Different slide? You're in the text. I'm just on the slide. Okay, so what do we think? Dr. Standaert, you have it open in front of you, what do you think?

Chris Standaert: This one we have to break down a lot more, I think. I think we can't count this all as one thing. We have burns, thermal injury. We have surgical wounds. We have pressure ulcers of various sorts, and we have individual data on all of these things. This issue of nonhealing wounds in nondiabetic patients.

Craig Blackmore: So, start us off. Pick one.

Seth Schwartz: Can I ask a question first. This is Seth Schwartz. I have a question for our vendor. On the crush injuries, it says there's one fair quality RCT, but then the quality of evidence is very low due to insufficient evidence. Can you separate those things? Just – what was the disconnect between a fair RCT and the low quality?

Karen Crotty: Sure, the fact that it was just one and there were just 36 patients in that study. So, while the internal validity was good, usually when there's just one study on anything that's included it gets a very low, but it is the study that is quoted over and over again for approval of HBOT for crush injuries. It did find a significant benefit, but it's small.

Seth Schwartz: So, I would have, I guess, two followup questions on that. One is, is the reason for that, that there's no alternative other than amputation for these patients and that was considered to be enough evidence. That was question one, and the second question would be, can you tell us anymore about that study so we can – in other words, why did you downgrade it from good to fair?

Craig Blackmore: Is there anything besides sample size, I guess.

Joann Elmore: And the fact it's only one.

Craig Blackmore: I mean, I don't know what the alternative treatments are for crush injury. You can amputate. You can try to, you know...

Chris Standaert: I mean, the numbers of that one study are fairly impressive. I mean, 94% healing versus 56, NT of 3. There's only 36 patients, though. In crush injuries, again, you're going to have a very mixed

bag of what you have in severity. I mean you'd usually see in 36 patients, you may not average that out very well. The equivalency of the groups could be – I mean, all sorts of things. That's probably why it's fair. It's just too small to sort.

Craig Blackmore: Crush of what?

Chris Standaert: Exactly.

Seth Schwartz: Do we know what was included in that? Is it soft tissue injury that's crushed?

Chris Standaert: Well, they look at time to healing amputation rates. So, it's, you know, crush of a foot, of a limb, you know. It's not just – it could be a digit. It could be the whole...

Seth Schwartz: I'm just curious what was actually in the trial, I meant.

Chris Standaert: Sorry, I wasn't catching that. So, we have crush injuries. We have ulcers. Ulcers are tricky, because they mix – we have very small studies, and they mix the types of ulcers. So, we have a decubitus pressure ulcer thing but then venous arterials, which are really different diseases in a way, and they are all lumped together, and it isn't overly-enthralling, the data. They have a small RCT of 16 showing no real difference in wound at 18 weeks. They have ulcer and then they have another study of 30 of mixed ulcers showing improvement in 30 days, but that's not much.

Craig Blackmore: Alright, so we're getting more information on crush. So, we can talk about ulcer while we get information on crush.

Joann Elmore: Ulcer flaps and grafts have a summary of low quality of evidence, but if you compare 11% for HBOT delayed healing versus 55% in the control. That's notable.

Michael Souter: And I would make the same observation that Chris did with regard to osteomyelitis. The consequence of a flap or a graft being lost. Those circumstances would be significantly disabling. So, I think they are very much a special case.

Craig Blackmore: I think these are very different. Flaps and ulcers are totally different.

- Chris Standaert: Flaps and grafts are different than ulcers.
- Michael Souter: Are we just doing ulcers at present, then?
- Craig Blackmore: Well, I don't know. We're kind of mixing it all, and I just want to make sure we separate them. So, I think if I look at slide 34, ulcers is not on here. Maybe it's somewhere else and I'm missing it, but I think we can consider flaps under surgical reconstruction. We can consider crush. We can consider thermal burns, and then I would consider ulcers meaning venous, arterial, or...
- Joann Elmore: Slide 26...
- Craig Blackmore: Slide 26, thank you.
- Joann Elmore: ...has the grafts and flaps and the ulcers.
- Craig Blackmore: Nondiabetic, nonhealing wounds. Okay. Okay, so let's start with flaps, because here's one where the data is terrible, but the consequences are big. There's not a lot of other options. Is that a fair summary? How do we want to go on flaps?
- Chris Standaert: We don't have much data on flaps.
- Carson Odegard: I believe there's a lot of data, but I don't think you have much choice except to, in my opinion, except to go with some kind of coverage, because it's a desperate situation. You lose a flap, you know, it is probably going to result in something catastrophic.
- Craig Blackmore: It's a very uncommon clinical condition. It's very high consequence. The data's not great, but there's something.
- Carson Odegard: Probably unusual.
- Craig Blackmore: Okay, so flaps. Noncoverage?
- Chris Standaert: And these are talking about compromised flaps and grafts, too, as opposed to a healthy tissue.
- Michael Souter: That's what we treat, compromised flaps and grafts.
- Craig Blackmore: Salvage. It's not we're putting on a flap so we're gonna give HBOT. It's, there's something wrong with the flap.

- Chris Standaert: Right, yeah. Compromised flaps and grafts.
- Craig Blackmore: Okay, so inclusion on the list of conditions for coverage would be compromised grafts and flaps?
- Joann Elmore: Yeah, the graft survival was 64 with oxygen versus 17% with mutual care.
- Craig Blackmore: Okay, so I have to do this again. If you want to keep it on the conditions, please give me your hands for surgical reconstruction compromised grafts and flaps. Okay, so that's most of us. I don't want to go too fast. If I'm going too fast let me know, but I want to keep us moving also. So, the other one is – do we have crush? Did we find out more? Still working on crush, okay. Thermal burns.
- Carson Odegard: I don't think there's any evidence that it really works at all.
- Craig Blackmore: It's inconsistent. It's not good evidence. Any other thoughts on burns?
- Chris Standaert: Where did the burn data go?
- Craig Blackmore: Common condition.
- Joann Elmore: And the evidence is mixed with the two studies. One said yes, one said no.
- Craig Blackmore: Okay, are we ready then? Let's vote on burns. Again, I'm going to try to do this consistently. So, if you do not think we should include burns as a condition, please raise your hand. This is voting no. And that's most or all of us. Alright, ulcers, slide 27 I think we said.
- Joann Elmore: 26, okay.
- Craig Blackmore: Nondiabetic, nonhealing wounds. Two different types. We already talked about flaps and grafts so that's done. Then the other would be venous and arterial ulcers and pressure ulcers, which can be treated the same or separately.

- Joann Elmore: I have a question. The clinical practice guideline, what was the reason that Nice did not include diabetic ulcers?
- Craig Blackmore: Okay, we're on nondiabetic. So, that's a good question. Store it up. Nondiabetic healing wounds. So, we've got – does anybody want to summarize.
- Chris Standaert: They rate it as insufficient evidence. They cite one case series, which is of questionable help, and two other studies, one of 30 patients with mixed wounds of all sorts showing at 30 days improved coverage of the wound in the HBOT group, but then in another study of venous wounds showing by 18 weeks really no difference. They're both rated as fair RCTs. So, it's relatively mixed but it's relatively weak evidence.
- Carson Odegard: Clinically, a lot of these patients are fairly marginal, and you're basically in a situation where you're trying to salvage a limb or you're trying to protect them from sepsis. You know, healing ulcers you're trying to make them smaller. That's obviously a clinical judgment call, but it seems to me there is some short-term benefit even though there's really overall there's low to insufficient evidence and I realize that the state coverage said that this is not something that we should cover. My view of this is that there may be situations where it should be covered because of the alternatives really don't exist.
- Chris Standaert: There are alternatives. I mean, there are standard wound-healing practices. So, for decubiti, if there were evidence that this really helped decubiti, decubiti are a major source of disability and cost and illness in the chronically and injured population, but we don't have a study on it.
- Michael Souter: And it's not uncommon.
- Chris Standaert: It's not uncommon at all.
- Carson Odegard: I guess maybe I'm not even talking about the pressure ulcers. I'm thinking more like the arterial ulcers and the venous ulcers. That's why these are all jumbled together at present, but the one study on venous ulcers did not show any benefit at 18 weeks. That's the one study they did where they sorted them out, and we don't have a study on decubiti, which are very common and very

costly, and if there was data I'd be all for it, but I don't see the data.

Seth Schwartz: Christopher, I just have one question. I mean, I think that you're saying there's no evidence at 18 weeks, but I think the problem is one of numbers here. I think it's difficult to say, but you're still looking at a double – I'm saying the numbers are too small but with only 16 patients the difference needs to be enormous to show a difference, and you're really – if you look at the raw numbers, it's basically twice as many patients healed. So, again, I'm not saying this is adequate data. I'm just saying I don't think it's fair to say there's nothing there. It's an under-powered study. You can say we don't have studies, but that one's under-powered. My other question is, what were the entrance criteria to these studies. So, you're right. There's a lot of people that get decubiti. Are they just treating anybody who has a decubitus ulcer in place of doing standard wound care or are they having someone who has a decubitus ulcer for X amount of weeks or months and it's not getting better using traditional therapy and then they're offering HBOT, and I just don't know what's happening in these studies. So, I would be curious to our vendor what the entrance criteria were for these studies to even be able to assess what they mean.

Craig Blackmore: Particularly the, well no, that's – I mean, are decubitus ulcers even in here?

Chris Standaert: They're mixed in. The pressure ulcers are mixed into that one study of chronic nonhealing wounds. The one of RCT of 30 patients.

Craig Blackmore: So, it's 30 heterogeneous patients?

Chris Standaert: Yes.

Group: There's no evidence. Inadequate. No coverage.

Craig Blackmore: Alright. So, in terms of chronic nondiabetic, nonhealing wounds, where is the committee in terms of coverage. I'm going to ask it the same way. Please raise your hand if you would not include this as one of the conditions for coverage. So, we're a little inconsistent but mostly not. Okay. I think it was like seven to two.

Seth Schwartz: I want to know more. I don't know if it's because we don't know it or it wasn't presented clearly enough to us.

Michael Souter: Seth, when is that not true? I was going to say, I want to know more. Is this just boiling over after months and months of doing this?

Seth Schwartz: I know, but a lot of times we want to know more and the information is not available. I feel like I want to know more, but there is more here that we're just not understanding. At least I'm not understanding.

Craig Blackmore: So, what do we need to know? You want to know the inclusion criteria?

Seth Schwartz: Yeah, I'm trying to understand what wounds they're looking at, because I think it makes a difference. I mean, I agree that there's no reason we should put someone whose got a decubitus ulcer for two weeks in the hyperbaric chamber. That seems obvious to me, but if we're saying you've got somebody with a decubitus wound for six months and nothing else is working, and we have evidence, even though it's a small study, that they're twice as likely to improve, then that may be meaningful.

Craig Blackmore: Can we find out the inclusion criteria for the fair RCT on slide 26 up there that had the 16 patients?

Chris Standaert: Those are venous wounds. The 16 patients are venous wounds. The 16-patient group you're talking about is a venous wound study.

Craig Blackmore: Oh, right.

Chris Standaert: It's not a decubitus wound study.

Craig Blackmore: The decubitus are mixed up in the chronic nonhealing wounds and equals 30 study.

Chris Standaert: Yeah.

Kevin Walsh: You can't tease it out.

- Seth Schwartz: What were the entrance criteria?
- Joann Elmore: Chronic nonhealing wounds 59% versus 26% reduction.
- Seth Schwartz: How did they define chronic nonhealing wound? Is that in the paper? Do we have that evidence? Dr. Hampson, do you know the answer to that?
- Neil Hampson: Yes, I do. It was defined as patients that were followed in their wound clinic for six weeks with no reduction in size of the wound with standard wound care, and they were not arterial insufficiency wounds, and they were nondiabetics. It was done in Sweden, I believe. I strongly think that you need to separate the kinds of wounds that you're talking about here, because arterial insufficiency wounds mean that there is no blood going to the wound. Hyperbaric oxygen therapy is not going to work if it isn't carried there by some blood flow. Revascularization is the treatment for arterial insufficiency wounds. Decubitus ulcers are a form of arterial insufficiency wounds. They're there because the pressure is compromising the blood flow, and the treatment for those is offloading. I could go on, but.
- Craig Blackmore: You know, one RCT of 30 heterogeneous patients...
- Michael Souter: And only wound area reduction, not wound healing.
- Chris Standaert: I just don't see the data. I would love to think it helps some of these, but I don't see the data to help me. Even if you break it up into categories, I don't see the data that it helps any particular category to any sufficient degree.
- Craig Blackmore: Okay, are we – how are we on the crush injury piece?
- Karen Crotty: So, the question that was asked originally was why was it downgraded from good to fair. We're talking about one study for crush injury, and there were several reasons why it would be considered fair and this was part of one of the Cochran reviews and how Cochran looks at risk of biases. They determine whether or not there was a low or a high risk of the bias rather than starting with good and then downgrading, but they found that there was – it was unclear as to what the methods were for the allocation concealment, as well as the generation of the random numbers. It was also unclear of whether or not it was free from

selective reporting. So, while it was fair in everything – it was good in everything else, it wouldn't be considered a good internal validity study. If you need to know anything else about that particular study, I have it up. It was a study of 36 patients. They were randomized within 24 hours after surgery to treatment either with HBOT as an adjunct to standard therapy, which was anticoagulant, antibiotics, and wound dressing, and they measured transcutaneous oxygen pressure, etc. So, the rest you know essentially, which was that the result was quite significant.

Chris Standaert: So, they were tracking soft tissue healing of crush injuries of extremities that went to the OR and had a fracture repaired? Is that what they're doing? They were crushed, they broke a bone, they went in, they did ORIF, and then they gave them HBOT to address the healing of the soft tissues assuming there's some complex mechanism of tissue damage from the crush?

Karen Crotty: Yeah.

Chris Standaert: And they're tracking soft tissue healing.

Karen Crotty: Yes, and randomized them to that.

Michelle Simon: Is this the Boucher study of 1996? Okay, so the title of that is crush injuries and suturing of severed limbs? So, we're talking about not just crush injuries, correct?

Craig Blackmore: This is a rare and catastrophic clinical scenario where treatments are not great, and there's one, only one, but there is a randomized trial that seems to show some benefit. That's my bias.

Michael Souter: Well, didn't the Garcia Study, as well, show that?

Carson Odegard: Page 137 of the appendix.

Craig Blackmore: So, I think...

Carson Odegard: Short-term benefit anyway.

Craig Blackmore: I think probably the committee is close together on this. I'm going to – and if we're not, we can drill more. I'm going to ask again for the non-inclusion on the covered conditions first. So, crush

injuries the non-inclusion people please raise your hand. Those who would like to include this as a condition for coverage, please.

Carson Odegard: This is for crush injury?

Craig Blackmore: Crush, yes. Thank you. Alright. We are making good progress. So that handles the nonhealing wounds. Now, we're down to the diabetics, basically. I think the only category we have left is diabetic nonhealing wounds, including foot ulcers. So, in your booklets, slide 22.

Seth Schwartz: No, it's slide 20.

Craig Blackmore: 20, sorry. Slide 20 and 21.

Karen Crotty: I dug a little deeper for some of the data that you were looking for on this if you want me to provide it first?

Craig Blackmore: Yes, please.

Karen Crotty: There was a discussion on the Faglia study, in particular, and you were trying to get a sense as to whether there was any stratification by wound severity, and that was the one study that there was. So, again, we're talking about one study. It had a total of 60-odd, 70 patients in total. When you break them down by wound type there were four patients in the HBOT group that had Wagner grade 2, five in the control group, nine with Wagner 3 in the HBOT group, eight in the non-HBOT group, and 22 patients with Wagner grade 4 in the HBOT group versus 20. So, as you can see, the numbers in grades 2 and 3 were very small, and when you look at the evidence for – and the main outcome here was major amputation, and for the patients with grade 2 there were zero of four patients had an amputation with grade 2 in the HBOT group and zero of five in the non-HBOT group. For Wagner grade 3, it was one of four versus zero of eight. That was not significant, a P-value of 0.33, and for the Wagner grade 4 is where you saw the big significance where you had two of 22 versus 11 of 20.

Craig Blackmore: Thank you. So, I think...

Seth Schwartz: Can I just ask, were there any intermediate outcomes in the lower grade groups or just amputation?

- Karen Crotty: They looked at both major and minor amputation. They did not find a benefit. I'm pretty sure, I'll double check it. They did not find a benefit for minor, but there was some conversation during the public comments section of this where somebody was suggesting that sometime minor amputation kind of comes at a price for the major amputation. So, I don't know whether that's something of significance, but it was something that came up during the public comment phase.
- Chris Standaert: Definition of a minor amputation?
- Karen Crotty: Yeah. In other words. You take a finger to save the hand.
- Chris Standaert: Okay. So, there's some definition of major versus minor amputation of a limb.
- Karen Crotty: Exactly, they do – yes. The risk down is considered minor, and the ankle.
- Craig Blackmore: Hands are optional.
- Joann Elmore: What about other outcomes other than amputations?
- Karen Crotty: In this particular study?
- Joann Elmore: Mm-hmm.
- Karen Crotty: They just looked at major and minor amputations. Let me double check that.
- Craig Blackmore: I want to frame this again. I think probably the committee is not at the point of saying we should cover all wounds in diabetics, even the ones you can't see, but I'm thinking that on the more severe wounds that there may be sentiment that we should cover and the challenge will be how we make that division. So, I guess I should confirm first that committee members do think that in severe, however we define severe wounds, that we would endorse and cover the HBOT. I'm seeing a lot of nods. Is that? Okay. So then the question becomes, how do we draw a threshold, and I think we need a threshold. Is that fair as well?
- Michael Souter: Can we rely on the precedence of what previous determinations have been using a grid 3/4?

Craig Blackmore: Well, I think that's the question. I mean, I think we have to have a threshold and we can either use 3, 2 as no and 3 as yes, or we can come up with criteria to make our own.

Chris Standaert: We also have a prior description of what a 2 versus a 3 is. Three implies you're down to bone and you're at risk for serious problems, osteomyelitis, other things, which are going to lead to very bad things. Grade 2 you're not. Grade 2, in their study, none of the grade 2 patients in either group went on to amputation. I mean they both healed. Or all 10 of them healed or whatever, those groups healed. So, from the data we have and the knowledge of the problem, it would seem like a line between 2 and 3 would be relatively appropriate based on our data and the pathophysiology.

Seth Schwartz: I have one question here. When we looked at the data that showed that it was beneficial based on the pooled data over the multiple randomized trials, they excluded the one that had the high-risk patients. So, I'm – which was in 21.

Craig Blackmore: No, they excluded...

Michael Souter: High risk of amputation.

Craig Blackmore: They excluded the opposite. They excluded a study that excluded high risk.

Seth Schwartz: I'm sorry, okay.

Craig Blackmore: Which supports the idea that it's the high risk that are deriving the benefit and not the...

Kevin Walsh: I want to disagree with what you said. I think in the numbers that I just heard, the distinction is between 3 and 4, not 2 and 3, because the amputation rates with hyperbaric oxygen therapy without in 3s was almost indistinguishable. I'm not advocating that we start parsing it out ourselves. I advocate that we use the standard that everybody else is using, because I don't think we have the evidence to make another determination.

Chris Standaert: I would agree. In drawing a distinction between 2s and 4s and then saying pathophysiologically there is a big difference between

a 2 and a 3, I would agree. Totally, that's where the distinction has been drawn elsewhere, but that's probably the rationale for it. I wasn't just going on the data. I was going on the physiology.

Craig Blackmore: Okay, so I – I mean, I think we're in the same place and the suggestion would be then that we include diabetic nonhealing wounds grade 3 or 4 as a condition for coverage, and I'll just have people raise their hands if they agree with that as a description of the...

Seth Schwartz: I thought we were going to do not. You keep doing not.

Craig Blackmore: I know. I was trying to be consistent, and it just makes it even more confusing. So...

Seth Schwartz: We needed that, thanks.

Chris Standaert: So, are we doing not or are we doing for.

Craig Blackmore: We can't do not, because not – there is no – it's not binary.

Marie Brown: Can the vendor tell me why the NICE recommendations didn't include this?

Karen Crotty: Well, I can tell you what the report said.

Marie Brown: Yes.

Karen Crotty: They recognized – they agreed that there was moderate level evidence of effectiveness. So, I have to assume that it was based on cost. They actually stated that there was moderate level evidence of effectiveness for the use of HBOT for diabetic nonhealing wounds. Now, whether or not there is significance to the fact that they were looking only at inpatients, and I did not come across a guideline from them that looked at the treatment for other diabetic foot ulcers.

Michael Souter: And I would bet if you ask our clinical expert, there's considerable differences in the prevalence of hyperbaric units in the U.K., as compared to the U.S. I mean, it really is [inaudible].

Neil Hampson: There are about 1000 hyperbaric units in the United States. There are six in the U.K.

- Craig Blackmore: Alright, I'm going to move on then.
- Seth Schwartz: Now, wait a minute. There's a different population, too. So, that's not a strict comparator.
- Craig Blackmore: Yeah, we have four times more people. Okay, so, alright. We're going to vote for using 3 and 4 as a criterion for inclusion, alright? So, that gets us through this very lengthy list. Well done, team. The other key questions we've tried to address, we're not real good with – I guess the question would be, do we want to look at some of these other things as conditions, including age, race/ethnicity, comorbidities, and I think we've done that as best we can in the course of the discussion.
- Chris Standaert: And there's no good data to help us sort that out that seems to be the condition from what we have.
- Craig Blackmore: Yeah, and then I guess the only other thing that we've talked about a little bit is number of treatments and that sort of thing, and I personally don't know that I would be one who should be making that distinction, given the lack of evidence.
- Chris Standaert: It sounds like they looked for systematic reviews that looked at that question. I was listening for that, but if you looked at systematic reviews and there were no systematic reviews looking at that question, so the assumption being there really is no data really assessing that question well in this type of format.
- Karen Crotty: That's right. I mean, I can say a couple of things in that you're right. Nobody looked at it. Some people tried within their studies and there wasn't enough data. What I can tell you is, there is some – there is a table in here under that question that just gives the range across all the studies. So, there was a question earlier about mode. So, while the range of frequency was huge when you look at it, from very few sessions to hundreds of sessions, I would say that the vast majority of the studies were somewhere between 20 and 40 sessions typically. So, that isn't evidence in that nobody set out to look at that, but if you're looking across 157 studies and you're looking at what was the typical number of sessions, it was somewhere between 20 and 40, but I'm not sure how that helps you make a decision.

Carson Odegard: And that kind of matches our agency data, too. So, it kind of coincides with the data that we see in the state.

Craig Blackmore: So, I'm going to draw the committee's attention to the HTCC coverage and reimbursement determination analytic tool, which is in your packet at the end, the last bit – nearly the last bit before the big tab. So, we are very familiar with this. It just states the purpose of the committee and determinates that we use in making our decisions and we will turn now to the health technology evidence identification and we generally go through and talk about the various outcomes and make sure that we discuss the relevant outcomes and there are a million outcomes listed here because we had so many different conditions. I think personally that we have done a good job defining the outcomes as we have gone through each of these conditions, but I would definitely entertain thoughts from the committee if there are outcomes or considerations that we did not discuss.

The first voting question, as we go through our procedure, I will draw your attention to the tan cards and the first thing we do is make a determination if there is sufficient evidence under some or all situations that the technology is effective, safe, and cost effective. The way we have structured things today, you would vote for more effective if you thought HBOT was more effective for anything. So, if there was any one of the conditions we defined where it was more effective or more safe, or more cost effective, you would vote more. You would vote less if you thought it was less in all of the conditions, and equivalent in all and unproven in all. So, if I could have please the yellow cards for effective. Okay.

Josh Morse: 10 more.

Craig Blackmore: And then the yellow cards for safe.

Josh Morse: One equivalent.

Craig Blackmore: Two equivalent. And then for cost effectiveness.

Josh Morse: Seven unproven, is that right? Three more. Eight unproven. Sorry, seven three.

Craig Blackmore: So, based on the evidence, the committee may be ready to take a vote on coverage. Is there further discussion or do we feel ready? Okay. So, this is the binding vote, and we will use our pink cards, and we will vote – we will make a vote for cover, cover with conditions, or no cover, and the conditions that we have defined we now need to formalize. So, if I could get a piece of – a blank on the screen, and we'll write this down, so...

Chris Standaert: Can I make a suggestion?

Craig Blackmore: Yeah, go ahead.

Chris Standaert: So again, we go back. We have an NCD to deal with, and I think the NCD, much of the language is already well written for the things we decided to cover. We don't totally parallel the NCD. The NCD includes the conditions that were excluded from the review, as the state already decided they were covered. They're all on this list, and the NCD has fairly clear language for the diabetic wounds that follows exactly what we had said. It has fairly clear language. So, it's on the agency medical director report, page five and six. The NCD is laid out. The only differences between what we said and what the NCD said is that we use flaps. They talk about the preservation and preparation of compromised skin grafts, not primary wounds, but they don't mentioned flaps, and we mention flaps. They talked about actinomycosis and acute peripheral arterial insufficiency and acute traumatic peripheral ischemia, which we didn't look at, but we could borrow the language from the NCD for much of the things we did, because they phrase it fairly well, I think, and it would give us a good place to start, rather than just en novo creating all the language. Then, we can eliminate or add a few words, or take away a few words if we want. That would be what I propose.

Craig Blackmore: So, this is slide 10 of the agency medical directors, 10 and 11.

Chris Standaert: It's 9, 10, and 11.

Craig Blackmore: Okay, well nine we don't have to worry about, because that's excluded from the assessment.

Joann Elmore: Or, we could look at slide 28 to see their recommendations and tweak that a little.

- Craig Blackmore: I like Chris's idea of using the NCD, because at some point we have to define why we differ from the NCD. So, I mean, we shouldn't conform to the NCD if it conflicts with what we want to do, but if it has language, I think that's a great suggestion.
- Michelle Simon: The CMS coverage policy is pretty good, too, on slide 64. It's all on one page.
- Chris Standaert: Well, that would be the same...
- Craig Blackmore: Well, the NCD should be the same.
- Richard Phillips: CMS on 64.
- Michelle Simon: It's just it's on one slide, 64.
- Chris Standaert: Slide 64 of which presentation?
- Michelle Simon: Oh, sorry, the events vendor, right before the coverage reimbursement determination tool.
- Richard Phillips: Page 32 of the booklet.
- Chris Standaert: There's a little more language in the NCD than the agency director's slide. So, as opposed to saying just chronic refractory osteomyelitis, it says chronic refractory osteomyelitis unresponsive to conventional medical and surgical management. I think the agency director has the actual wording from the NCD, and this looks like a reader's digest version of the phrasing.
- Craig Blackmore: Okay, Josh has pointed out that the language of the CMS decision is actually included in your decision tool at the back. So, that's going to be on the – you know, the decision tool that we were just looking at. Page three of that.
- Chris Standaert: She pulled that off the website.
- Craig Blackmore: She pulled that off the?
- Chris Standaert: Off the CMS website.
- Craig Blackmore: Alright.

- Chris Standaert: So, there we go.
- Craig Blackmore: So, right, but now there are aspects of this that are outside of our scope, and that would include certainly the first four.
- Chris Standaert: So, do we – question for the agencies. So, you excluded things from the search, because you assumed they're already covered. Should we list them in our coverage or should we not? Because we're going to say it's covered for these conditions only, and you've already taken conditions and said we're going to cover it for them already. You've already taken like 8 conditions, or 6 of them, and said we're going to cover it for these before you asked this question. So, should we put those on the top of our list, or should we not list them at all and then you'll have to somehow clarify what you're talking about?
- Kerilyn Nobuhara: Well, they were outside of the scope of the assessment.
- Chris Standaert: Right, but we're not going to mention them as covered conditions, even though you cover them.
- Craig Blackmore: So, staff, when they prepare the findings and decisions is going to be explicit in saying that the following are outside of the scope.
- Kevin Walsh: Well, I would say the agencies, when they implement, they would have this aspect.
- Craig Blackmore: No. No, it has to be in the decision, because we are saying these are the only covered indications. They can't cover for other things that we didn't look at. So, we're saying we didn't look at these. We are making no decision about the following. So, it has to be in our decision that we're not deciding. So, you'll take care of that piece, which is this slide, saying the following conditions were not included or outside of the scope of this decision. Then, we will say among – just say they're outside of the scope and then we'll say we will – we will endorse coverage for the following. That's a very, very good point.
- So, in terms...
- Chris Standaert: The first four can go.

- Craig Blackmore: The first five can go.
- Chris Standaert: I'm looking at her slide.
- Craig Blackmore: Yeah, but the fifth one is on this.
- Chris Standaert: So, take out the first four, because they are explicitly on their list already. She's got a different list than this. This isn't on their list. We can take it out, because we didn't talk about it.
- Craig Blackmore: It's on the covered diagnosis excluded from assessment.
- Chris Standaert: This is the NCD. Oh, I got you. Okay, I got you. Oh yeah, take them all off, okay.
- Craig Blackmore: So, she took off the first – take out the next one, acute traumatic peripheral ischemia was outside of our scope. Crush injuries we voted to include. Do we like the wording? We can get rid of the 'as in the previous conditions.'
- Chris Standaert: It being our first condition.
- Craig Blackmore: Do we like that wording? Loss of function of limb or life is threatened.
- Group: Yes.
- Craig Blackmore: Progressive necrotizing infections is outside of our scope.
- Chris Standaert: That was outside our scope.
- Craig Blackmore: Okay, get rid of that one. Acute peripheral arterial insufficiency is outside of our scope. Preparation and preservation of compromised skin grafts, and we said and flaps.
- Chris Standaert: Yes, we added flaps.
- Seth Schwartz: And we didn't talk about preparation, only preservation.
- Craig Blackmore: We did not talk about preparation. Preparation of compromised skin. So, preservation of compromised skin grafts and flaps, please. Dr. Hampson, do you have something for us?

Neil Hampson: The preparation was taken out by Medicare about five years ago, because it was being used as just [inaudible] nonhealing wounds, and Medicare didn't have that as an indication. So, that's why they said in primary treatment wounds. So, it just should say...

Craig Blackmore: Preservation.

Neil Hampson: ...[inaudible] skin grafts and flaps.

Craig Blackmore: Okay.

Chris Standaert: Yeah. So, at the end flaps, skin grafts and flaps. Preservation of compromised skin grafts and flaps.

Marie Brown: Do we need to say preservation?

Craig Blackmore: We don't need the preservation. Just say compromised skin grafts and flaps. Chronic refractory osteomyelitis unresponsive to conventional medical and surgical management, and we were going to leave the definition of that to our agency directors. Osteoradionecrosis as an adjunct to conventional treatment, and we like that one. Soft tissue radionecrosis as an adjunct to conventional treatment. We said yes to that.

Chris Standaert: We said yes to that one.

Craig Blackmore: Cyanide poisoning is excluded. Actinomycosis should be dropped off the list. Delete those. Diabetic wounds of the lower extremities in patients who meet the following three criteria: They are diabetics, they are three or higher, and they have failed an adequate course of standard wound therapy. Do we like the wording?

Chris Standaert: Did we talk about upper or lower extremity?

Seth Schwartz: That was the only thing we didn't talk about.

Chris Standaert: We didn't specify the extremity, I don't think.

Seth Schwartz: It may not be an issue in upper, I just don't know, but we didn't talk about it.

Neil Hampson: It's not an issue.

- Chris Standaert: Yeah, I've never seen it in an upper.
- Craig Blackmore: I think I would favor getting rid of the lower extremities, because we didn't talk about it.
- Chris Standaert: And then if it never comes up, it never comes up.
- Craig Blackmore: No. No, just get rid of...
- Chris Standaert: Just get rid of lower extremities.
- Kevin Walsh: And I would question, what does diabetic wounds mean? Isn't it nonhealing wounds in diabetic patients that we're talking about?
- Chris Standaert: Yes, it says that at the bottom. Patients who failed adequate course of standard wound therapy.
- Kevin Walsh: But what is a diabetic wound? I don't know what that means.
- Seth Schwartz: A nonhealing wound. It's a nonhealing wound.
- Craig Blackmore: Do you just want to say wounds of the – so...
- Carson Odegard: Nonhealing diabetic.
- Joann Elmore: But this language is [inaudible].
- Craig Blackmore: But under 6, the words lower extremity should be taken out. Not 6A, but 6.
- Seth Schwartz: Can we just say nonhealing wounds in diabetic patients.
- Neil Hampson: It's standard jargon.
- Chris Standaert: Take out the lower extremities there.
- Marie Brown: What's standard jargon?
- Neil Hampson: Diabetic wounds.
- Marie Brown: Diabetic wounds?

- Carson Odegard: Nonhealing wounds in diabetic patients.
- Seth Schwartz: That's covered in C.
- Craig Blackmore: Okay. Did we decide on any that are not on that list? I've got to find my right page, here. Late radiation, we have. Refractory osteomyelitis we have. We have ulcers, no. Flaps and grafts, yes. Diabetic nonhealing wounds. We're not done with ulcers.
- Neil Hampson: You decided to cover [inaudible].
- Seth Schwartz: Oh yeah, the tooth extractions and radiated bone.
- Craig Blackmore: So, that – do we, so can we see the list again? Can you scroll up for us? Should we say osteo...
- Chris Standaert: Say osteoradionecrosis or as an adjunct to conventional treatment.
- Neil Hampson: That's established osteo.
- Seth Schwartz: Yeah, no. I think that's right. We...
- Craig Blackmore: But do we want to say...
- Seth Schwartz: For prevention of osteoradionecrosis in radiated mandibles.
- Craig Blackmore: Okay, can we...
- Seth Schwartz: Anticipation of tooth dental extraction or something like that.
- Craig Blackmore: We'll add another one after, between four and five we'll have another category. It's for prevention of osteoradionecrosis following tooth extraction.
- Seth Schwartz: The only thing I would say about that is I think sometimes they give – they start treatment before extraction.
- Craig Blackmore: This is for prevention of.
- Seth Schwartz: Yeah, no I – but you said after, so.
- Craig Blackmore: Did I say after?

- Seth Schwartz: Or following extraction.
- Craig Blackmore: So, for prevention of osteonecrosis – well the osteonecrosis is following tooth extraction.
- Marie Brown: With tooth extraction.
- Craig Blackmore: No, the following is modifying.
- Seth Schwartz: So, it just should be for patients – for history of...
- Chris Standaert: Following tooth extraction in patients with prior...
- Carson Odegard: Joann, how should it be.
- Kevin Walsh: But what the point is that the treatment is given before the tooth is extracted so to say following is limiting.
- Craig Blackmore: Technically it is – following is part of the prepositional phrase and is modifying the osteonecrosis.
- Kevin Walsh: Then, I guess the condition would be anticipate – would it be anticipated dental extraction in patients with prior radiation to the mandible. That might be a more clear way of saying it.
- Chris Standaert: For prevention of osteonecrosis in...
- Joann Elmore: Patients with anticipated tooth extraction.
- Seth Schwartz: Because we're talking about what's the indication? The indication is anticipated tooth extraction.
- Craig Blackmore: How about for prevention of osteonecrosis associated with tooth extraction. Can I say that?
- Joann Elmore: That allows the before and after.
- Neil Hampson: [inaudible] novel and revolutionary if you just combined all of those three and said chronic radiation tissue injury or [inaudible] injury, because they're all the same.

- Craig Blackmore: We're not that novel. Alright, prevention of osteonecrosis associated with tooth extraction in a radiated field.
- Chris Standaert: In a previously irradiated field.
- Craig Blackmore: Say in radiated field. So, after extraction, the words in a radiated field.
- Chris Standaert: A radiated field.
- Joann Elmore: A radiated. Field.
- Seth Schwartz: No, A space radiated.
- Craig Blackmore: Perfect. Okay, and then so what else have you on this page. We're trying to get rid of it.
- Chris Standaert: Get rid of the rest of that stuff.
- Craig Blackmore: Yeah, get rid of all that. Get rid of everything else. No, get rid of those. Keep going.
- Chris Standaert: We don't need to specify those.
- Craig Blackmore: We don't need to specify. Scroll back up, please. Scroll back up. Starting at letter B, get rid of everything below that. Just get rid of everything else. Keep going. Okay. Get rid of the program reimbursement. We'll be limited to a chamber and the following conditions, everything above the one, okay. Get rid of the A.
- Chris Standaert: Before covered conditions, because we have no B.
- Richard Phillips: You voted on noncovered conditions.
- Craig Blackmore: What's that?
- Richard Phillips: We have noncovered conditions.
- Chris Standaert: We don't have to specify those.
- Craig Blackmore: Nope, we voted to define what would be on our list of conditions.
- Chris Standaert: Right, okay.

Craig Blackmore: Okay, so that gets us to the pink cards and so you have three choices. You vote for no coverage, or you vote for coverage under all conditions, or you vote for coverage with conditions, and the conditions that will be covered if you vote for cover with conditions are those that we have discussed and are listed here. So, if I could please have – this is the binding vote.

Josh Morse: Ten cover with conditions.

Craig Blackmore: So, we are required to make a determination as to whether our decision corresponds to the Medicare National Coverage Decision, and it corresponds very closely, and the areas where there are differences are small and related to our perception of what we have sufficient evidence to state one way or the other.

Chris Standaert: Within the scope of what we could look at.

Craig Blackmore: And, of course, we excluded a lot of things that were outside of our scope, and that wraps up HBOT.

Carson Odegard: Craig, one other question. I noticed we didn't bring up the issue of cost at all, not that there was any data there. I was wondering if we should have made a statement on the cost.

Chris Standaert: We voted on it.

Craig Blackmore: We did vote on cost effectiveness in our nonbinding.

Carson Odegard: So, that was in nonbinding, okay.

Craig Blackmore: Yeah, there was a lot of ambiguity.

Joann Elmore: And they talked about it, and it was just very difficult to estimate.

Carson Odegard: I appreciate that. I was just wondering if we had to make a statement about it.

Craig Blackmore: So, is lunch ready?

Group: It is.

Craig Blackmore: Okay, well it is 10 after, so we will resume at a quarter of 1, on schedule.

Well, welcome to those of you who have just joined us. This is the Health Technology Clinical Committee meeting and the afternoon agenda; at least the initial part of the afternoon is focused on surgical spinal fusion for degenerative disk disease. This is a public meeting, so we're being recorded and members of the committee I will remind you to please identify yourselves, particularly early on and to speak into the microphone. Those of you who have joined us from the public, we will start this session with an opportunity for scheduled and open public comments. I would ask anyone who does address the committee to please identify yourself, tell us who you represent, if there's an organization or a group of individuals, and also tell us if you have any conflicts of interest and if anyone has paid to have you come to the meeting or some other financial incentive. So, the first piece is, again, the scheduled and open public comments. We have had a number of individuals contact us in advance, so we will start with those. We also have a – there's an opportunity for people who have not signed up in advance to speak, and there is a signup sheet right outside the door.

Josh Morse: It's actually right here right now.

Craig Blackmore: Oh, it's actually here. So, if you want to speak and you're not already on our list, please let us know and we'll give you an opportunity. Because of the number of speakers, we are limited in time. So, we will be limited to five minutes for those of you who have scheduled in advance and then three minutes.

Josh Morse: I think we're actually okay for five minutes. We have four speakers.

Craig Blackmore: And then three minutes for those who have signed up onsite. So, first on our list is Dr. Joseph Chang.

Joseph Chang: Hi. Thanks for letting me talk today. I'm Joe Chang with – I'm from Vanderbilt but I'm here representing not only the joint section of spinal disorders and peripheral nerves from AANS/CNS, but this is a multi-society collaboration, so I'm actually here representing AAOS, NAS, AOS, Scoliosis Research Society, along with the Washington State Neurosurgeons. One of the things I

just wanted to point out in my talk, and I'm just – I was actually had some updated slides I was going to show you, was one of the things to point out as far as surgical versus nonsurgical care is that very few people have surgery as a first line treatment for something that can be easily treated nonsurgically. So, if you look at the incidence of spinal surgery, absolutely it has been increasing tremendously. As you noted in your studies, eight-fold. Interesting enough, though, if you take the data from Medicare and you plot it against, and I'm happy to show you the slides at a later time if you like, if you plot it against epidural steroid injections, you'll notice that spinal surgery is less than a fraction of the amount of epidural steroid injections being done. If you take epidural steroid injections and plot it against new physical therapy visits, because physical therapy has both initial visit versus return visits, you notice that epidural steroid injections are only a fraction of that compared to say chiropractic manipulation, which are even higher. So, for example, for every growth of a million in new physical therapy visits for spinal disorders, chiropractic care will grow by eight million, and that's all based on the Medicare database that you guys can see here.

So, the issue is, if you look at the relative utilization of the last 10 years, spinal surgery is actually under-utilized when you compare it relative to the population. So, when we talked about the denominator of patients, the baby-boomers, coming up to an age that needs care, you're realizing that compared to all these nonoperative treatment, surgery is actually less than all of that. So, one of the things about it I think is maybe misconstrued that we're over utilizing surgery in expense of the other modalities when in reality it's not. Getting back to the task at hand, that's one of the concerns we have about these restrictions for treatment. So, without kind of going over these things in detail, one is these points clearly made in the slides in your handouts about the heterogenous patient groups. Unfortunately, even someone with cervical stenosis and myelopathy is not the same. You have some due to disk protrusions or some due to posterior ligamentous issues, or you have some that are due to congenital stenosis. So, by lumping in all these different patients, I think that's one of the things we have to differentiate is that. One of the things we recommend and ask you to do is, with this analysis, the reason we disagree with this is because it is not risk adjusted based on a number of things and is based purely on the available literature, which has been certainly significantly down-sampled.

That's why a lot of the things you're looking at are only based on a few articles versus the list of things that we have available overall.

Certainly, some of the other things we've pointed out were the use of all available data. I understand that arthroplasty was not part of this literature; however, arthroplasty, the literature does have comparison groups to fusion with a lot of good data from that, and I think by ignoring that and using only older RCTs or only older papers may be creating some type of bias, as far as how they assess this at all. We also think that some of the mortality discussions were presented out of context, and that's the mortality for cervical fusions was certainly less than – or really a small part of that overall. This is also part of our slides and our response as far as the comparators used in analysis, which I won't belabor this. The same thing with limited decision analytical model. We really have concerns, and this was key question number four, about the robustness of the decision-making models that were used, along with the input, and certainly this is something that I've published in and cost utility, comparative effectiveness, and cost of care with quality added life years. So, certainly we're concerned about these issues as well, and this kind of gets back on into some of the details. While we think the model assumptions were flawed, and so the results and the conclusions may be taken out of context. This is, again, just some of the assumptions that were made, including the Persson paper looking at the outcomes that is why we don't think that this was a relevant model to use for answering the key question. This leads to the inaccurate use of the qualities and some of the recommendations that were made. So, for example, you know in the ICER graded evidence rating saying that spinal fusion versus conservative management with physical therapy and collar is equivalent actually also doesn't seem to make a lot of anatomic or medical sense, because you may be talking about different processes. Again, the incorrect estimate of value and treatment is something that we pointed out, as well.

So, in summary, we think the report highlights the need for meaningful inclusion of content experts, and one of the things we're happy to do as a national organization is to help provide you with that and collaborate to make sure that we have appropriate content experts for that. The other thing is that we don't think that different treatment indications for spinal fusion versus decompression, such as discectomy and foraminotomy is

valid as well, and some of the other slides that you noted trying to compare fusion versus decompression may not take into account various patient factors, which would lead a physician to make one decision or another. So, I guess, in summary, we would ask you to revise and reconsider the recommendations of this report and as a national organization, we unfortunately don't agree with it and would ask you to reconsider it.

Craig Blackmore: Thank you. Next is Jason Lerner.

Jason Lerner: Good afternoon. My name is Jason Lerner. I am representing DePuy Synthes Spine. I work in the evidence-based medicine division there. I want to thank the committee for the open and transparent process and for inviting us to participate in this. We actually appreciate a lot of the changes that were made from the draft to the final report, but we still have some significant concerns about key question four and about some of the structural assumptions that are applied, particularly to the core analysis of patients who had either conservative care or cervical fusion. We also have some concerns about the lack of data that is available to come up with a credible estimate of cost effectiveness for ACDF versus discectomy alone.

I will take the first situation that we're concerned about. The structural assumption in the economic model assumes that patients who have conservative care have a pretty much linear improvement in four years, such that by four years they are exactly equivalent to the excellent results that we see in ACDF. So, I think the excellent results have been born out and proven in high quality randomized controlled studies. The same level of rigor was not applied to selection or necessarily the availability of data from a conservatively-managed cohort over a four-year period of time. The actual source data that was used from the Persson study, which was just mentioned by Dr. Cheng, indicates that actually the best measure of multidimensional quality of life, which is the sickness impact profile, which was used in that study, actually shows the patients in the nonoperative cohort declined in quality of life from the four-month to the 16-month period in the physical dimension of the sickness impact profile, and that's the best measure of quality of life, the highest quality evidence that we can rely on. That's from a 1997 paper from the same publication that preceded the 2001 paper. So, the generalized

ability issue, I think, with that study goes without even saying, and Dr. Cheng just alluded to that.

Now, the second piece of the economic model that we're concerned about are the implications for anterior cervical fusion versus discectomy alone. There really aren't sufficient data for anterior cervical discectomy to understand the natural history, well not the natural history, but the history after there's a kyphotic deformity that develops in the spine. We do know that a kyphotic deformity develops much more commonly in patients who have an anterior cervical discectomy rather than patients who have a concomitant fusion. Now, in fairness, we don't know whether or not there will be economic or clinical consequences of this radiographic finding, but we do think that it's not plausible with the current data available to estimate over four years, let alone a lifetime, for a given patient what the incremental cost effectiveness ratio would be with any degree of certainty for anterior cervical discectomy and fusion versus discectomy alone. So, with these limitations in mind, I would ask, and we ask that the committee consider allowing surgeons and patients to have the same benefit of all this information that's being shared in this form now including the evidence report, the findings from the final evidence report, such that this honest, open, shared decision making between the surgeon and the patient about all the findings in the literature, including radiographic, clinical, and economic. Thank you very much.

Craig Blackmore: Thank you. Next, Dr. David Flum.

David Flum: Thank you. Good afternoon. Hi, my name is Dave Flum. I'm a surgeon and outcomes researcher over at the University of Washington. I have no financial disclosures to make related to this presentation, but I do for the sake of transparency have to say that I was a medical consultant to the HTA in its early development and it gives me great pride to see the evolution of the committee. It's been a wonderful asset to Washington State citizens, and I appreciate all the hard work that you do. I know just how hard it is. So, that's why I appreciate it even the more. It's during the time that I was involved with the HTA that I realized that one of the major limitations of this construct is that it relies on the availability of published data, and when it comes to surgical interventions, I have always been very concerned that it's not as reproducible as a pill, a surgery. It's a very complex

intervention and understanding how those interventions work in the real world seems to be a very critical thing. It's the essential thing if we want to understand whether or not a coverage decision is a good one or a bad one. It's, in part, recognizing that Washington State surgeons have organized in multiple communities, clinical communities of interest to understand the real-world effectiveness of the procedures that we're doing, one of the few states that have done this. I am here today with Neal Shonnard who is a practicing surgeon. Neal, raise your hand so they know who you are. He is a practicing spine surgeon. Now, I'm a surgeon but I'm not a spine surgeon and in fact I'm totally agnostic about all the procedures that the real world surveillance activities we do, I'm totally agnostic about their value. I try to gather evidence about the way real-world data looks so that stakeholders, like yourselves, can benefit from them.

SCOAP is the name of this initiative. I mentioned it several times in the last couple of years, but SCOAP has grown as a grassroots entity across almost every hospital in Washington State. It's now at 60 hospitals and incorporates almost all of the general vascular, bariatric, and most recently spine surgery in this state. It's real-world data. My plea to you today is not as an advocate for any kind of procedure but as an advocate for the use of effectiveness data that currently exists in Washington State, either through CHARS, which is one of the unique administrative databases that allows looking at hospitalized care, or through SCOAP that allows you to look at real-world granular information about cervical spine surgery that's being done. It may not be completely ready for your assessment today, but it will be during your reassessment at 18 months, and it will be for other procedures that you're looking at that are related to the spine or those other conditions that I mentioned.

SCOAP works by surveillance but also through check listing to change the quality of care that's delivered. Remember, if you approve a procedure today but its quality is poor, you're approving a poor-quality procedure. Linking surveillance of how these procedures work with an initiative that drives their performance improvement is the way that you're going to help the residents of Washington State accomplish the goals of the HTA. We do that through check listing, through initiatives like Strong for Surgery that helps make patients stronger and more optimized for operations, and we have literally bent the cost

curve. The blue curve is the cost of SCOAP hospitals. The red curve is the cost of non-SCOAP hospitals.

We've built this in spine over the last year, and I wanted to just tell you that we have about 4000 cases now at 18 hospitals. It's not in every hospital in the state, but an HTA decision to cover with evidence development, cover linking any procedure that you're going to cover today to ongoing involvement in the spine SCOAP registry would allow you, in 18 months, to have 100% knowledge about how the coverage decision you make today is playing out in the real world, and I encourage it.

Just to give you a sense of the variables that are in SCOAP, it's really focused on safety, quality, and outcomes but the beauty of this is that we're including patient-reported outcomes at baseline through to two years, functional outcomes like the ones you've been looking at in your HTA report, the Oswestry Disability Index, the NDI, the ODI is coupled with a visual analog scale of pain. This patient-reported patient-centric surveillance metric is going to allow you to know whether or not the procedures you approve today are actually working at 18 months, and I think it's an essential role but we'll only know that if the hospitals participate in spine SCOAP, and hospitals will only participate in spine SCOAP if they think it's a good idea, because they volunteer for it or because the payer uses its influence to compel them to join, and that's where the challenge is for the HTA today. You've made coverage with evidence development decisions before around autism care, and I encourage you to do that today.

Just to give you a little glimpse and a tease of the data, there are 4300 patients that are currently in the database, and it's really in its first year of full running at these 18 hospitals. A lot of prior spine surgery, a third of these patients, as you know, are having repeat spine surgery. I want to show you the types of granularity of the data. This is the – this shows you what percentage the patients are having, surgical fusion for neurological symptoms. In other words, folks that are actually having the indications that you're looking at today and though it's happening in over 93% of patients, that's not what's happening at every hospital in the state, but this is what I really want to leave you with. We are looking at change scores of pain and functional activity that you can use in 18 months to reconsider any decision you make today. Remember, this will only be at the hospitals that are involved in

spine SCOAP and though the Bree Collaborative has agreed this is a community standard, we need payer pressure, the type of payer pressure that the HTA can bring to bear to make this a universal activity, and that's what I'll leave you with today. I want to thank you for the time and opportunity to talk today. I look forward to being involved in future decisions.

Craig Blackmore: Thank you. Next is Dena Scarce.

Kerilyn Nobuhara: She didn't have testimony.

Josh Morse: They did provide a letter.

Craig Blackmore: Oh, I'm sorry. Okay, thank you. So then we have – that's all the prescheduled, and then we have one individual who has signed up here and we certainly have time to allow five minutes, as well. David Yam, have I pronounced that right?

David Yam: Hi. Thanks for having open discussions about these very important patient issues. I'm David Yam. I'm a practicing neurosurgeon in Walla Walla, Washington. Obviously, I've been just in practice for a little while, but the main issues are that I saw on this issue are how am I going to take care of my patients based on the decisions that you make and what evidence and what data are you using in making these decisions, and I thought it was important to come and talk. So, the main thing I saw looking at the data, looking at the models that have been built, and looking at everything is that the key question asks, looking at cervical degenerative disease, neck pain, and radiculopathy and lumping them all is one thing, and of course in practice, when I see a patient those things are never lumped together. The patient may have cervical degenerative disk disease. A patient may have neck pain. They may have radiculopathy. They're all separate, and you can't lump them all together. So, when you're looking at treatment decisions and you're looking at all the models that have been constructed like the ICER model in particular, they're looking at neck pain. The whole model is built on neck pain, but when I see a patient in my practice, that's the least important thing if I'm making a decision about doing any type of procedure on the patient's neck. I'm actually looking at what are their radicular symptoms, what are their nerve compression symptoms, what are their functional limitations, and how is the patient doing in terms of things that radiculopathy cause, not neck pain? Do they have

weakness? Does the patient have findings that aren't indicated in any of the data you're looking at today, and I think critical to my patients and their care, if you don't look at the more important picture of radicular symptoms and isolate that out from the data and the evidence that's presented today and say, can we make a decision on radiculopathy versus can we make a decision on neck pain surgery, I don't think you have that data today, and I think the SCOAP and future randomized control trials, some of the better peer reviewed data and literature that's there to hopefully come out and be the primary discussion that you guys have today will steer you in the direction that yes, cervical fusion is a valid treatment for patients, and the decision needs to be made carefully with the surgeon and the patient. Not every patient with degenerative disk disease needs fusion. In fact, most of them don't. Not every patient with radiculopathy needs fusion, but the reality is, is there are some patients with severe symptoms that if you lump all of these terms together and group them as one thing, you will harm a significant number of patients, restricting their care.

And so, I ask that you, as a group, just weigh the evidence carefully, look at what the model is looking at. If it's looking at neck pain, does that apply to radiculopathy? If it's looking at visual analog pain scale, what is that for? Is that for neck pain? Is that for overall body pain? Is that for radicular arm symptoms? Just look closely at what's actually being presented, because when I look at it, I don't see a lot that says you can make any justification or any determination on actual nerve symptoms. You can make tons of judgments, I think, in my opinion on degenerative disk disease and fusion alone, and that's up to you, obviously, as a well-informed committee to look at, but I think the reality is please look very closely at what the models are saying, what they're actually looking at, and it would make a tremendous difference to my patients if you don't restrict this very valid and very useful, very cost effective procedure for patients with cervical radiculopathy. Thanks.

Craig Blackmore: Thank you. Andrew Skelly, do you want to speak? No? Okay. Is there anybody who hasn't – whose come later that hasn't signed up that wanted to address the committee whose here? And we'll need to check the phone, as well.

Is there anyone who is joining us on the phone that wished to address the committee on cervical spinal fusion? Okay, we'll re-mute the phones, and we will move on.

The next item on the agenda is the agency report.

Gary Franklin: Christine, is that up here?

Christine Masters: It is a button push away.

Gary Franklin: Is it up here?

Christine Masters: It's not on...

Gary Franklin: It's not on here?

Christine Masters: No.

Gary Franklin: Okay, and you have a clicker?

Christine Masters: I thought you had it.

Gary Franklin: I'm going to stand over here, if you don't mind. I'm Gary Franklin. I'm representing the agency medical directors today on the issue of cervical spinal fusion. I can't see these things too well, so I'm going to speak from here. As you know, chronic neck pain is prevalent and so is degenerative disk disease. L&I sees a lot of this stuff, as do all of the agencies. There are multiple treatment options that are used, including rehab techniques, injections, and surgery. L&I has been dealing with the cervical fusion issue for many, many years. The first time we did a cervical radiculopathy guideline, which was probably in the early 1990s, we were told that whenever the neck is operated on it to decompress the neck for a cervical radiculopathy that a fusion had to be done, along with the radiculopathy. So, L&I's guideline over many, many years has been, because there was no other evidence available. This was our committee's consensus opinion was that whenever you need to do a decompression of the neck, even a unilateral decompression following, adding on a cervical fusion was what needed to be done, so we went along with that, and that's been our policy all these years. There's a lot more data now, which is in your report, and I will be addressing that today.

So, cervical fusion is really done for two principal reasons. One is for chronic neck pain that frequently happens after whiplash injuries, and for cervical degenerative disk disease associated with radiculopathy either from a disk or spondylosis, osteophytes, etc. So, there are combinations of these things, for which, as someone mentioned, the procedures are being done.

Cervical spinal fusion is the most common surgical procedure in the U.S. for patients with symptomatic cervical degenerative disk disease. There was a huge increase between 1990 and 2004, an eight-fold increase in cervical spinal fusion in the U.S. Utilization is increasing disproportionately in the older populations compared to younger populations. The cost is, as you have in your report, is quite high, and the safety and effectiveness of the procedure are of concern. Reoperations rates of the procedure are high, either at the same or at adjacent segments, and adding fusion to cervical decompression in our view and in the view of the report may do more harm than good.

On the efficacy, chronic neck pain is not necessarily caused by DDD, even with radiographical evidence of DDD. Spinal fusions may be performed on patients without radiculopathy or myelopathy, which in our view operating on people with just chronic neck pain with this invasive procedure is not necessary.

Then the main question, I think, today is whether fusion should be added to other decompressive procedures when there is radiculopathy. The scope of this report did not include myelopathy because we believe that should be left up to the surgeon, if someone has myelopathy, as to what kind of a procedure they might do. So, we cover that, and that's not part of this decision making process. We're only talking about fusion for neck pain or fusion for radiculopathy.

The average cost per procedure is actually paid amounts of \$24,000. It can be way higher than that, and the agencies, altogether, paid 63 million dollars for cervical spinal fusion just in this four-year period that we looked at.

The agency medical directors' concerns when we originally prioritized this topic were, we had medium concerns for safety. We now feel like those concerns are high considering the report. We had high concerns on efficacy and high concerns on cost.

There aren't that many topics that we have picked over the last several years that were high in all three categories. The current state policies are that Labor and Industries requires prior authorization through Qualis. When there is entrapment of a single nerve root, you have to demonstrate by objective means that there is entrapment of a single nerve root and that some conservative care would have been done. So, we do cover spinal fusion as an add-on procedure, as I mentioned earlier. It is not covered for chronic neck pain without evidence of radiculopathy or myelopathy. Medicaid actually is now using the exact same prior authorization techniques, because we jointly procured our UR recently, so we're using exactly the same guidance and review criteria. The Department of Corrections requires prior authorization but don't have specific criteria, and Regence requires prior authorization but do not publish the criteria.

These are the numbers over the last four years in the agencies, the Public Employees Benefits Board, Medicaid, and L&I. You can see that the totals are quite high and the average is, as I mentioned earlier, around \$23,000 to \$24,000 per procedure. The numbers have gone up, as you can see here in PEB. The patient numbers with fusions in L&I have stayed relatively stable.

This is a breakdown, two different kinds of breakdowns, and how the costs break out. Breakdown #1 are professional services and facility costs, and breakdown #2 are preop, fusion, and postop, etc. This is in PEB primary, PEB (Medicare), two different kinds of payments. They're paid slightly differently. I think you've seen this before in some of the prior topics. Medicare has its own sort of payment mechanisms. L&I is a little bit lower. Here's the total allowed costs and then total paid costs. Among all the agencies, the total paid, again, was 62 million dollars.

This is of some interest, the PEB patients tend to be older. The average age is 51 to 65 among those that are receiving cervical spinal fusion, whereas in L&I, we have a younger population that is receiving cervical spinal fusion. So, we suspect that the issues of myelopathy and radiculopathy more complex bony issues are occurring in the PEB population, and L&I is dealing with less of that in our population.

Medicaid is kind of a mix. It's about the same, evenly distributed in those two main age groups.

This is, in the PEB, the proportion of the patients that have radiculopathy or myelopathy and it's been pretty steady over the years and again, reflecting this younger population with less myelopathy. L&I is mostly radiculopathy plus or minus chronic neck pain, but not too much myelopathy, and Medicaid is kind of in between.

This is the where, in L&I, the cervical fusions are occurring. There aren't that many occurring in ASCs, but there are quite a few occurring in the hospital outpatient arena and this slide is about whether there are Emergency Room visits within 30 days or 90 days following a cervical fusion at L&I, and you can see the largest proportion of you want to call it morbidity requiring Emergency Room visits in a short time after cervical fusion, for some reason are recurring from these outpatient cervical fusions more commonly than from the inpatient cervical fusions. I'm not really sure why that would be. And this is a little more detail with the kinds of causes of those Emergency Room visits, and then there are a number of patients that had more than one Emergency Room visit within 90 days following spinal fusion.

We are concerned about the reoperation rates in these patients. So, if you just look at these four years, in L&I 12.2% of the patients that got a first cervical fusion had another spinal procedure in the neck within that four-year period and 5.8% of the PEB patients, 43 reoperations in PEB were done in 38 patients, 196 reoperations were done in a 163 L&I patients, and there are a number of patients that had three, four, or five procedures. This is one of the banes of L&I in both the low back and the neck is repeated spinal surgery.

There was a very modest randomized control clinical trial that I wanted to mention that was not mentioned in the report because it was just published. It was a study of 63 patients but including function-based measures of outcome, including strength, exertion, range of motion in the neck and the arm. So, on the issue of pay – and these were patients that had radiculopathy. This was structured physiotherapy alone versus anterior fusion plus physiotherapy and the outcomes in this particular population were exactly the same. There was no difference in outcome of the conservative treatment versus the fusion plus the same conservative treatment.

Our state agency questions really have to do with treatment success. There was no difference found in six higher quality RCTs, except in one RCT, which I'm sure you'll talk about, and a meta-analysis using two RCTs on treatment success showed no difference. In pain or function, there were no significant effects of treatment on pain observed in four of the five RCTs. Quality of life, there was no difference. Return to work, the ICER meta-analysis direction only favored discectomy at 12 to 24 months, although that was not statistically significant. There was another November, 2012 systematic review that was published that occurred after the final review that ICER did.

Is there something happening here? I don't know what I did wrong. The thing disappeared up here on my screen. Thank you.

November 2012 systematic review of 10 RCTs using pooled risk differences showed no additional benefit of fusion with anterior discectomy on pain, recovery, and return to work. There are no RCTs in terms of evidence for cervical fusion for chronic neck pain, as opposed to radiculopathy. So, in summary, efficacy of cervical fusion, there is little or no difference in patient-centered outcomes between fusion and conservative therapy in the long-term. There is little to no difference in patient-centered outcomes between decompressive procedures, plus or minus fusion in patients with radiculopathy. The risk of adverse events is much higher for patients with cervical fusion that have conservative treatment, and the risk of reoperation at the same or adjacent levels is substantial. The cost effectiveness data in the ICER report is, I think, pretty self-explanatory.

Our recommendations are that cervical fusion as an add-on procedure to a decompressor procedure for cervical radiculopathy is not indicated according to the evidence, and cervical fusion for chronic neck pain in the absence of radiculopathy should not be covered, as that is our current policy. The agencies, of course, would continue to cover decompressor procedures for radiculopathy and fusion with or without decompression for myelopathy. Thank you very much, and if you have any questions, I am happy to take those.

Craig Blackmore: Okay, I wanted to just go back to where you talked about the indications for the fusions that have been done in the state, and

you talked about not covering fusion for axial pain, for pain without radiculopathy, in essence. So, I wondered what the individuals you described who didn't have myelopathy or radiculopathy, what indications they had, such that they were getting funded.

Gary Franklin: Pain. It's just for pain, and nobody knows where the pain is coming from.

Chris Standaert: But you don't cover neck pain as it is.

Gary Franklin: Sorry?

Chris Standaert: You already say you don't cover cervical fusion for axial neck pain. So, how could they be patients in L&I getting all those cervical fusions for axial neck pain.

Gary Franklin: Well, because not everything we say we do actually happens, you're aware. There is a doc that would call and argue and offer some compelling reason to still do it. Maybe there's a little stuff that's questionable radiculopathy. It's not a pure population. I think that if somebody only had neck pain, and they had no findings at all on any of the tests, they probably wouldn't get it, but we do, you know, docs can appeal the review. They get to talk to a peer match doc within two weeks. So, it's not a line in the sand. Some do get approved.

Chris Standaert: So, is there going to be, I mean, I have a number of issues I want to get at. I find myself in a very odd spot with this report being a nonoperative spine person looking at this stuff, but the – we have to get a definition at some point. I would think we would get them with a vendor, but these, the indications for all the surgeries would be important. I mean, the reality is most cervical surgery, I would argue, is not done for neck pain and degenerative disk disease. The surgery is a decompression of the spinal canal or of the foramen, and that's what they're doing. Then, the fusion is done as an adjunct to that depending upon the approach the surgeon had to take to decompress. The primary goal of the surgery isn't actually to fuse most of the time. It's to decompress. So, looking at – we have to talk about this as we go through the data, because it really does matter what we're talking about, but I have questions about all those other diagnoses. I find it hard to believe they are all neck pain. If they're all neck pain, then you all

aren't doing a very good job filtering your patients and letting a people through getting things you say shouldn't be done.

Gary Franklin: The thing is I agree with you completely, you know. There's no evidence for neck pain and fusion, and the main issue here is, should fusion be an add-on to a decompressive procedure when there is a single unilateral radiculopathy. If there are multiple levels of problems or myelopathy, you know, myelopathy is not included here. We agree completely that the surgeon should make that decision, but as I said earlier L&I has covered the add-on of fusion when the indicated procedure is a decompression and whether that add-on fusion is necessary or not, and whether it leads to better outcomes, as a balance, what the adverse of that profile is and what the cost effectiveness is, that's the main issue, I think.

Chris Standaert: But I think...

Gary Franklin: I don't think the main issue is chronic neck pain.

Chris Standaert: No, it would depend on the – and we'll get to it, but it would depend on the approach for the decompression, I would suspect. I have a couple of questions on this. If other people have questions, they can go, because I have a couple of questions on the studies you mentioned here that aren't in the other reports. If other people have questions, go ahead, then I'll come back to them.

Carson Odegard: Slide 10, I think it is. It's the one on patient event rate following the cervical spine fusion. Did you get the same kind of data for non-CSF cases? In other words, did you get to see what happened to discectomy patients versus CSF patients?

Gary Franklin: No, we did not do that.

Carson Odegard: Okay.

Chris Standaert: So, a couple of questions on these studies you mentioned. So, again I'm a nonoperative person.

Gary Franklin: The Peolsson Study?

Chris Standaert: Yeah, well the Peolsson and the Middlekoop. I mean, I'm a nonoperative person, and amongst the things I was rather surprised to see is how universally effective my care apparently is for people with cervical radiculopathy. I wasn't aware of that. So, when I looked at the Peolsson study, I pulled it and read it, and this is a study of 63 randomized patients, only 49 completed. It was an intent to treat.

Gary Franklin: Okay, I'm sorry. Can I just add one thing to that? They did all complete. Only 49 had the performance based, but they all had self-reported measures.

Chris Standaert: Right, but they didn't do an intent to treat on the data they didn't have.

Gary Franklin: Right.

Chris Standaert: They estimated that they were under-powered and they needed at least 300 patients to find the kind of differences they were looking for, and they had 49, and they looked at only functional outcomes, which were dexterity, grip strength, range of motion, and neck strength. Again, if you're doing radiculopathy, if you're treating a C6 radiculopathy, that doesn't really affect grip strength, particularly. So, I'm not sure these are very valid outcomes. They didn't look at pain. They didn't look at neck disability and actual global functional outcome at all. They mentioned one of their exclusion criteria was having neurologic symptoms within the past year, which would seem to be a radiculopathy, which I thought was odd, and their PT program is not what you at L&I cover. Their PT program is 34 hours of physical therapy over 20 weeks, plus having a PT available by phone whenever you want for the next 13 weeks. I don't recall getting my L&I patients 34 visits of PT as a routine event before cervical surgery. Even their conclusion, really, was that you should consider a structured nonoperative rehabilitation approach before fusion. That was their conclusion, which I wouldn't disagree with personally, but that's what the study says, which I don't – so it's.

Gary Franklin: Well, were you surprised at how effective your own techniques are?

- Chris Standaert: No, in general I'm surprised. The study doesn't say that much. It's a small under-powered study.
- Gary Franklin: The only reason I mention it is because it was a randomized trial.
- Chris Standaert: I know.
- Gary Franklin: That was new and had not been mentioned in these studies, because it wasn't included in the timeframe...
- Chris Standaert: Right, and the only reason I'm talking...
- Gary Franklin: ...and compared to what we, L&I decided 20 years ago.
- Chris Standaert: I know. I'm just discussing it because it's not going to be in their report. The vendor won't know about this study, because they didn't pull the study. So, if people have questions, you brought it up.
- Gary Franklin: Absolutely. Absolutely.
- Chris Standaert: And then when I looked at the Middlekoop one you brought up also was a study, it was a review of ACDF, so discectomy with fusion versus discectomy without fusion, they don't really specify their long-term outcomes, and they say that they don't look at, as our report did not look at, disk collapse and sagittal alignment as an outcome, which, as we'll talk about anatomy and what you do when you do a cervical fusion, the long-term kyphosis and angulation of the spine is one of the primary reasons why people theoretically fuse as opposed to just doing a discectomy, but they didn't look at that as their outcome at all in the study. So, again, I read it and I go, that doesn't help me a lot, personally. So, I'm just pointing that out because you brought them up and they're not in the report.
- Gary Franklin: Thank you.
- Craig Blackmore: Any other questions.
- Carson Odegard: One other question, maybe it's a comment. Maybe you could comment upon it. You talked about those complications being handled more in the outpatient setting. Could that not be

because Medicare now classifies most anterior cervical fusions as outpatient procedures?

Gary Franklin: It probably is why. I mean, I don't know. That probably is related to the payment mechanism.

Carson Odegard: I think most of them are done as outpatients. I don't know whether that means outpatient hospital or they can be done at a care center.

Gary Franklin: That was outpatient hospital.

Carson Odegard: Okay.

Gary Franklin: And the only point – I wasn't trying to make a point about why it was happening outpatient. I was trying to make a point about surprising that the Emergency Room visits in the first 30 days or 90 days was more frequent in the ones who were being done outpatient than the ones that were being done inpatient. I don't know.

Carson Odegard: Oh, yeah. I see that. Thank you.

Seth Schwartz: I just had one question about the utilization data. This is Seth Schwartz. You say that – we heard two people say so far that there's an eight-fold increase in the frequency of these procedures, but when I look at your utilization data, at least over the four years, there has really been no meaning.

Gary Franklin: That eight-fold was between I think the earlier time period. So, it may have reached a peak and plateaued. I don't know. That was national data.

Craig Blackmore: Thank you.

Gary Franklin: Thank you.

Craig Blackmore: Alright, next on the agenda is – would be the evidence report.

Daniel Ollendorf: Thank you. Thanks. It looks like it's up, okay. So, I want to thank the HCA for the opportunity to complete the report and to present our findings. My name is Dan Ollendorf. I'm the chief review officer at the Institute for Clinical and Economic Review,

the organization that conducted the report and the review. So, just to review quickly what the structure of my presentation will be, I will focus on the project scope, the comparators of interest for our evaluation and the outcomes of interest. We'll then talk about the systematic review. We'll talk, in brief, about the quality of the available evidence, the findings and comparative clinical effectiveness of fusion to its comparators and the potential harms. We'll also talk about comparative value you've heard during the public comment period that in this particular instance, ICER created a de novo simulation model to assess the potential cost effects and cost effectiveness of cervical spinal fusion versus conservative management and other comparators, and then we'll tie it all together.

So, we can skip over some of the introductory text, in that I think everyone here knows what the basic scope of the project was, that we focused on spinal fusion versus surgical and nonsurgical alternatives in patients with cervical degenerative disk disease. Our comparisons were to, as I mentioned, both surgical and nonsurgical alternatives. The one exception was that we did not include evidence comparing fusion to artificial disks. It was felt during the scoping of the project that because the committee had already evaluated the evidence on artificial disks in comparison to fusion, we would not do that with this project. Our focus, and the way the key questions were described, was on adults with or without radiculopathy and/or spondylosis. So, as was mentioned, we excluded patients with symptoms of cervical myelopathy. We also excluded other populations, acute trauma, spinal cord injury, malignancy, etc. that were not associated with DDD, and we excluded comparisons of fusion variants. So, if an RCT or comparative study was available, that compared one type of cervical fusion to another that was not a focus of our review. We focused on fusion surgery versus alternative approaches.

I should say to qualify that last point a bit; there were some comparisons within the fusion category that were of interest. One was comparison of anterior to posterior approaches to fusion. Another was single versus multilevel fusion surgeries, and the third was by setting, fusion performed in inpatient versus ambulatory or outpatient settings.

So, in terms of comparators, this is not an exhaustive list. There are examples here based on what we thought we would come

across and what we did find. So, we talk about continued conservative management. So, our target population for this evaluation was patients would have already had a trial of conservative management and continued conservative management, and the studies we found included physical therapy, immobilization with a cervical collar or interdisciplinary rehabilitation, which would have included behavioral components, physical therapy, workplace and ergonomic interventions, etc. Some possible minimally invasive procedures would have included spinal injection, such as epidural steroids, as well as minimally invasive procedures, such as radiofrequency denervation. Other surgical approaches primarily what we came across was discectomy alone and foraminotomy, so a procedure that was focused on widening the nerve root opening, or the foramen.

Outcomes of interest, some measures of effectiveness for our review included treatment success. So, there are a variety of sets of criteria available in some of these studies to evaluate in a categorical fashion whether treatment was successful, typically focused on the persistence of symptoms. So, one example is Odom's criteria, which categorizes patients into four distinct categories based on whether symptoms are completely resolved, partially resolved, unchanged, or worsened. There are a variety of pain scales that were included in these studies, as well, visual analog scales for arm and/or neck pain, standardized instruments, such as the McGill Pain Questionnaire, etc. Measures of function, standardized instruments, such as the disability rating inventory were also available. Quality of life instruments and measures of return to work, which could have included absenteeism data, data on days of work lost, lost productivity, information on return to work or return to work evaluated on a time to event basis.

We focused on two major types of potential harms. These were harms that occurred during the peri-procedure period, so during the operative episode itself or within 30 days following, which could have included mortality and other complications, such as hardware failure or nerve damage. We also looked at longer-term mortality and other adverse events. So, for example, pseudoarthrosis, which relates to the nonunion of a fusion after a fusion has been successful or adjacent segment degeneration or disease when there's degeneration occurring in segments adjacent to where the fusion or other procedure was performed.

In terms of the types of studies we included, randomized control trials, of course. We also included what we termed comparative cohort studies. These were cohort fusion patients compared to a pre already defined control population, which could have included one of a number of interventions. We also looked at case series data on fusions, specifically. If these criteria were met, they had to be relatively large series. Sample sizes greater than 50 patients. Followup had to be greater than 12 or more months, and data had to be available on the outcomes and/or subgroups of interest. So, our key question three focused on differential effectiveness in key subgroups, which could have included things like age, sex, duration of symptoms, and/or number of levels affected to name a few.

So, turning to the studies that were included in the evaluation. We identified 14 studies that met our criteria for inclusion, comprising approximately 1200 patients. Nearly all of these studies were conducted in patients with radiculopathic symptoms and x-ray confirmation of nerve root compression. So, this is essentially a radiculopathy population that we're talking about. There was one comparison to conservative care in the RCT data. Other RCTs compared primarily to discectomy alone and/or foraminotomy. All of these studies were relatively small and conducted in single centers. We'll talk about other quality issues in a minute, 10-50 patients per treatment arm in these studies. For the comparative cohorts, there were seven studies that met our criteria. A little under 1000 patients from six of these studies and then one large database analysis of a large inpatient database in the U.S. that comprised about 100,000 subjects. Six of the seven comparative cohort studies were retrospective in nature.

Moving on in terms of further element of these studies. These RCTs were conducted in single centers, so there were not any large, multicenter RCTs available. There were no studies, neither RCTs nor comparative cohort studies comparing fusion to minimally invasive nonsurgical techniques, and there were no studies in patients with generalized or axial neck pain. So, again, we are talking about radiculopathy. We found variability in the RCTs in terms of whether procedures were performed by the same or different groups of surgeons. There was also a fair amount of variability in studies that compared surgical procedures in the post-surgery protocol, whether the patients had structured physical therapy or cervical collar immobilization after the surgery

itself, whether that was left up to the discretion of the surgeon and the duration of that sort of protocol. There was also a fair amount of heterogeneity in the patient populations themselves. These were patients with pain on a VAS scale at baseline that was moderate to severe, but quite a large range wide standard deviations in those baseline measures of pain.

One thing that we did look for, although it wasn't part of any of the key questions, it is something that we always look to see when we're talking about a surgical procedure, and that is whether there is any published evidence linking surgeon experience or the number of procedures performed by a particular surgeon to outcomes. The so-called learning curve issue, and we found very little information available on this for cervical spinal fusion.

So, in terms of clinical benefits, our key question one, the first comparison fusion versus conservative management, there was one RCT. The Persson RCT that has been previously mentioned, and one comparative cohort study in our sample. This was a study of a workman's compensation population. We found in the RCT that there were statistically and clinically significant levels of improvement. So, clinically significant in various ways of categorizing this relates to movement along a VAS pain scale, for example, of 10 or more points. So, in this particular RCT, the improvement was clinically significant in the comparison of fusion versus cervical collar immobilization at three to four months, but this difference was no longer statistically significant, and I should correct that. That's actually 16 months of followup, so there was one time point where outcomes were measured at four months and other outcomes were measured 12 months after that first time point, so 16 months from baseline. At no point during followup in this RCT were there any statistical differences versus physical therapy, and no statistically significant differences in quality of life or return to work measures in either study. As was mentioned before and as I mentioned as I introduced the evidence, this was a small RCT. There were 81 patients randomized to three different treatment arms and because it was surgery versus nonoperative, the outcome measures, or the outcome assessors were not blind – were un-blinded to treatment. This is just a graphic depiction of what I was describing. So, at baseline you can see that the groups were relatively comparable and then you do see while the comparison

is statistically significant in comparison to cervical collar, the green bar, there is a relatively large numeric difference in comparison to physical therapy, as well, at month four, and at month 16 the bars are much closer together, and no statistical differences between groups.

Moving to the bulk of our RCT data, which related to fusion and comparison to other surgical procedures, there were 13 RCTs and one comparative cohort study available. There were measures of treatment success. I should go back and mention in the comparison to conservative management there were no categorical measures of treatment success available, so that is why they are not described on a slide. In this particular comparison, there were measures of treatment success available in six higher quality RCTs. Rates of treatment success did not statistically differ by a type of surgery in five of those six. In one of the six, an RCT by Barlocher and colleagues from 2002, there was a higher proportion of excellent or good outcomes on Odom's criteria with microdiscectomy with titanium cage fusion in comparison to microdiscectomy alone, but there were two other comparison groups, autologous bone graft fusion and PMMA fusion and then there were no statistical differences between those groups and microdiscectomy alone.

In terms of measures of patient reported pain and function for fusion and its surgical comparators, there were similar levels of improvement at all time points and no statistical differences between groups in these studies, and there was very little data available on quality of life in this comparison group. This is one of the meta-analyses that we conducted. There are others in the report on VAS arm and neck pain. This is on return to work at 12 to 24 months comparing fusion discectomy with fusion to discectomy alone and there is – you'll see on the pooled estimate that it is in the direction of favoring fusion, but this is not a statistically significant difference, 12 to 24 months. After publication of the draft report, one of the public comments we received was that if fusion effects on pain and function in the Persson RCT and other RCTs appeared to be early, then maybe we should look at return to work at early time points as well, so we did a secondary analysis with available data from two of these RCTs looking at return to work at six months and found mixed results. One study favored fusion. The other favored discectomy

alone, and again, no significant difference when the two-study estimates were pooled.

Turning to harms, key question two, our estimates ranged widely across studies. There was a lot of heterogeneity in the extent and the categorization of harms reporting, so we made a decision not to meta-analyze this data but simply present results in terms of ranges of outcome. We can say with some confidence, though, that perioperative mortality and rates of serious complications were very rare, less than 1%. The most frequent periprocedure complications were more transient in nature, so dysphagia or difficulty swallowing. Again, you see the wide range in reporting there, and hoarseness as well. In terms of longer term adverse outcomes, the most frequently reported included adjacent segment degeneration and because followup was differential across these studies, we're reporting these results here on an annualized basis, so 7 to 17% on an annualized basis for adjacent segment degeneration, neurological decline, which again was one of those measures that was very heterogeneous in terms of how it was reported, 3 to 23% and rates of reoperation of 1 to 22%, so very wide ranges.

In terms of key question three, benefits or harms in key subgroups, there was very limited subgroup data available from the RCTs in our sample. Some of the key findings from comparative cohort studies and case series included no differences in measures of benefit or harm when fusion was compared in inpatient versus outpatient settings. In terms of anterior versus posterior fusion, posterior procedures were associated with higher rates of mortality and complications. We recognize that these procedures are among the minority now. The anterior approach is much more common and typically reserved for patients with more severe and disabling condition. So, while the administrative database studies that looked at this question attempted to control for some differences between patient populations, the clinical detail that they were able to control with was relatively limited.

In terms of single versus multilevel fusion, there were higher rates of dysphagia with the greater number of operative levels involved, and this last bullet point really could be a bullet point for any intervention. Older age and duration of symptoms longer than 12 months were associated with poor outcomes.

So, turning to questions of comparative value. There is very limited, prior data that examines the economic impact and cost effectiveness of cervical spinal fusion. There was a relatively recent cost effectiveness analysis published by Carreon and colleagues, which estimated costs per quality adjusted life year, or QALY gained of about \$25,000 at five years. An important flaw in this study in our minds was that this was a comparison to baseline levels of quality of life and cost, not to alternative treatment approaches. So, this is not cost effectiveness and it's relative to any comparator of interest. It is cost effectiveness versus baseline. In addition, we felt that the assumed cost of fusion of \$15,000 was relatively low in comparison to other studies that we have seen and data coming from the HTA. So, this, in part, the lack of available evidence was in part what convinced us of the need to try to develop a new model. Other comparisons had been published, but primarily these were limited to fusion variants only. So, for example, comparing autograft versus allograft fusion with plating.

So, one thing I should clarify, and I apologize for some of the misleading text in the report. I think the report talks about the Canada population for the model as being patients with cervical pain. These were patients with pain symptoms that came from radiculopathy. So, again, this is a radiculopathy population that we used as the basis for our model. Symptoms persisted in these patients after a 6 to 12 week trial of conservative care. Their neck pain and radicular symptoms were moderate to severe, so one measures the neck disability index and the literature estimate we used for the base population had an NDI of about 50, so that's moderate to severe, and our primary comparison was anterior cervical discectomy with fusion to continue conservative management using physical therapy. We also made comparisons to other surgical and nonsurgical options in secondary analyses, and we analyzed the data over a time horizon that went from one to three years. So, three years on the outside. We used what's termed a public payer perspective, which really basically means we focus primarily on direct medical costs. We did a secondary analysis that also included the cost of lost work, but we used payment estimates from the HCA as our estimates of treatment costs. So, that's why we're calling it a payer perspective.

So, this is kind of a very simplistic depiction of the model structure, and we tried to keep it as straightforward and parsimonious as possible. So, you see in the upper left that patients come into the model with symptoms of cervical pain and radicular symptoms. After intervention, they could have resolution of pain and symptoms as you see on the right and that resolution could last throughout the duration of the time horizon of the model, or they could actually relapse and fall back into having symptoms of pain and other radicular symptoms. At any point during the analysis, patients could actually die of other causes, as well.

So, key model inputs and assumptions and we should note that based on some of the public comment we received on our initial version of the model, we did make substantial modifications to the primary analysis and to some of the secondary analyses, as well, but essentially following on the major findings of the randomized comparison to conservative care, there was a clinical improvement gap, so there was a clinical benefit of fusion over conservative care at an early point in time in the model, but that gap in clinical improvement narrowed over time. So, essentially it was on par at three years of followup. We, of course assumed that patients with unresolved neck pain and radicular symptoms had a decreased quality of life and incurred costs. Importantly, for our primary analysis, we did not assume any reoperation during this three-year period, so anyone with unresolved pain had continued physical therapy. So, there was no reoperation assumed. We assumed a benefit for fusion in terms of fewer days of work lost because of that quicker return to function and resolution of pain. We also assumed no mortality differences attributed to the fusion procedure itself in our primary analysis, as well. So, mortality was simply based on unrelated causes over that three-year period. As I mentioned, we estimated the cost of treatment based on payment data from the Washington HCA.

In terms of key measures of output, primarily our two measures of interest were treatment response, so the percent of patients with resolution of their pain and symptoms and quality adjusted life years. Essentially, for those not familiar, that simply relates to taking the amount of time in a particular state of health and multiplying it by the utility or an estimate of the quality of life associated with being in that state. So, the utility data vary between zero, which is equivalent to death, and one, which is

equivalent to perfect health. I believe based on our estimate of the population at baseline, which actually came from one of the larger RCTs comparing fusion to artificial disks, utility at baseline was 0.54, so relatively significant impact of radiculopathy and pain on quality of life in these patients.

We included estimates of the cost of initial treatment, adverse effects and complications, and continuing treatment for unresolved pain, and we expressed cost effectiveness as the cost per additional treatment responder, alternatively, and the cost per QALY gained.

So, this is just a graphic depiction of our modeled resolution of neck pain. We made alternative assumptions in secondary analyses that essentially involved the benefit of fusion persisting over the three-year period at different levels, and we'll talk about that in a minute, but in our primary analysis, we assumed this narrowing in the gap in clinical improvement.

This is kind of a busy table. I apologize in advance, but this is a comparison of anterior cervical discectomy with fusion to a variety of comparators. So, the first column depicts the incremental costs over a three-year period of fusion in comparison to the comparators. So, let's look at the conservative care comparison first. So, the additional cost of fusion versus conservative care over those three years was about \$25,000. A little less than 4% of patients in the absolute difference in response – treatment response, was about 4% for fusion versus physical therapy, which translated into a QALY gain of 0.07, which is about a month over that three-year period. The cost per responder, \$680,000, and the cost per QALY gain about \$350,000.

In the U.S., there are no real tight thresholds for what determines a cost-effective therapeutic intervention. Generally, most decision makers think of interventions that are less than \$50,000 to \$150,000 per QALY gained as representing a cost effective use of resources, but again, there's no standard threshold as there is in other countries.

In comparison to foraminotomy, the cost of fusion and foraminotomy were very similar. We assumed a smaller incremental fusion response based on the studies we provided. We used numerical data so even though there were no statistical

differences between surgeries and outcome, we did assume a small numeric advantage for fusion. The incremental QALY gain, however, was about four days. So, very comparable in terms of cost and outcomes. We had the same estimate for outcome for discectomy alone, but based on the HCA data, the discectomy with fusion is about \$7,000 more expensive than a discectomy alone, so again, there are fairly high, large cost effectiveness ratios displayed on the right side.

We also made a comparison to epidural steroid injections despite the fact that there were no studies directly comparing the two interventions. We used expert input and other series data to come up with these estimates, found in this particular case that the fusion response was much greater and persisted over time in comparison to serial steroid injections resulting in about three months of quality adjusted life years gained and cost per responder and cost per QALY that were much lower.

So, there are certainly detailed analyses available in the report in terms of our secondary and alternative analyses. We found cost effectiveness ratios that range between 200,000 and 900,000 or so per QALY gained across a variety of such analyses. Just to highlight a couple of them, we conducted one analysis in which we assumed anyone failing conservative therapy would have a fusion procedure, and 3% of those undergoing fusion would require a repeat procedure over the three years of followup. That generated a cost per QALY gained of about \$210,000. We found that for the cost effectiveness ratio to go below \$150,000 per QALY gained, fusion would need to be 50% more effective than conservative care and that 50% difference needed to persist over three years. Not surprisingly, as the level of disability at baseline got milder, the cost effectiveness ratios increased. Conversely, as the disability index measure got higher, cost effectiveness ratios decreased.

So, just to summarize, we found no evidence supporting the use of cervical spinal fusion in patients with cervical degenerative disk disease whose only complaint was generalized neck pain. There was no evidence comparing fusion to minimally invasive nonsurgical alternatives. In patients with radiculopathy, there were limited data comparing fusion to conservative therapy that suggested early clinical benefits with fusion but that those benefits, relative benefits, diminished over time. Fusion's clinical

performance was felt to be similar to alternative surgical approaches, discectomy alone and foraminotomy. In terms of our modeling results, the results suggested that the benefits of fusion versus conservative management came at a relatively high cost across a range of assumptions and alternative scenarios. Effectiveness and costs were similar for fusion and foraminotomy, and fusion was also felt to be clinically comparable to discectomy alone but at a higher cost. So, we at ICER use what we call an integrated evidence rating to try to summarize these results in kind of a letter grade format, and on the Y-axis on the left are ratings of comparative clinical effectiveness. So, in this particular case, we are talking about fusion versus conservative management, and on the X-axis below are letter ratings associated with a comparative economic value. So, the higher case letter relates to the clinical effectiveness, and the lower case relates to the value. So, as we discussed, in patients without evidence of radiculopathy, there was insufficient evidence to make a determination one way or the other on the comparative clinical effectiveness. In situations like this, we don't ever get to the point of modeling the comparative value, because there's no evidence available to distinguish the treatments clinically.

In patients with radiculopathic symptoms, again there was evidence suggesting early benefits with fusion, and the benefits persisted with fusion, but improvement with conservative management came later but did eventually "catch up." Given that, and given that there are small but nonetheless non-zero risks of complications of surgery, we felt these two to be comparable. Because of the cost effectiveness results, however, we are calling fusion a low economic value intervention in this particular situation.

It's, of course, the case that in patients with more severe symptoms whose return to function and work is much more important, or not much more important, but can provide greater levels of relief, you might think about fusion potentially as incremental in that situation. Conversely, however, in patients with very mild symptoms, it may be that fusion is somewhat inferior to conservative management, or you might not even think about it as an alternative at that point. So, again, there are definitely shades of grey. So, in terms of our rating for fusion versus the major surgical comparators, again, insufficient evidence to rate these comparators to fusion in patients with only

generalized neck pain and not radiculopathy. In patients with radiculopathy, we found the clinical performance of fusion to discectomy alone or to foraminotomy to be generally comparable, and based on the cost effectiveness findings fusion in comparison to discectomy was also felt to be low value. Fusion in comparison to foraminotomy was felt to be a reasonable or comparable value. So, that concludes my comments, and I thank you for your time.

Craig Blackmore: Questions from the committee?

Carson Odegard: I have a question regarding the safety and harms. On slide 14, I think it was, you had the – you gave some data, I guess. It was about the harms. Is that associated with just the CSF, or does that – I guess the problem I'm having is, well here, let me start over. The question we have to ask is safety, and I didn't get any data from your presentation that shows that the anterior cervical fusions are, or any of the fusions, are less safe or more injurious than using alternative surgical procedures. So, I guess the question is, could you embellish that a little bit?

Daniel Ollendorf: Yeah, and I hesitate. There is an appendix to my slides, and slide 28 actually has a comparative table. It is very busy, crowded. I'm not sure if we're actually able to see any particular line. So, there is comparative data in the report looking at some of the harms where data were available comparing fusion to alternative. So, for example, in terms of adjacent segment degeneration, 7 to 17% was the rate reported in fusion studies. What was available in studies of discectomy alone was 2.4 to 8.3%. So, there are comparative data, as well. So, these harms should not necessarily be thought of as only relevant for fusion. They are also relevant for other surgical procedures, as well.

Carson Odegard: I guess the question is now, are these just based on the randomized control trials, or did you go to registry data, too?

Daniel Ollendorf: We went to randomized controlled trials and comparative cohort studies in our sample.

Carson Odegard: Okay, and there's no difference?

Daniel Ollendorf: That is really impossible to say, because of the heterogeneity and how these harms are reported, the number of studies in which harms reporting was incomplete, and the way these were

categorized. So, it's really difficult to say with any certainty whether rates were higher, universally higher with one procedure versus another. Certainly, there are harms that are particular to fusion. Pseudoarthrosis is one of them, because it's talking about the union of the fusion itself.

Michael Souter: Going back to your description of the original included studies, the 14 RCTs that met criteria, you mention the fact that nearly all were conducted in patients with radiculopathic symptoms. How consistent are those studies and their definition of radiculopathy? Because, there are some – they're all a systematic review from last year, 2012, which actually alluded to significant variability in the definition of cervicoradiculopathy in the literature.

Daniel Ollendorf: So, the one thing that was consistent about these studies was that there was some radiographic evidence of nerve root compression. In terms of how the symptomatology of radiculopathy was described or was used as an entry criteria, and it was highly variable. So, in some cases, it was based on data primarily coming from the patient. In others, it was based on objective clinical testing in terms of strength and that kind of thing. So, it was highly variable.

Chris Standaert: I have a number of things. We'll get them as people talk. I found a number of parts of your report very troublesome, myself. First, the way we're talking about this, as I said before to Gary, you keep saying surgery for degenerative disk disease and cervical fusion for degenerative disk disease. The condition being treated is either myelopathy, radiculopathy, foraminal stenosis, central canal stenosis, disk herniation. These are the conditions being treated. The treatment is not for degenerative disk disease for the most part. As you said, I completely agree with your first statement. Fusion for degenerative disk disease for axial pain has no literature base. I don't think that people out in the audience are advocating for that frankly, but the idea that you're willing to say all these things are the same and cervical fusion is how you treat all these. They're not all the same. The reasons you do the fusion is not to treat the primary problem. The primary problem is the canal stenosis, the foraminal stenosis, the disk herniation, the myelopathy, the radiculopathy, one of those is what you're trying to treat. They're all somewhat different, and they can be combined. You can have central canal and foraminal stenosis. You can have myeloradiculopathy. You can have all these things.

A number of your operative studies have very tight inclusion criteria, so when they look at the foraminotomy studies, they are really limiting, taking out patients with significant central pathology because they don't have canal stenosis. So, if you were to do a foraminotomy in this – so, you can't apply all these things the same. When you do a cervical – I've read the operative report of what you had as a cervical fusion in your report. It reads a lot to me like a posterior microdiscectomy for a lumbar spine surgery. It's very different than the cervical spine. The reason people are fused is the surgery is done anteriorly. They go in, they have to – you have to clean out the central spinal canal and decrease the – increase the overall dimensions of the central spinal canal. They take out the entire disk. If you have a central disk fragment, you have a central osteophyte, you have central canal compression they have to take out everything from the front. You can't access it from the back, because you can't go through the spinal cord to get there. Once you've taken everything out, you decompress it, but you took out your disk to access that space. You can take out the disk as a primary treatment. You're taking out the disk as an access maneuver. Then, the question is do you put something back in there? If so, what? Do you put in a cage? Do you put in a disk replacement? Do you put in bone? Or do you put nothing in and let it fuse after you take the disk out? If you do the latter, which is something you didn't really look at. If you take the disk – cervical disks are wedge shaped. Lumbar disks are flat. Cervical disks are wedge shaped. If you take out a wedge from the front of the neck, the concern is it would become kyphotic. They tip. So, you take out a wedge and the spine goes oomph and becomes more straight, and I would argue that's probably the primary reason why you never really see an anterior discectomy without fusion in this country. I don't think I've ever seen one in my entire career that people fuse. If you look at one of these studies, there is the Yee study, which is a study of cervical fusion versus AC – fusion without – anterior approach fusion, no fusion. They actually looked at rates of fusion and rates of kyphosis, and the rates of kyphosis were extremely high, 75% of the people had just a discectomy without fusion and became kyphotic and of them, they had a very low fusion rate, as well, 63% versus 90%+ for the people who had bone graft put in. All this gets very troublesome when you start saying these things are equivalent and you start modeling and saying they're equivalent. You're treating very different diseases with these things, and again, the primary intent of the surgery is not to fuse for the most part. The primary intent

of the surgery is to decompress, so we should be talking about the effectiveness of decompression or treatment of radiculopathy or myelopathy as opposed to fusion. Fusion is just one of several things that goes along with that procedure, so I have trouble with that, and I think it becomes very – it confuses the language all the way through your report, and all these studies get jumbled together and you create this model of all these things that are equivalent, well they're not because you have very different patient populations that are being considered for different procedures because of this question of how they have to access the pathology they're treating. Does that make sense?

Daniel Ollendorf: It does.

Chris Standaert: So, I find that troubling, essentially all the way through. I don't know if you want to get to that now. I do want to talk about the nonoperative study you looked at. I'll let other people go, in case they have questions about what I just said, but I want to get the nonoperative study you looked at in your model, as well. There's some issues with that. I'll throw that out for people to consider.

Craig Blackmore: Do you have questions or do you want to save the rest of it for the team discussion here, or...?

Chris Standaert: I can ask a particular question. So, if I say that in general that I find that troublesome, I will get to your model and your nonoperative issues. You mentioned – so I'm a nonoperative person. Again, I was rather surprised by how well nonoperative care seems to work in everybody, so I wanted to go look. So, I looked up the studies you talked about. You mentioned two. One was a cohort, a Meyer study, and you all said this was a cohort comparing fusion with multidisciplinary care to no fusion with multidisciplinary care. So, a chronic pain program run by Dr. Meyer. So, that's not what the study is. I looked up the study. It's written by Tom Meyer. Tom Meyer runs a multidisciplinary pain program in Texas. He has written prolifically on sort of the treatment of patients through his multidisciplinary pain program. What the study looks at, and I will pull up the actual inclusion criteria he states. What the study really looks at is they take people who were in the workman's compensation system who had a cervical fusion for radiculopathy then went to rehab and failed PT. Then, they said well they failed PT, let's put them in the pain program and see how they do, and they put them in the pain

program to see how they did. Then, they compared that to their traditional cohort of pain program patients who really weren't neck pain patients. He actually describes the patients they put in. Their study group represents, "A worse case cohort of ACF fusion patients who had failed other forms of postoperative rehab or previously noncompliant in meeting reasonable outcome goals." They were looking to see if these people could be rehabbed in a multidisciplinary setting. It was not remotely a study of the effectiveness of the fusion. That shouldn't have even been in your study, and you cite it as one of the things that gives you consistent evidence of equivalency of nonoperative care, and that really isn't what the study is. So, I find that troublesome too.

The Persson study is an interesting study. The Persson study is, as you said, 27 patients in three arms. The mean of pain in these people was three years. Most of them were under workman's compensation system. Most of them were smokers. The fusion procedure they did was a [inaudible] procedure, which is not the standard procedure done anymore, and they used an anterior procedure with a bovine graft. They didn't use an allograft. They didn't use a graft – they used a bovine graft in the neck. They don't talk about radiologic followup, and yes they tracked them in their equivalent, but this is very small. It's 27 people, and if you looked at the data, you all mention in here for significant improvement you should have 30% reduction in pain. Of the three treatment groups, the only one that had 30% reduction in pain was the surgical group, and you really should look at the data and wonder, do we have type 2 error here? We only have 27 patients. If you had 150 patients or 200 patients, you might well see a difference, but these are people with three years of pain done with almost a 20-year-old study, nonstandard current surgical techniques, and that's what you built your entire model on, and your model insumes that everything works. I read through your report, and you said well epidural should work the same as manipulation should work the same as they all should work the same. If you really follow that, why do we do anything? Everything works. Everybody gets better. Whatever we do, they all become the same. I don't really believe that, and I think there are – I'm not an advocate for cervical fusion for everybody by any means. I'm a nonoperative guy, but there's a population of patients who are very refractory to nonoperative care who have severe pain, severe functional limitations, and neurologic deficits where really this has become something you think about. And

defining the surgery as a cervical fusion and saying you can't do that because it's equivalent to everything else really misses the point of the primary purpose of the surgery and what you're trying to do. So, those are my comments, and I'm not sure how you would like to respond about the model issue, particularly, in the nonoperative study, but in my reading it really undermines a lot of what you're saying and makes it very difficult to come to the conclusions you're stating.

Daniel Ollendorf: I will see if I can unpack this a bit. So, I guess starting with the discussion of the model and the discussion of the Persson study and to a lesser extent the Meyer comparative cohort. I think our focus was on the RCT and our analysis and description. Certainly, if there were more recent RCTs with more recent versions of the procedure available to compare to whatever the comparators were, we would have included them.

Chris Standaert: I believe you. The problem is building a model off of a study that has many, many flaws and is very small and then estimating out some tremendous numbers from it. You extrapolated a lot of data from this one little study with enormous error bars if you were to put them on all your ranges of your data, because you assumed a lot of stuff.

Daniel Ollendorf: And I think that's precisely the reason why we tried to test that assumption rigorously in the alternative analyses we did. So, we did as a primary analysis try to make some translation between the pattern of effects on pain and function in the Persson trial recognizing its flaws and its caveats, but then we also did alternative analyses assuming that there was a benefit of fusion that would persist at varying levels over the three years. So, those results are available, as well. And it's often the case when a modeling exercise is undertaken that one of the reasons it's undertaken is that there's not sufficient and robust clinical data to draw conclusions on from the get go. So, if there were 10 RCTs that all had 300 patients each and were conducted in multiple centers around the world, we wouldn't even be talking about a model, because the clinical data would be there. So, we had to draw conclusions on what we found. We recognize that there is certainly limited information available in terms of comparing fusion to conservative management, and there are limitations in those studies that are available, but I guess feel like if we were saying something completely different from what other

systematic reviews have concluded and in fact what clinical guidelines from some of these clinical societies are also describing, so, I'm looking at the detailed text behind the North American Spine Society's recommendation comparing fusion to conservative management, and the Persson study flaws are described, but so are the primary conclusions, that outcomes are similar after longer-term followup. So, it certainly is the case that there is always heterogeneity and you very eloquently described a lot of the clinical nuance that goes into a decision about whether to perform a fusion or not, and the various subpopulations are of interest that are available, but I guess if we – I'm not sure what we would have concluded about any of these studies if we broke all of the discectomy RCTs, for example, down into their component subpopulations and tried to draw comparisons there.

Chris Standaert: Well, you would have been looking at the indication for the surgery, which would have been helpful, personally I think.

Craig Blackmore: To me, it kind of gets at the – at what are we trying to prove or disprove, and I think, you know, as a committee we're looking at a technology and we're trying to evaluate whether there is evidence for that technology, but it's harder if a technology is established because then it's a matter of which are we evaluating? Are we evaluating conservative care, because that's the radical departure from what happens, or are we evaluating cervical fusion because that's the radical departure from what happens? Or are we evaluating both? And I mean, if we look at all these studies that are described and all their flaws, one could easily conclude that well if all we have is this nonstandard randomized clinical trial from some time ago then we don't have anything. We don't have any evidence for the effectiveness of fusion. But at the same time, if we believe that fusion has been the standard of care, and where the new change is discectomy without fusion or the new change is actually conservative care, then everything flips. What I've just heard in this interface between the two of you is the data is lousy, which, of course, we're used to. But, it's a matter of what's the level of proof and what is the level of proof on which side, and that's what we're going to have to struggle with over the next two hours. But, to bring us back to where we're supposed to be at this point, which is specific questions and then I'm sure this aspect of the discussion will continue into the afternoon, but there are sort of questions of clarity about the report that we might work on at this point? And I have one.

On your slide 14, in your des- and this is about the harms, and you said something that I didn't really understand. You said that these numbers were annualized? Is that right?

Daniel Ollendorf: Right.

Craig Blackmore: So, what do you mean by that?

Daniel Ollendorf: So, basically, because the observe rates reported in the trials were observed over differing periods of followup. So, in some cases six months in other cases three years, we reported rates on an annual basis so that in our evidence table so that side by side comparisons of the studies could be made.

Craig Blackmore: So, when I look at these numbers, I mean, obviously you're not talking about carry out, but the last line says the most frequent long-term adverse outcomes were saying that 7 to 17% of patients have adjacent segment degeneration every year so that over five or 10 years, it's basically nearly everyone? Is that the way I should interpret these data?

Daniel Ollendorf: Right, recognizing that most of the RCTs and cohort studies were relatively short-term studies. So, it may be that the rate over a period of followup is closer to the 17% than to some multiplier of that.

Craig Blackmore: Okay, but this is...

Daniel Ollendorf: And we're not talking about perioperative arms.

Craig Blackmore: Yeah, but this is per year, which is what I wanted to understand. Other questions?

Carson Odegard: Just in that very slide, that just applies to the fusion, too, correct?

Daniel Ollendorf: Well, the ranges of rates that are reported are for whatever procedures the data were available for. So, this is not just fusion. Actually, I'm sorry. What is shown parenthetically here is for fusion. There is a table in the report that has the comparison where available of some of those harms for other procedures.

Craig Blackmore: Other questions?

Seth Schwartz: Yeah, this is Seth Schwartz. I'm just trying to better understand this slide number nine, looking at the comparison of fusion to conservative therapy, and you say there's one RCT and one comparative study, and I'm trying to figure out – you said they were small so there's 81 patients in it and three arms, and it wasn't blinded, but I'm trying to figure out what the inclusion criteria was. So, how did they, particularly in the randomized trial, what patients did they randomize and how did they elect surgery versus alternative arms?

Daniel Ollendorf: So, in the RCT the major inclusion criterion was cervicobrachial pain of more than three months duration. So, what I said was that outcome assessment wasn't blinded, not that the – there was random – there was concealment. There was random allocation of these patients to procedures or to the conservative interventions.

Seth Schwartz: And how long was the followup in that trial?

Daniel Ollendorf: 16 months.

Craig Blackmore: Related to that trial, you said the differences were no longer statistically significant after 12 months.

Daniel Ollendorf: That should have been 16.

Craig Blackmore: Sorry, 16 months. Was the study powered to detect clinically significant differences beyond 16 months?

Daniel Ollendorf: That is not described. So, the – as, I think, some of the guidelines mentioned and as was discussed here, there's the possibility of type 2 error, but there's no description of what the study power calculations were, if there were any.

Seth Schwartz: And as a followup to that, in the next slide down, you show the bar grafts of where people fall out and used the visual analyst pain scales and said there's no statistically significant difference. I'm just curious, is there, based on those VS scales, is there a sense of what is a clinically significant difference?

Daniel Ollendorf: Again, I think that it depends on – there are a number of different groups that have come up with guidelines or guidance for what

should be considered a clinically significant difference on something like a VAS scale, and in some cases it's something like 20 to 30%. I think the minimal clinically important difference from another group was 10 points. So, looking at the numeric differences on the graph, you can kind of see where that falls.

Marie Brown: What was the dose of the PT in slide 10?

Daniel Ollendorf: In the Persson RCT it was a three-month treatment duration. There were 15 sessions, one to two sessions per week, each of them 30 to 45 minutes long.

Marie Brown: Thank you.

Craig Blackmore: I'd like to ask a question about slide 21, which, what I think I heard and you can help me. You said something about the baseline QALY being 0.5? Did I get that right?

Daniel Ollendorf: Right, our estimate of quality of life at baseline in the model was 0.54. It came from trial by Sasso and colleagues. That actually compared ACDF to artificial disks.

Craig Blackmore: So, that's very severely impaired.

Daniel Ollendorf: Yes.

Craig Blackmore: You're in a wheelchair, basically. So, this is not patients with radiculopathy. This is patients who are...

Daniel Ollendorf: In that particular trial, there were patients with radiculopathy, there were some with myelopathy as well, and there was no sort of separate reporting. I think the majority of the patients had radiculopathy as their primary complaint.

Craig Blackmore: And they had a quality of 0.54?

Daniel Ollendorf: So, we assumed a higher quality of life estimate in our draft report. Based on the public comments received, we essentially decided to recreate the model in a way that I think gave, again with limitations to the data as the backdrop, gave most of the conceivable advantages to fusion, that there was a severe impairment at baseline and there was a significant bump up in

quality of life from resolving pain, which is not something we had assumed in our draft.

Craig Blackmore: Right, and I think maybe for the committee, can you just sort of give us an idea of comparable conditions that might have a QALY in the 0.5 range?

Daniel Ollendorf: Stroke.

Craig Blackmore: Yeah. That's the point I want to make. This is not my arm hurts and I'm having trouble using it. This is...

Chris Standaert: And that's based – and that's based on the Sasso study – the cervical arthroplasty versus disk – versus fusion study.

Daniel Ollendorf: Right. There was a paper by Richardson and colleagues that mapped data on baseline function and pain to utility estimates.

Seth Schwartz: I have a question about slide #11 where you're looking at the clinical benefits of fusion versus discectomy alone, and I guess I'm – I'm still trying to understand clinically how these decisions are made to use one treatment modality over another, and I think based on what Chris said, if you're doing a discectomy and you're removing things you don't want to miss or leave an unstable spine, unless you're going to do a fusion in that situation. So, I'm curious how they randomize? Were these patients who had small enough procedures that they didn't need to fuse or how could they – how were these studies actually done that they could make that kind of determination?

Daniel Ollendorf: Well, these were prospective RCTs, so there was a decision made before intervention to allocate the patient to one arm or the other. There wasn't a decision made during surgery on whether to fuse or not.

Seth Schwartz: So I guess the question is, what were the preoperative assumptions? In other words, were these patients with only a bulging disk or only something limited? I mean, I just am curious what types of patients were included in those trials, or was it everybody?

Daniel Ollendorf: If you want, at the break I can get some more detail on that.

Chris Standaert: It's a whole collection of things. I mean, they're – some of them are foraminotomies, which are studies looking at particularly foraminal stenosis with osteophyte, and they exclude central canal stenosis or central migration of disk fragments and things like that, and there are a couple of studies that really are anteriorly taking out the disk and just basically burring down the endplates and letting it drop back down on the endplate below versus putting a graft or some sort of fusion device in. There are a couple of those in there too, and the way you report it all, the way I read it in the studies too, the outcomes clinically are similar, except they don't talk about kyphotic angulation and sagittal alignment of the spine after the surgery so that they – there are only a few studies that do that, that really seem to show that they've become – the rates of kyphosis are higher.

Seth Schwartz: I mean, forgive my ignorance. I'm trying to just understand why that's a bad thing. I mean, it sounds bad, but if it doesn't affect pain, it doesn't affect function, it doesn't affect anything else, why is that bad? And then we look – and then somebody thought maybe it's a longer term issue? Is their whole spine going to collapse and then they're going to be paralyzed? Or, and I'm not seeing that. They're not showing us that, at least in terms of it being long term, so I'm just trying to understand.

Chris Standaert: I mean, the data's short term. There's the Yee study and they had a fusion rate of 63% versus again 93% or something for the bone graft folks, so the fusion rate is lower. The kyphotic rate is higher. I think the theoretical concerns are – it's harder to keep the foramen decompressed, because the whole thing collapses down, and they become kyphotic, which messes with angulation and I personally, we ought to ask Dr. Tredway if there are studies that follow this out for 10 years to see what happens if you just do a discectomy with no fusion and you let them go for 10 years. Do they collapse and become too kyphotic? I don't know.

Seth Schwartz: It seems like that's kind of what we would want to know. I mean, if we're talking about saying, okay, yeah you can do a discectomy because that's indicated.

Chris Standaert: Right.

Seth Schwartz: But you can't fuse them, are we then...

- Chris Standaert: But they didn't. They didn't use all the...
- They didn't use alignment and fusion rates as outcomes measures in their review.
- Seth Schwartz: Well, I understand. We may not have the data we need to answer the question, but I don't want to answer the question based on – on data we don't have that may be dramatically important down the road. So, I guess I would ask Dr. Tredway, do we have any natural history of data, long term data, what happens to these patients if they don't fuse them?
- Craig Blackmore: So, procedurally there's a couple things.
- Seth Schwartz: Sorry.
- Craig Blackmore: First of all, we have to introduce Dr. Tredway who is our clinical expert, and if you could please, thank you for coming and just say hi and tell us who you are.
- Trent Tredway: Thanks, Trent Tredway. I'm actually at the University of Washington Medical Center. I'm a neurosurgeon. I've been there for nine years. I trained in Chicago, Dr. Cloward actually was hanging around in that area at one point in time. I did a fellowship in spine surgery. We do a lot of cervical spine surgery. As far as my disclosures go, I have received some honorary money for teaching courses from Synthes and also from Escalab, and I'm here today to be the clinical expert witness, I guess.
- Craig Blackmore: Thank you. So, the expectation is that you're here, which we appreciate, and we will have questions for you. We don't have a dedicated time for you to talk to us and our job is to evaluate the evidence that's presented to us by the vendor, and then you provide the clinical context, but we will, I am sure, have a lot of questions for you.
- Trent Tredway: Sure.
- Craig Blackmore: That being said, it's also 2:30, so I think we seem to be moving off from the evidence report and into the more free-flowing discussion that we have to go through, so I'm going to call a 15-minute break, and we will resume at 2:45.

I'm going to bring the group back and call the meeting to order. The committee – Richard's not back. Everybody else is back. We'll give him one more minute.

Alright, we're back in session. Richard will rejoin us, I'm sure, shortly. So, as we finished up, a question had been raised about long term complications, which I don't think we've answered yet. Dan, do you have data that you can share with us on long term complications? Is that something you found out much about?

Daniel Ollendorf: So, I think that the [inaudible] discussion was about kyphosis. So, I've just been looking through the available RCTs. We did not look at kyphosis or sagittal alignment as an outcome of interest in our review. I've just been pulling information from available RCTs on this outcome. The longest follow-up I could find was four years. It was not on the entire intend-to-treat population, but it was on a subset. Would you like me to go through what I found?

So, I've so far gotten through seven of the RCTs comparing discectomy with fusion to discectomy alone. Kyphosis was measured as an outcome in four of these. The Yee study that was mentioned previously have a very substantial difference in kyphosis at the end of follow-up; 75% for discectomy alone, no difference from baseline in either of the fusion arms. In the Barlocher RCT, the rates of kyphosis were 24% for microdiscectomy versus 13% with PMMA fusion and 3% with bone graft. In a study by Ruten, rates of kyphosis were not statistically significantly different, 12% with fusion, 8% with microdiscectomy. I'm sorry, yeah, 8% with microdiscectomy, and the one study with a four-year follow-up was by Savalinen. Slight kyphosis, and you can probably weigh in on how that's clinically defined with 63% for discectomy alone and the two fusion arms, the range was 40 to 44% at four years.

Craig Blackmore: So, Dr. Tredway, can you help us understand the whole sort of milieu of why you do fusion and kyphosis and...

Trent Tredway: Sure, I'd be happy to. I think Dr. Standaert said a lot earlier and was very, very spot on to the point that I questioned if he is just doing conservative management anymore and is not doing surgery on his off-time. To be honest with you, when we talk about cervical discectomies and fusions or treatment of cervical radiculopathy, there has been an evolution. Forty years ago, we

started doing fusion surgeries, or my predecessors I should say, did fusion surgeries, and we talked about one the of the randomized control studies with a Cloward procedure. Cloward procedure would be where you go in and do a discectomy. You actually make a circle and it was a [inaudible], and you would drill down, and it was between the actual disk and the actual vertebrae and actually you'd go all the way down, take it out, and you would actually take bone off, usually from the hip, and put that in. I started doing my training in about 1997, and we did a few of those at that time, and it was one of the scariest procedures I'd ever seen. Since that time, we've actually changed quite a bit. We've gone to where we just do a discectomy and not put a bone graft in, and we did see a significant number of patients get kyphotic deformities, as Dr. Standaert described, and it would lead to radiculopathy secondary to the foraminal narrowing. So, then we moved on to basically putting a piece of bone, usually from the hip, an allograft, and we would fashion in there, and that would be the anterior cervical discectomy and fusion. We didn't plate it. People did fairly well with that. Then, we moved away from actually taking bone from the hip, because it would cause a lot of localized pain and people would be in the hospital a little bit longer, just from the hip pain than from the neck pain. So, then we moved to basically using instrumentation so we don't have to use any collars or anything. So, right now, our standard procedure would be an anterior cervical discectomy consisting of doing an aggressive discectomy, cleaning everything out from the front, placing an allograft typically, which is a bone dowel that's already premade, usually from a cadaver, or sometimes some implants or other implants that are out there, but usually an allograft, then, using a plating system on that. Those rates are as high as 90 to 95% fusion rate with very, very little morbidity or mortality.

So, it is really one of our standard procedures, and when we talk about some of the things that HTA has done, as well, they have looked at some disk arthroplasty and all of those disk arthroplasties, all those studies, the standard procedure that they were comparing against was anterior cervical discectomy and fusion with allograft and plate. So, this is a standard procedure. This is what we do, and as a neurosurgeon, this may be a little bit more of an opinion, but it's also a disclosure, it's one of our more successful surgeries. There's no doubt about that, but only for indicated patients, and I think that that's why we're here.

Craig Blackmore: So, does anybody have any other questions before we sort of get into the more free-form discussion?

Marie Brown: Can someone help me understand the registry or the SCOAP study that's going on with some tracking of information and what role that would play in our consideration?

Joann Elmore: It's volunteer.

Chris Standaert: Yeah, I mean I can tell you – as a disclosure I've been involved somewhat in the development of SCOAP. I go to their meetings. I give them some advice. I don't have a formal position on there, but I certainly know Dr. Flum and Sonnard quite well and have been talking to them for about two years about the project. Dr. Flum started years ago a surgical SCOAP, which was to look at general surgery procedures and to track rates of utilization, infection, bleeds, other complications by hospital and compare the data and let the hospital see what other hospitals were doing in terms of prep and infection and all this and by sort of opening up community rates of things, hoping that people would see, oh wow. We're way off. We have many more infections than the other hospital. We better clean up what we do so we're back down to the norm. The idea was sort of community pressure to track – to bring people to some baseline. They expanded it to spine. The initial part of the whole – it's – the initial part of it is really the same thing. It looks at complication rates, all this sort of thing. They have started trying to put in outcome data, but it's very difficult, and in all honesty, they had funding early on, and now they're trying to look for and find alternative funding to keep the whole model going. It's very expensive, and they have 4,000 patients. Some are cervical, some are lumbar. They have a disproportionate number of lumbar fusion. That's a particular thing they're working on how to incorporate true outcome data like VAS and functional scales in there, but the last presentation they had two months ago was challenging. It's very hard to get good compliance on that, so it's a registry in process. It's voluntary with the hospitals. As you said, there are 18 hospitals participating in the spine part of it, and who pays the cost of all those data abstractions, unclear, all that sort of stuff. So, it's a great undertaking. It's a thing in progress. How we would interface with it or mandate that people use it, that seems very difficult to me personally. I understand why he would want that,

but it seems very difficult to me, is my personal opinion from what I know. So, there's my disclosure.

Craig Blackmore: And there's no comparison group. I mean, there's no data on conservative care. It's only if you get surgery then you might get entered into this.

Chris Standaert: Right. Yes, it attracts surgical patients and complications and other sorts of things.

Michael Souter: I just had a question for Dr. Tredway. Just on, again, going back to this question of the variability and the definition of radiculopathy, are there any more commonly accepted standards known evolution, other than anything that we see presented in the literature?

Trent Tredway: Not to my knowledge. I mean, as you know, with radiculopathy, there are a couple of different ways that can present. It can present as pain in a specific dermatome. It can present as weakness in a specific muscle group, or it can present as numbness, tingling, or loss of sensation in a specific dermatome, and that's what makes it kind of difficult. When a paper says that a person has radiculopathy, that could be muscle, you know, motor weakness, sensory deficits, or pain. Myelopathy is a little different, because it's a spinal cord injury. It's a sign of long tract sign. So, basically, you're going to have increased reflexes. You're going to have difficulty walking. It's interesting that some of our myelopathy standardized ways that we actually determine myelopathy, like the Japanese scale, it's basically based upon using chopsticks and then some of them are like a nurse going back to work. It has nothing to do with really the function. So, there is a little bit of a problem with some of the things that we see out there on the actual scales, but radiculopathy can present in many different ways and sometimes you can actually test it with EMG in specific nerve roots, but at C5, you may pick up a little weakness in the deltoids, and it gives you a lot of neck pain, but nothing into the hands. So, some of these studies have shown there is no weakness in the hands. It wouldn't have picked that up at a C5. So, that's where it's very difficult to kind of look at all these studies and say all radiculopathy is created equal, and it's just not, so.

Michael Souter: In terms of, you know, affecting a minimum standard, I mean, granted, I fully accept the variability of the clinical picture and that either being pain or neurologically symptom-orientated, as you said, but is there any kind of minimum standard that you actually have to have at least one or other of these in order to be classically defined as radiculopathy. Because, as I have said, one of the systematic reviews from last year, we found a great deal of variability and some people just, you know, all it took in some papers to be classed as radiculopathy was just the presence of neck pain, which would seem to be an insufficient criterion to actually go on ahead, and it's whether or not that actually accounts for some of the variability and results that we see and whether there's an attempt by any bodies in this profession to actually address that, what I see as a failure to address a minimum standard.

Trent Tredway: Yeah, I totally understand what you're saying, and that's the beauty of it and that's the problem with it, you really can't. So, everybody that has neck pain doesn't necessarily have radiculopathy, and as you guys know, some of you folks will actually do the EMGs, there are people that have radiculopathy on exam, weakness and sensory deficits, and it may not even be picked up on an EMG, which I will use EMGs a lot, but I know it's not 100% sensitive or specific. So, you're exactly right. Neck pain is a difficult thing to put a finger on. Usually we talk about radiating pain that goes down the arm, is more of a radicular type when you're talking about cervical radiculopathy, but then you have the cervicgia and then you have folks that are in cervicgia with cervical radiculopathy, and it's a little bit of – it's kind of muddy to say the least.

Seth Schwartz: I'm trying to get a slightly better understanding of when or how you make the decision to move along with surgery, because what we're looking at here is they're showing us some data on conservative care versus surgery, and at least what they're showing us is that they're fairly comparable, but I'm still quite skeptical about that, and I'm trying to figure out how you make a decision on which direction a patient is going to go, and maybe you can shed some light on that clinically. I'm not sure how that works.

Trent Tredway: Sure, for instance, everyone that comes in, as long as they don't have a spinal cord problem in the sense of they don't have

myelopathy and they're losing function in front of you, most of those patients can be treated with conservative management, and that would include some of the things we talked about, basically physical therapy, epidural steroid injections. I will always try to give the patient at least six to eight weeks of conservative management, and I will try to push that even a little bit longer. In the sense that – a patient that I just had the other day that works at our institution comes in with a C7, excuse me, C6 radiculopathy, weakness and pain, numbness and tingling in her first two digits, and she is having quite a bit of issues. So, she started some physical therapy. She got an injection, has done quite well, still came back at six to eight weeks, still has some problems, and some people may say oh, we should do some surgery. I even waited a little bit longer. She needs to come back now, absolutely has a little bit of numbness and tingling in her fingers, not going to have any surgery from me. We've basically treated her without having surgery. She may have an exacerbation down the road. If that's the case, we can actually treat her conservatively again. The problem of it is, once they have failed conservative therapy, and I will push it eight weeks, maybe even three months if possible. If they fall into that criteria of a surgical candidate we have to see what the actual pathology is and what the problem is. When we talked about some of the data that they're presenting with microdiscectomy, as Chris said earlier, doing a microdiscectomy on a lumbar spine is pretty standard, but doing a discectomy in the cervical spine, going from a posterior approach, that disk has to be very lateral, very accessible, or you're going to injure their spinal cord. If you go from the front, then you have to worry about doing a fusion. If they just have foraminal stenosis out laterally, then you can just do a foraminotomy and then they don't have to have a fusion. They don't have to have a discectomy, and so all these patients that are presenting with different problems still will have cervicalgia, cervical radiculopathy, and they can be treated a few different ways, and that's really the key, and I believe that's the way most people are actually out there treating patients. As a fellowship director at the University of Washington and actually training residents and fellows, this is what we actually talk about in our indications, and this is what we hope everyone else is doing and also looking at some of the national guidelines that are out there, especially AANS, CNS. These are the things that we look to and kind of use as a guide to basically let us do our surgeries when

necessary, but the majority of my patients don't need surgery. I hate to say that, but that's the truth, so.

Seth Schwartz: And just as a follow-up to that for our vendor, so, is it my understanding then that these would be the types of patients that were included in this randomized control trial that you looked at and you would interpret the data of this to say that – so say you take those same patients and you elect not to operate on any of them, the ones that have already failed conservative therapy, and you just have them continue that for a little bit longer, by four months, they're going to be – they're all going to be the same?

Daniel Ollendorf: So, it's difficult to tease out with the way the inclusion criteria were described in this study what actually happened, what was done to the patients before they entered the trial. We know that they had pain and symptoms of at least a three-month duration and in some cases it was much longer than that. I think on average it was 15 to 30 months. So, presumably, they had something tried before then, but we don't know what it was. Essentially, they were then randomized to conservative management or surgery. Remember that the outcome difference favored fusion at four months. It was at 16 months where things came together.

Seth Schwartz: It wasn't statistically significant versus physical therapy?

Daniel Ollendorf: Right.

Chris Standaert: These were, I mean, these patients are, if you look at the data, I have the study up. I mean, the mean pain in the surgery group was 34 months, physiotherapy 40 months, cervical collar 28 months. These are three to four years. It was 5 to 120 months of symptoms. So, they said three to four, but nobody was under five and they had somebody up to 10 years of pain. Dr. Tredway gave you some very nice answers, I think, and the trick becomes what is the problem? So, cervical disk herniation, for example, you wouldn't expect to hurt for 34 months. Somebody could have excruciating pain and progressive weakness of their arm and need surgery fairly rapidly because of a disk herniation, or they could get a little bit of weakness and bad pain and sort of make it through and you wouldn't think by three years it would still be markedly symptomatic. So, it depends on the underlying pathology. So, you're getting into a somewhat recalcitrant group

by this time. It's sort of curious. They all did so much better. They had pain for three years. They must have been treated, so the study is very confusing to me looking at this trying to know what to make of this and who they were treating and what this is. I mean, it's what I do, so I'm trying to get in the [inaudible] was hard. I couldn't really understand what they were – who these people were.

Richard Phillips: It doesn't talk about the other comorbidities, for example, myofascial syndrome happen in the intermittent.

Chris Standaert: No.

Richard Phillips: Other neurological syndrome.

Chris Standaert: Cervicobrachial pain.

Craig Blackmore: So, this is always an interesting process and always an interesting discussion. I am struck by one thing that hasn't really been talked about, and I'm not sure I know the answer to it, but you know, our job is to look at the technologies and figure out what evidence there is to prove that they're effective, and in this whole discussion we've kind of been talking about it backwards. We've kind of been saying how do we know that's as good as surgery or how do we know this would be as safe? And the reality is we have seen no evidence to show us that cervical fusion is better than doing nothing. Have we? Have I seen that?

Richard Phillips: In the short term.

Craig Blackmore: Or the long term. I have not seen good randomized clinical trial data where a bunch of people got nothing and a bunch of people got cervical fusion.

Chris Standaert: I don't know that there is such a study.

Craig Blackmore: There isn't. That's my point.

Chris Standaert: There – the people extrapolate out from all the disk arthroplasty studies, as Dr. Tredway said, were cervical disk – basically in a disk arthroplasty. So, you put in a disk replacement. You do the whole procedure short of the actual fusion. The next question is, what do you put in? Do you stick in bone and a plate? Do you stick in a

cage, or do you stick in a disk. So, in those studies, that's what they did, and from those studies you could track from baseline down and see what kind of outcomes you got for the whole things. They don't have a non-treated cohort, though. Fusion versus so...

Craig Blackmore: That's my point.

Chris Standaert: Your question of the natural history in the untreated state of these people, I don't personally know of any long-term data doing that.

Craig Blackmore: I don't – that is exactly my point. We have seen no data to tell us if surgery is better than non-surgery, none. Now, personally, I feel like I'm a little bit stuck here, because it's the standard of care and has been for decades, and so would one expect a randomized clinical trial to be performed sort of in the recent era? And I'm not sure that would be a fair expectation either. So, I'm faced with – there's no evidence to show that this works, but there probably wasn't a lot of perception of need for evidence, because everybody seems to think it works. Now, that's also not an unfamiliar place, but this one seems like it is established for such a lengthy period of time that I'm struggling a little more. It's almost as if the new intervention is not surgery with fusion. The new intervention is sort of surgery without fusion, and the questions we have been asking are, is surgery without fusion as good as surgery with fusion, which is kind of backwards, but it is also, I think, a reflection of where we are.

Michelle Simon: So, that's a good question, because it seems like that exists – that situation exists in the literature and in the studies, but not in the real world, and that's what I'm having a hard time with. It doesn't seem like people that are doing the surgery without the fusion, right?

Chris Standaert: I don't – personally, I think in the real world people don't do a cervical discectomy...

Michelle Simon: That's what I mean.

Chris Standaert: ...without fusion in this country. I don't know that they do it anywhere, but they don't do it in this country, and if you ask this question, you probably go, for foraminal stenosis, can you do a

discectomy – can you do an anterior discectomy and fusion for foraminal stenosis versus a foraminotomy? That would be – I don't know – I mean, that's what some of these people are trying to get at in their studies, but then you're really defining a – that's – unfortunately what our study, or our report didn't do, was define by the indication for surgery. So, radiculopathy was foraminal stenosis, then which is the best? Do you need to do an anterior discectomy and fusion for foraminal stenosis with radiculopathy? That would be a fair question to ask, I think.

Craig Blackmore: I think the fair question to ask is, is there any data to show that surgery is better than not surgery? And the answer is no.

Chris Standaert: I know, you asked that already.

Michael Souter: But, are we being asked that question? I thought we were looking at what the agency medical directors have put to us is that cervical fusion as an add-on procedure to a decompressive procedure for cervical radiculopathy. So, they're still asking, and we need to clarify this, but they're asking, you know, should you be doing cervical fusion after a decompression? And that's what we're basically being asked here, and as far as I can see, there appears to be good technical reasons presented by a variety of people that indeed that should be the case.

Craig Blackmore: Okay, so it gets back to the argument should there be evidence that fusion is better, or should there be evidence that non-fusion is better? What do you do when you don't have evidence? Do you default to fusing or do you default to not fusing, because I don't think we have evidence. You know, we can criticize what they found and we can say oh you didn't have good enough evidence to make your model, but the actuality is, you didn't have good enough evidence. So, is the more conservative option, which is the new technology in effect that we're evaluating? Are we saying that the standard is you don't fuse and we're evaluating the new thing – the add on that is fusion, or is the standard that everybody is getting fused and the new experimental thing that we're evaluating is to not fuse? And that to me – where do you need the burden of proof? Do you need the burden of proof that fusion is better or do you need the burden of proof that non-fusion is just as good? Does that make sense?

Carson Odegard: I think that makes perfect sense. I think it's right, but I think it also what – I think, you know, Chris has brought up is very important, too, is that the approach that you take to the surgery, i.e. the rationale for the decompression is the thing that drives it, and I'm not sure you can get those to compare directly one or another.

Craig Blackmore: I don't think we can...

Carson Odegard: And it may not be possible to come up with that.

Craig Blackmore: We're back where we always are, which is the data is not very good. So, how do we respond to that?

Michael Souter: I'm still not clear about the question that you're asking then. I mean, really what are the choices that are being presented before us? I mean, as far as I'm looking at slide of the agency medical director's thing, which is they're saying that they really want to know whether or not you should do a fusion with a decompression for cervical radiculopathy.

Craig Blackmore: So, if the question is, is there evidence that fusion is better than non-fusion, the answer is no, in my opinion. I don't think there's good evidence to say fusion is better than non-fusion. Now, does that mean we don't pay for fusion, or does that mean we do pay for fusion because the novel intervention that hasn't been studied is not doing a fusion? Do you understand what I'm saying?

Chris Standaert: Yeah. I know, you're going another way.

Craig Blackmore: Like if you don't pay for the new thing...

Chris Standaert: Right, I think, and intertwined with this, this still goes back to the issue of the indications for – the primary surgery is a decompression. It is not a fusion. The primary surgery is the decompression. That is the goal of surgery. The fusion is an artifact of what you do. So, the question of can you decompress – this is why the agency – they're not saying should you be able to decompress somebody with a cervical radiculopathy. That's not what they're asking us. They're asking us, if you decompress them, do you have to fuse them?

Michael Souter: Exactly.

Chris Standaert: And I think we run into trouble, because the only studies we're going to have that really – they found the studies that would get at that, but they're – and this is where it gets jumbled up, in the idea that nobody's talking about doing fusions with a foraminotomy, doing a posterior approach with a fusion with a post – nobody's talking about doing that, so we could say – but I don't know if we really even looked at that question. This is where...

Seth Schwartz: I think the problem is that if, in my mind, as we kind of run around this, the question we're getting at is, I think, based on their recommendations that they agreed that discectomy or whatever the decompressive procedure is indicated for radiculopathy. We're not being asked whether or not that's the case. That may not be the case, but that's what it seems like we're being asked. So, the question then becomes, is fusion necessary if you're going to decompress, and I think your way of looking at this, the chicken and the egg phenomena, is a good question but the problem I'm having with this is, I'm not sure that they looked at the right outcomes, because it may be that pain and back to work time and all that stuff is, there's no difference, because there may be no difference, because that's not the point of doing the fusion. The fusion is what happens seven to 10 years down the road, and that's your – your head falls off your neck and it seems to me that the neurosurgeons, as this procedure evolved, the reason they stopped doing decompressions without fusion is because that was what they saw happening, and we're not seeing any data on that, and maybe it's because there is no data because they started seeing kyphosis and they said kyphosis means their head is going to fall off their neck. We're not going to do that anymore.

Craig Blackmore: But we don't have data and we're not going to get it, and that's where we are. We can come up with any number of ways of criticizing the data.

Seth Schwartz: No, no, but we do – I think we do have. I mean, what – what we just heard was that if you actually look at the outcome of kyphosis, now I don't know if that's a good outcome to be looking at, but if you look at that outcome, that there is a significant difference between fusion and non-fusion.

Craig Blackmore: Yeah but what does kyphosis mean?

- Seth Schwartz: I don't know.
- Craig Blackmore: It's an x-ray finding, right? I mean, does it – does it connote worsening outcomes? And the answer is, we don't know. I'll concede that you're going to get more kyphosis if you just – if you don't fuse a disk.
- Michelle Simon: I thought Dr. Tredway also said that eventually that leads to radiculopathy.
- Craig Blackmore: Yeah, but we don't have data.
- Michelle Simon: There's no data on that?
- Trent Tredway: We may need to go back and look at a little bit of literature on that, and I think that would be very important, but I can tell you right now that there – I don't know of any orthopedic or neurosurgical surgeon that would actually perform an anterior cervical discectomy and not provide some anterior stabilization, because you're destabilizing the spine. We have done some very minimally-invasive approaches called anterior foraminotomies where you go down and you don't take the disk out, you just go off to the side, but very few people do that because the vertebral artery is right there, and there have been many, many injuries that most people don't do that. So, to do an anterior cervical discectomy and decompressive spine, reasonable to not do a fusion, that's going to create a lot more problems. We've – I think there are some papers that will show the kyphotic deformity, 75% we've already heard in one study without fusion. That's a big deal. So, the tenets are decompress the nerve root, but you don't want to make the environment worse by having a kyphotic deformity. So, I don't know anybody that does a discectomy without doing a fusion right now, in the anterior cervical spine.
- Craig Blackmore: See, I think we're in a backwards position. I think the novel treatment here is to not fuse, and I feel like because fusion is the standard, if we're doing a compression – if somebody's doing a decompression that for us to say you can't fuse it would be to force them to do something that's unproven. And that's what I'm trying to get at, with the whole thing is kind of backwards.

- Chris Standaert: You, I mean, you'd be forcing them to do something that is well outside the standard of care, and I think most of them would be mortified at the idea of doing and be petrified of what might happen to their patient if they become grossly kyphotic, which is why they don't do it.
- Seth Schwartz: Yeah, so Gary, this is your fault.
- Marie Brown: Well, this is just the opposite of what is on the medical director's site. It says adding fusion to cervical decompression procedures may do more harm than good. So, it's just the opposite really.
- Craig Blackmore: Well, I think – it may, but it feels like the burden of proof is that non-fusion should be – we should have to have evidence that non-fusion is better because fusion is the accepted standard, if that makes – and I hate to say that. I really hate to say that.
- Chris Standaert: Yeah, you're flipping the whole standard of care.
- Craig Blackmore: But I feel like that's where we are, that we can't...
- Chris Standaert: If somebody wanted to prove what they're trying to get at, that you don't have to fuse them, somebody would have to do the study to – and follow these people to show that you don't have to fuse them. Fusion is the de facto outcome of what they do.
- Craig Blackmore: Yeah.
- Chris Standaert: Yeah, I agree.
- Craig Blackmore: And I don't like it. I think we should be going where the evidence tells us, not going where we are because the evidence doesn't tell us. Anyway, that's my opinion. I'm soliciting more input.
- Carson Odegard: If that's the standard of decompression is going from the anterior and you removed the disk, just the common thought would make you feel like that is a – and you didn't fuse it, whether you knew anything about kyphosis, the thought of it is scary.
- Chris Standaert: Oh, yeah.
- Joann Elmore: But we can't make our decision based on whether the thought of something is scary, right?

Chris Standaert: Well, we can't establish a totally new standard of care with no data either.

Michael Souter: Common sense would argue that.

Chris Standaert: Yeah, common sense would argue that.

Craig Blackmore: I don't know that, I mean, I'm struggling – go ahead.

Richard Phillips: Can I ask a question? Now, this may be out of bounds here, but what I'm wondering is, do we have enough information from this study to make a decision, or do we need to send it back with a request for more information in order to make a good determination, and I guess that's a - I have no bias one way or the other. Do you think we can act on what we have right now and make a decision?

Craig Blackmore: I think we have what there is. I feel very comfortable that we have what there is. I mean do others disagree?

Michelle Simon: Well, I disagree. I think we're missing the piece about the long-term effects of kyphosis. We really didn't look at that data. We pulled something up about some 75%, but we don't really have any sense whether that's just a radiologic finding or if there's actually radiculopathy that ensues.

Craig Blackmore: That data doesn't exist. We've got all the...

Michelle Simon: But how do we know that? Do we know that?

Craig Blackmore: Do we know that? I mean, we looked – you looked for long-term complications following.

Daniel Ollendorf: So, at the time we scoped this, we made the determination that outcomes like radiologic evidence of fusion or non-fusion or kyphosis, or sagittal alignment was not part of the focus of the review, and we were focused on harder patient outcomes.

Craig Blackmore: But we looked at...

Daniel Ollendorf: I can't say definitively, but if you ask me, I am 99% certain, if you ask me to go to the literature right now and find long-term data

on the natural history and outcomes of kyphosis and issues with sagittal alignment, I wouldn't find anything.

Craig Blackmore: But you looked at the long-term clinical outcomes.

Daniel Ollendorf: Yeah.

Craig Blackmore: So, I mean we can...

Daniel Ollendorf: Presumably, if these issues become pronounced, they will manifest themselves in reoperation.

Craig Blackmore: Yeah, but we can concede the fact that their x-rays look funny.

Daniel Ollendorf: And we found overlap between...

Chris Standaert: But you're tracking four years out. You're not tracking 10 years out, right?

Daniel Ollendorf: We tracked as long as we could the studies.

Chris Standaert: I know, but the long-term follow-up – it's not you track, sorry. The studies only went four years out, right?

Daniel Ollendorf: Right.

Chris Standaert: I didn't mean to put it that way, sorry.

Daniel Ollendorf: I'll have to go back and double check, but yes.

Craig Blackmore: If there were long-term outcome information, clinically relevant outcome information post these procedures, you would have identified that for us?

Daniel Ollendorf: Right.

Craig Blackmore: Thanks.

Kevin Walsh: I have a problem with where we are.

Craig Blackmore: I have a lot of problem with where we are, but...

Kevin Walsh: Well, where we've talked ourselves to, I guess. I mean, realistically all of these studies are talking about doing decompression and cervical fusion versus conservative therapy versus not doing the surgery.

Chris Standaert: No, there's only one study doing that. There's one study doing that, conservative therapy versus fusion, there's only one study.

Carson Odegard: Also versus discectomy and...

Chris Standaert: So, if we try to break this down, if you just sort of looked at this, we have the issue of, if you accept the two halves and do an anterior decompression, how we change the standard that says you can't fuse, I don't know. The only issue would be, do you have to do an anterior decompression and what are the criteria for that? Do you mandate there has to be canal stenosis of the central disk, something like that? Then the question becomes ACDF versus a posterior approach, which would be a laminotomy, a foraminotomy going through far lateral stuff and you could define where that may be and what the extent of the bounds of that may be, I suppose. There are people who do posterior approaches and do posterior fusions but they are rare, and there are posterior fusions done for big decompressions, but they are rare too, and as the vendor pointed out, they are probably in very complicated patients with all sorts of problems, and you could get into that, if that's where your – if you get into sort of where these lines are, my question would be, if people are getting – if somebody does a foraminotomy and a fusion, do they have to do that? They have to put in a posterior plate with a foraminotomy? I wouldn't think so, but we didn't look at that.

Craig Blackmore: Let's not – let's not get absurd.

Chris Standaert: I'm not getting absurd, but that's where the question comes of where you would, where would an extraneous fusion be? An extraneous fusion would be, in some procedure that does not really destabilize somebody, so a posterior approach maybe, or it would be in people who have the wrong symptoms, who have neck pain as opposed to radiculopathy or myelopathy.

Marie Brown: So, if we're trying to change – if we think about changing the standard of care without adequate evidence to change the

standard of care, it's hard enough when we have adequate evidence to change the standard of care. So...

Craig Blackmore: I have no problem with changing the standard of care based on adequate...

Marie Brown: But there's no data.

Craig Blackmore: It's just the question of what you default to. Well, we're running in circles, but – so, there's a couple of issues. The first issue is who do we cover surgery for at all and then the second issue is, do we differentiate between surgery that involves fusion and surgery that does not, and most of what we talked about has focused on the idea of fusion versus non-fusion in patients who are getting surgery, but we also need to come back to the larger question of who gets surgery. So, we have told – we've been told in our scope that myelopathy is off the table. That's going to be covered. We understand that there is a distinction between radicular symptoms and axial pain. We're told by our clinical expert and others that radicular symptoms is the accepted indication, but we also – the agency directors seem to believe that a lot of the surgery that goes on is for people who do not have radicular symptoms. So, we need to address the question of what are the indications for surgery and how do we define them, or, if we put any limitations on the surgery.

Chris Standaert: Using our data, we could do a couple of things. We have no studies on neck pain. We can say you can't do a fusion for neck pain, for example, right? You can't – we can defer degenerative disk disease. They found no data. There is no support. There is nobody supporting that, so we could say that. We do have, you know, the non-operative study does say, you know what, maybe this does help and saying you should pursue non-operative care for a certain amount of time before going to fusion in the absence of severe neurologic deficits could be another reasonable thing to say, for example, and we have data to base that sort of statement on. So, we could put some parameters around when – around when to go, but I think for us to say if you feel you have to do an anterior decompression and decompress the canal and you can't fuse.

Craig Blackmore: Okay, we put that aside.

- Chris Standaert: I know.
- Craig Blackmore: I want to focus on the indication.
- Chris Standaert: The other kind of boundary – we can put on boundaries about requiring non-operative care or not fusing for neck pain, and we have data. It's in our report.
- Craig Blackmore: So, I want to get input from other members of the committee on the question of who gets surgery.
- Richard Phillips: Do we have the data from the agencies that these patients are getting surgery for just neck pain? I thought that was mostly myelopathy. I mean, mostly radiculopathy.
- Daniel Ollendorf: We would need to do a more in-depth sort of outcome. I think somebody suggested, you know, should we do a little more research, except it probably would take longer than three months probably, but we'd be happy to take a look at that if you think there's more information. It would only be for [inaudible]. We can't get detailed outcome data [inaudible].
- Richard Phillips: Yeah, right.
- Craig Blackmore: So, we did see slides.
- Marie Brown: There are clinical guidelines, which I know are no more evidence based than what we can do, but that's one place to start.
- Michelle Simon: So, if we say that conservative care should be followed before surgery is considered, do we even know what that is in our state? Do we know what's approved? Do we know what's considered conservative care?
- Chris Standaert: Unfortunately, the details of that weren't part of this. So, is it chiropractic? Is it PT? Is it injections? Is it whatever? We didn't look at that. Is it medications? We didn't look at that, and there's a whole – as you know, there's a whole panoply of things that we do.
- Craig Blackmore: Okay, so I want to focus on the specific indications, because we need to do that, and the groups that have been broken out are myelopathy, which is beyond our control, radiculopathy, and axial

pain. I think I've got that approximately correct. Why don't we, in fact, go to our key questions, which are in the big report. Alright, okay, the key questions. The first is comparative clinical effectiveness of fusion relative to conservative management approaches and other forms of surgery, adverse effects, differential effectiveness according to preexisting conditions, demographics, etc. I am on page three of the key questions – the main report, but I'm not sure I'm getting what I want. I'm still trying to understand the scope. I thought we were focusing on these three groups. I'm trying to organize the rest of the discussion.

Carson Odegard: What are you looking for exactly? I have the document in front of me.

Craig Blackmore: I have the document, too. So, alright, so if I go to the agency director's page, slide 25 of their presentation on page 13 of their presentation, they make some recommendations, and I'm not just going to accept their recommendations, but I want to use that as a framework for discussion because it gives us an idea of why they ask that we look at this topic. I want to talk about the second bullet point on slide 25, which is should we cover cervical fusion for chronic neck pain in the absence of radiculopathy. I think we – we know what can be known about that. We have the data, and I'd like us to talk about that. Anybody want to take a start on it?

Seth Schwartz: I think the literature says no.

Craig Blackmore: Says no because of the absence of good data or because.

Seth Schwartz: The data that we have says that the outcome is not a lot different.

Chris Standaert: Well, they didn't find any studies comparing it. There just has not been – there's no data, they didn't find any studies on cervical fusion for axial pain, correct? There's just zero data. They looked. Nobody studied it.

Trent Tredway: Chris, could I – I don't want to make an opinion, but would it be okay to make a suggestion?

Seth Schwartz: What does slide 21 show, on the page of the study, the ICER study?

Chris Standaert: Oh, he said that was mislabeled. It's not supposed to be neck pain. It's supposed to be radicular pain on your graph. Your little graph of lines on your ICER.

Craig Blackmore: Slide 21.

Chris Standaert: It says resolution of neck pain, and you had corrected it, I believe. That's supposed to say...

Craig Blackmore: Dr. Tredway, you had...

Trent Tredway: Yeah, I was just going to suggest that there are very few surgeons out there that will actually just do surgery for isolated neck pain or cervicalgia. What I found very interesting in some of the studies that were actually left out of this research group was the randomized control studies of cervical fusion and disk arthroplasty. If you take a look at that data, what's very interesting is, the patients, whether they had an arthroplasty or a fusion, their neck pain did improve, which is one of the few papers out there, one of the few groups of patients, that axial neck pain actually improved on by having a procedure, and that's with both fusion and with arthroplasty, but that's not in your research. That was excluded, because arthroplasty had been looked at, at a different time. So, in my knowledge – to my knowledge, that's some of the only data that I know from a randomized control study that shows that axial neck pain actually does improve with surgery, and I was actually shocked to see that. I'll be honest with you.

Craig Blackmore: Weren't those patients who had a concurrent radiculopathy or myelopathy? They weren't pure axial neck pain patients.

Trent Tredway: They weren't but part of the visual analog scale and part of the outcome was not only radicular pain but was for neck pain, and that was the axial neck pain, and once again, that's a little bit murky, because it's hard to dissect them both out, but that's the one thing that I can say about cervical axial pain, so.

Craig Blackmore: I mean, it's more than a little murky, because there's no control group that didn't get the intervention, and there's regression to the mean, and there's trying to differentiate between radicular and non-radicular pain. So, I think it's very valid to not include that. I mean, that's a case series basically, because there's no...

Trent Tredway: Well, if it's an FDA randomized controlled study on all of them, so.

Craig Blackmore: But a comparison group is lacking for that comparison. So, all you have is a case series of people who got an intervention – a surgical intervention. There's no – a lot of them would have gotten better anyway. That's the history of back and neck pain.

Chris Standaert: It's also – I totally agree. It's not the patient population in question, those with axial neck pain. That's not who they were studying. There's...

Craig Blackmore: So, back to the...

Trent Tredway: I may not have made it better.

Craig Blackmore: Thank you for your comment. Back to the cervical fusion for axial neck pain. Joanne?

Joann Elmore: Show of hands?

Craig Blackmore: Show of hands?

Joann Elmore: Are we ready?

Craig Blackmore: Are we ready? I mean, is there further discussion we want to have around that? Okay, so, our informal show of hands, when we talk about limitations of coverage, one suggestion would be to not cover in patients who have axial neck pain in the absence of radicular symptoms. So, I'm going to ask for a show of hands on committee members who think that would be an appropriate exclusion. Does that make sense? There's a lot of negatives in there. Okay. Okay, so then, I'm assuming – no. I'm not assuming. We need to ask the question of surgical fusion, so surgery of any – actually, I'm going to ask it even differently. I'm going to ask it decompressive surgery with or without fusion versus conservative care in patients with radicular symptoms. Okay, so this isn't the question of do we put a plate on or a graft? This is a question, does the surgeon touch the patient if they have radicular symptoms, and again, we have seen the data that there is, such as it is. So, I would like a straw poll on...

Seth Schwartz: Craig, could you just add after a trial of conservative therapy?

Craig Blackmore: No. We're going to get – we're going to define that second. This is under any circumstance would you approve? Does that make sense? And then I want to drill down on specific types and specific this and specific that, but first I want to make sure we're on board with going through that exercise. So, under any circumstances, do you think we might cover surgery for radiculopathy? Okay, so now – now we've narrowed it down to surgery and now we should put what constraints, if any, we want to put on that. So, what would that look like?

Seth Schwartz: It's hard to define explicitly. I would say after an adequate trial of conservative therapy. Now, what exactly does that consist of? I think that's a harder question. I mean, it seems like it should be what the entrance criteria were for some of the studies, but it sounds like it was a minimum of six weeks, but it may be even longer than that.

Craig Blackmore: Yeah, and, you know, we can either define it or not depending on our comfort level, or we can defer that. Okay, so that's one suggestion is failure of conservative therapy of some timeframe and can we – she's working on it. And then Richard, you?

Richard Phillips: I have a question, I guess. Is there not an entity where you need to do acute decompression? Are there not some acute disks that require – you can't have the six weeks of therapy?

Chris Standaert: I was about to say for significant neurologic deficit. Somebody with progressive severe neurologic deficit you might think differently.

Richard Phillips: Yeah, that's what I was trying to say. I mean, I have no idea the frequency, but...

Craig Blackmore: Progressive nerve root deficit?

Trent Tredway: I mean, as far as progressive nerve root deficit, people will come in with motor weakness, and I will actually still treat those conservatively and be able to watch them, but if they start to get worse, or if there are any signs of myelopathy, spinal cord injury, more than one motor nerve root, they need surgery – surgical decompression.

- Craig Blackmore: So, myelopathy is covered.
- Trent Tredway: Mm-hm.
- Craig Blackmore: That's already listed. So, the only issue would be...
- Chris Standaert: So, progressive neurologic deficit.
- Craig Blackmore: Is that? Okay.
- Chris Standaert: Do you ever operate on a hyperacute severe – somebody comes in with a complete C6 root palsy?
- Trent Tredway: No. I typically don't. I want to give them that trial. The question of it is, is the timing, because I just saw one that came back a year later from another surgeon, and he's completely out and never getting any function back, so there is a window of time to operate.
- Craig Blackmore: And then, of course, the next question is, if we're just asking Dr. Tredway, are we really going with the evidence or should we defer this to the medical directors who can?
- Marie Brown: Without evidence, I don't know we know how long to wait or what timeframe to suggest.
- Richard Phillips: Well, we could set a minimum, at least, couldn't we? Wouldn't that be reasonable.
- Marie Brown: I'd feel better just to put a trial, an adequate trial of conservative.
- Michael Souter: Yeah, you need to be careful though, there. I mean definitions of adequacy in trials can vary from one to two days in the worst hands to what would be a common sense three to four weeks.
- Craig Blackmore: But we can – we can leave that to the preauthorization or whatever these guys do. Failure of conservative therapy might mean they're getting worse. I don't know. Okay, other things we need to put on here?
- Gary Franklin: Craig, I'm sorry. Right now, L&I guidelines on cervical – surgery for - cervical surgery for entrapment of a single nerve root, which would be decompression, you know, plus fusion says six to eight

weeks of physical therapy or medications or cervical traction, whatever, and then you have to have, you know, clinical objective and subjective findings of – objective findings of radiculopathy and either a corroboration of an imaging test or EMG. So, you know, it's objectively determined, but there is already a period recommended of six to eight weeks of any one of those things.

Marie Brown: Why would we change that then?

Craig Blackmore: So, I mean, I guess it's just an issue of do we put wording into our decision or do we leave it as?

Chris Standaert: I mean from, if we go with data alone, we did not look at data on non-operative care to see. I don't know. We'd have to go through the other studies that are brought up to see what would the criteria for the studies that you have, the RCT's, how long did they wait before they operated? Was it a minimum of 12 weeks? Minimum of six weeks? We'd have some data that way. So, if we put a number on it? I think it's quite appropriate to say we should mandate some type of non-operative care before surgery and we're a bit arbitrary in picking six weeks, but that wouldn't be out of bounds from guidelines or other things, I wouldn't think. Defining radiculopathy is tricky.

Michael Souter: Are there any NCDs?

Trent Tredway: The trials did vary, as someone mentioned earlier, fairly significantly, in terms of the trial of conservative management that was attempted before surgery that the RCTs of two different surgical approaches. There is very limited payer coverage policies out there. The few private payer coverage policies that we found described six to 12 weeks.

Craig Blackmore: Yeah, so the RCTs aren't actually going to help us, because if something went bad and you got surgery earlier, you wouldn't be in the RCT. So, I mean, the eligibility criteria for the RCT are for research, not necessarily reflecting clinical reality. So, the other decisions might inform us on some level, but I don't think the RCTs are helpful.

Joann Elmore: Given the constraints of the data and our questions asked of our committee, I would recommend we be brief and cover with conditions patients with radiculopathy and failure of conservative

care, that we not define radiculopathy, that we not define failure of conservative care. As a primary care doctor, my hope is that they will definitely give them a lengthy period of trial to improve their symptoms, but I don't feel that we have the data to say six weeks, 11 weeks, and what constitutes conservative care.

Craig Blackmore: So, I want to ask the agency medical directors how they would operationalize if we simply said failure of conservative therapy and radiculopathy? Is that operationalizable?

Gary Franklin: Well, that's what we do now. So, Medicaid and Worker's Comp both do the same thing through the same UR process. So, if that's the decision, that's what we're doing now, and that would not be a problem.

Chris Standaert: Yeah, and that way if you say patients with radiculopathy and failure of non-operative care, progressive neurological deficit would count as a failure of care. They're getting worse, and then we could leave it or we could take it out, but it's clean. Defining radiculopathy is hard, as we talked about. It's defined so differently in so many things, and is it dermatome or sclerotome or how, you know, how do you – it's hard, and you have to leave clinical judgment and some issue of corroborating objective findings on MRI or CT myelogram, whatever you have to do, which the agency can operationalize like they are.

Craig Blackmore: So, my feeling would be, after reading through this data and the complete lack of data of benefit and the very clear harms and costs of the procedure, that I would want to have a high threshold before the surgery would proceed, but I'm also not sure how to operationalize that, because I don't think there's evidence to help me guide that decision. So, I mean, that's just a thought and I'm definitely welcoming input from other committee members. So, should we remove the word progressive neurologic deficit? Remove progressive neurologic deficit or leave it there?

Joann Elmore: Yes, remove it.

Craig Blackmore: Let's remove that please.

Joann Elmore: And remove the definition of radiculopathy.

Craig Blackmore: Okay, so we say patients with radiculopathy and we leave the definition – we leave the definition up to the directors, because we don't have evidence that's going to be reliant on some sort of expert consensus.

Michael Souter: But some people are still using radiculopathy, as we've seen, just from the basis of neck pain, and they're saying that's radiculopathy, and I think that we want to be careful to distinguish that.

Craig Blackmore: I mean, I think we can say neck pain is not covered in the absence of radiculopathy, but I don't know how – I guess we could say...

Michelle Simon: We could say CT or MRI evidence of nerve root compression if you wanted to.

Michael Souter: But then we're down to definitions again.

Craig Blackmore: And/or EMG.

Michelle Simon: Yeah. Some objective finding.

Craig Blackmore: We could say patients with objective findings of radiculopathy.

Chris Standaert: The trouble there is pain is not an objective finding, and you can have severe pain and you can have a, you know, EMG – I do EMGs - but you could have 20% axion loss show up on a needle EMG. So, you have to have a significant – an EMG shows a significant radiculopathy, not a subtle radiculopathy and not radicular pain.

Marie Brown: Don't they already have...

Chris Standaert: So, it's an easy way to find some objective, but.

Seth Schwartz: Didn't they say something like objective findings of radiculopathy or objective signs of?

Marie Brown: It would...

Chris Standaert: If you say objective findings of radiculopathy or nerve root compromise so that way you throw in imaging, EMG, and exam.

Craig Blackmore: Dr. Franklin?

- Gary Franklin: So, this is a problem when, you know, we get requests and you are, I hear about it all the time from the docs who do the reviews, that there is some confusion around just radiculopathy versus clear-cut objective findings like EMG findings or clearcut sensory loss, or any kind of reflex change, or any kind of weakness, any kind of objective findings. So, maybe one cut on the severity part is radicular pain without any of these objective findings versus clearcut objective findings and radicular pain where you know, you're sure, kind of maybe something needs to be done. So, I don't know if that's a possibility or not, but we do get confusion at the request level to Qualus, our UR vendor, about well is this really radiculopathy or, you know, whatever.
- Chris Standaert: I mean, we can require nerve root compromise, because you have to have, I mean, it's a decompressive procedure, right, so you have to have some reason to decompress. So, saying you have to have nerve root compromise on cervical spine imaging is quite reasonable, and radiculopathy, I don't know. We don't have – we don't just do it, our studies don't really distinguish well for us pain versus weakness versus numbness and how that tracks to outcome.
- Michael Souter: Well, can you abbreviate then just by saying patients who have got clinical symptomatology of radiculopathy supplemented by appropriate imaging?
- Chris Standaert: Correlating to nerve root compromise and nerve root compromise.
- Michael Souter: Craig is shaking his head anytime it says imaging.
- Craig Blackmore: No comment.
- Richard Phillips: Would EMG be imaging?
- Michael Souter: EMG, yes.
- Richard Phillips: Oh, EMG. I thought you said...
- Craig Blackmore: I mean, we can add imaging evidence of nerve root compression if we think that's going to help limit this to the appropriate clinical group. I'm happy with that.

- Michelle Simon: I think we should say signs and symptoms of radiculopathy and MRI or CT myelographic, or EMG evidence of nerve root compression, and persistence of radicular pain following six weeks of conservative treatment.
- Richard Phillips: You said it.
- Michelle Simon: Which is kind of what they have.
- Carson Odegard: Isn't that what they have already?
- Kevin Walsh: Right. It's kind of just rewording the current L&I standards.
- Carson Odegard: Right.
- Michelle Simon: Or, leave what they have.
- Kevin Walsh: That's what I was going to say. Why, if we're not changing it, why are we messing with the words?
- Michelle Simon: Yeah, and I'm okay with that too.
- Marie Brown: It's the radiographic evidence that I think they don't have.
- Craig Blackmore: No, they've got that.
- Kevin Walsh: They said radiographic evidence or EMG. Isn't that the L&I coverage criteria now? The Qualus criteria?
- Gary Franklin: I'm sorry, I didn't hear that.
- Kevin Walsh: Isn't – didn't you say that the Qualus criteria now was the inclusion of either radiographic or EMG?
- Gary Franklin: It is, but again, I think there's a lot of pushing and shoving that occurs around radiculopathy alone and is it really radiculopathy and, you know, is there really an associated – it's not always that easy.
- Kevin Walsh: No, I know, but we really don't have any evidence to weight into that.

Gary Franklin: Well, you have evidence that decompression versus decompression plus fusion aren't that different. You asked a question, can you differentiate levels of certainty that somebody actually needs decompression and a fusion, or decompression, and all I'm saying is that we do get confusion at the level of the request of Qualus. They don't always see the fact that the radicular pain, per se, is clearly related to other things that would tell you that there is definitely a radiculopathy that needs decompression. And Chris, maybe you can be helpful here, I don't know.

Chris Standaert: I mean...

Gary Franklin: Well, we got a lot of people with all these degenerative problems, their neck and neck pain, and then they, you know, the docs are documenting some pain in the arm, but sometimes it doesn't go that much farther than that, and you do a CT or an MRI and there's maybe some decompression or whatever, but there's no other findings.

Chris Standaert: Yeah, I guess, you know, you could say patients with objective radiculopathy helps and you could say patients with predominant radicular symptoms, so people really have to have a lot more arm pain than neck pain. So you can't just have neck pain with a little bit of arm pain. You really have to have arm pain.

Gary Franklin: We have that now.

Chris Standaert: You've already been through the whole trying to – you've been trying to find the right words, and we're not doing much better. I think objective is difficult because pain is not objective. So, patients with radicular pain, I don't – I don't like the beginning of that section. That's where going back to Joanne's point of defining radiculopathy is really hard to do. I think defining some anatomic compression is perfectly reasonable to require, and I think requiring non-operative care for a decent amount of time is reasonable.

Gary Franklin: So, if you say what you said up here already and you said then all – anyone, you know, that stuff and either EMG evidence of definite nerve root problems or advanced imaging evidence at that same level of definite nerve root compression. So, if you had that combination, you'd be much more certain that what you

were getting at was a definite compressed nerve that had symptoms that maybe needed something done.

Seth Schwartz: That might respond to surgery.

Gary Franklin: That might respond to surgery.

Craig Blackmore: I think the – I think the committee is comfortable with that. So, Margaret, we would go, after radicular symptoms, towards the end of that paragraph, right before the word EMG where your cursor is, hit return and write the word and. Then, after the word evidence on that sentence, corresponding nerve root compression. Then, before the word failure, write the word and. Is that getting at what we're trying to do here?

Chris Standaert: The first section, pains with objective – pain is not objective so we can't say patient's objective findings and radiculopathy unless we're going to exclude pain. So, take out the word objective.

Joann Elmore: Signs and symptoms of radiculopathy.

Chris Standaert: Patients with signs and symptoms of radiculopathy, yeah. I like that.

Richard Phillips: What did we do with lumbar fusion? It was radiculopathy that we...

Chris Standaert: It would be pain in...

Michael Souter: I don't know if predominant radicular symptoms is actually doing the context of everything else there.

Chris Standaert: I guess I would get rid of the – personally, I would get rid of all the things after the colon.

Michelle Simon: Me, too.

Chris Standaert: Just patients with signs and symptoms of radiculopathy, and the EMG evidence, imaging evidence with the corresponding nerve root compression. Evidence of. Imaging evidence of corresponding – EMG – EMG doesn't show nerve root compression. It shows radiculopathy. I don't know if you need the EMG part, because even with the EMG you still need the

imaging. You need the imaging. They had a positive EMG but there's nothing on imaging, why are you operating, you know? I'd get rid of the – say advanced imaging evidence and corresponding nerve root compression.

Michael Souter: Well, it's just the fact that some people may not have actually, well, I'm just thinking. Signs and symptoms, yeah, okay. Scrap.

Chris Standaert: Just get rid of the words before your cursor there.

Joann Elmore: Keep the and.

Craig Blackmore: Dr. Franklin, are we implementable?

Gary Franklin: The only thing is, I mean, sometimes there are patients, I think, that you can't tell for sure the nerve root, what is pressing on the nerve root, but the EMG does show [inaudible] potentials are not... done in the same distribution that you're worried about. So, that's the only concern is that.

Chris Standaert: But people can't...

Gary Franklin: So, it was an or.

Chris Standaert: I know, but, so you guys actually have people who don't have anything on their imaging but have a positive EMG and you let them operate, even though there's nothing compressing the nerve? That doesn't make sense to me.

Seth Schwartz: Can we ask our clinical expert?

Gary Franklin: That's fine. [inaudible].

Trent Tredway: As you know, you can have a neuritis, so moderate radicular neuritis. You can have a brachioplexitis, so EMG can be positive and the imaging studies may be negative, so, but that's kind of an outlier, but it's possible, so.

Chris Standaert: You wouldn't operate on those.

Craig Blackmore: Okay, so I think we want to include some specific wording that neck pain in the absence of the above conditions referable to the nerve roots is not covered. Right, that sentence. Yep, the word

chronic before neck pain is not necessary. Alright, further comments? Okay, let's go to the tool.

Carson Odegard: Are there any other indications that might have to do with nerve damage in the neck, you know? And some of the other nerves, cranial nerves, you know, that sort of thing? Swallowing problems, other reasons that...?

Craig Blackmore: I think the swallowing problem could be considered a sign or symptom of radiculopathy.

Carson Odegard: I'm just wondering if we're missing something there?

Craig Blackmore: It wouldn't be nerve root. I mean, it wouldn't be cervical.

Chris Standaert: I mean, the only way we could tighten it up would be to say, patients who require anterior decompression, but then we get into issues of posterior fusion and indication. I guess that gets tricky, because people would – they have some studies on posterior fusion, and there are totally indications, so I guess we can't – we didn't go there. Stay away.

Craig Blackmore: Okay, so we have the tool and the committee is very familiar with the tool, and it's basically sort of defining the criteria that we use for decision making, and our job is to determine coverage based on whether technologies are safe, effective, and cost effective or providing a value. The staff has prepopulated this document with the outcomes that are relevant. There is a long list of them. Just take a moment and look at this list and see if there are any outcomes that we, as a committee, have felt to be important that have not been included. Also, the safety outcomes, as well as effectiveness outcomes, again that we have been taking into account. I guess we should note on here that we also considered progressive kyphosis, although mainly as a predictor – potential predictor of future radicular pain. So, that brings us to the first voting question and this is nonbinding and we use our tan cards. So, the idea here is we will make a distinction as to whether surgery, surgical decompression is unproven, equivalent, less, or more effective than conservative care for – in any situation – the cervical spine.

Chris Standaert: No, we compared to conservative care or to non-fusion.

- Craig Blackmore: No, we're comparing.
- Carson Odegard: Are we looking at fusion?
- Craig Blackmore: Sorry, I will restate. We are looking at whether decompression with or without fusion, under any clinical circumstance, is superior to conservative care, and the exception is we are not considering patients with myelopathy. Okay, does that make sense? So, if you think...
- Chris Standaert: Are we going to have a separate question on...
- Craig Blackmore: We're going to get to it.
- Chris Standaert: ...with or without fusion?
- Craig Blackmore: Yes.
- Chris Standaert: Okay, thank you.
- Craig Blackmore: So, we're going to, again, this is whether you think there is ever a reason to operate on somebody who does not have myelopathy. If the evidence tells you that surgery is better than conservative care, under any circumstance, for patients who do not have myelopathy, and the issues are unproven, equivalent, less, or more. So, now does that – does that make sense? It's a little confusing.
- Josh Morse: One unproven, nine more.
- Craig Blackmore: Alright. That's effectiveness, and then in terms of safety the same question.
- Josh Morse: Nine unproven, one less.
- Craig Blackmore: And then cost effectiveness.
- Josh Morse: Nine unproven, one less.
- Craig Blackmore: Okay, the committee has indicated that there is at least some circumstance when the surgery might be covered. So, now we will continue to the second vote. Is there any opportunity for discussion? Okay, so the second vote, this will be our binding

vote, and the vote, you will have three choices. Your choices are no cover, which means that with the exclusion of myelopathy, which we are not talking about, you would never cover surgery for neck pain, radicular symptoms, etc. Your other option is cover, which means that you believe we should provide coverage for neck decompression of any form for any patient without limitations, and then your third choice is cover with conditions, and the conditions that we would use would be that the patients must have signs and symptoms of radiculopathy, they must have advanced imaging evidence, and they must have failed conservative care, and we are making no distinction between decompression with fusion and decompression without fusion. Are the options clear? Alright.

Josh Morse: Ten cover with conditions.

Craig Blackmore: So, it is incumbent on the committee to determine if our decision is in conflict or agreement with the national coverage decision. I don't have a national – do we have a national coverage decision?

Josh Morse: There is no.

Craig Blackmore: There is no national coverage decision, so we are okay. We will charge staff with making a formal document of our draft when making decisions for the two topics discussed.

Richard Phillips: Are you sure it's not the – the key question was addressed cervical fusion, not just any decompression surgery. So, we've changed it. Our – so, what we've done is we've answered a different question than the key question, correct?

Chris Standaert: We just voted on decompression surgery.

Craig Blackmore: Well, let me make sure that I haven't done something wrong. Well, alright, well maybe we need to think this through a little more. I think – well, I think it might be cleaner if we rethink this, or at least revote, because it's been pointed out to me that the question we're asked only pertains to cervical fusion and not all forms of decompression. So, I think I'm going to ask the committee to revote and I'm going to rephrase the question, as we need to get our pink cards again. I apologize. So, the question is rephrased as, is cervical fusion a covered benefit? And again, I'll just restate the whole thing. If you vote no cover, that means we

will never pay for cervical fusion and we're excluding myelopathy, so that's a separate topic. If you vote cover, then the answer would be you'd cover cervical fusion for anyone, and if you vote cover with conditions, then we would vote for cervical fusion with the conditions defined here and actually our decision, then, would not apply to the other types of cervical spine surgery, which we did not discuss. So, thank you for clarifying that, and again, we will have a revote. That's not the key question.

Chris Standaert: Do we need to do the yellow cards, too? We talked about these.

Craig Blackmore: No, we're fine. Those are non-bindings.

Seth Schwartz: We'll just clarify that. I mean, that's what we were asked – cervical fusion relative to that of conservative [inaudible], but we didn't study foraminotomy, we didn't study all these other microdiscectomy.

Chris Standaert: Coverage is within regards to cervical fusion.

Seth Schwartz: It's agreed that the title is cervical fusion. I'm not comfortable with that.

Craig Blackmore: I mean, I think that, we can't - we're not – we're not commenting on other forms of surgery on the cervical spine. So, everybody understand the revised question, and again I apologize. Okay.

Josh Morse: Ten cover with conditions.

Craig Blackmore: Okay. Okay, thank you. If we look to the agenda, you will note that we have added a new feature to this meeting, and that is that we will take advantage of the presence of the committee to talk about draft key questions for upcoming topics, because committee input can be valuable in refining those questions going forward. We have – what have we got, Josh?

Josh Morse: You have in your binder the draft key questions for cardiac nuclear imaging. This is open for comment right now for the next two weeks. We, of course, invite insider comments on this. We also have the key questions for hyaluronic acid, which will be a re-review. They are in there, as well.

- Craig Blackmore: So, I'm just going to give the committee a minute or two to refocus on these two documents, and then we'll start to talk about cardiac nuclear imaging first, but let's just take a minute here.
- Marie Brown: Does the vendor decide on outcomes? Because if you look at the question, what is the clinical effectiveness, it's going to be used in conjunction with other treatments usually, and do we look at things like time to surgery, does it prevent surgery?
- Craig Blackmore: Well, I mean I think our job here is to provide guidance on what we want to know.
- Marie Brown: Okay.
- Craig Blackmore: So, absolutely.
- Seth Schwartz: I guess, in looking at this, I just – looking at key question one, the question that always comes up when we actually get here is, are we looking at the right comparator group? So, I just don't know, is stress echo the current gold standard for what they're using? Is that – is that what the studies are going to show as the comparator? Are there other comparators we should be looking at like cerebral angiograms? I'm sorry, coronary angiograms, or are there other things, other outcome measures or other comparators we should be looking at?
- Michael Souter: Is it a kind of first line evaluation, the stress echoes.
- Seth Schwartz: I mean, is that the way these nuclear medicine studies are used, as a first line evaluation?
- Michael Souter: [inaudible] would be my first protocol.
- Josh Morse: So, Dan, this topic is assigned to ICER who happens to be here. He has done scoping on this and Dan would you be willing to take questions on this?
- Daniel Ollendorf: Yeah, that's fine. We actually had some subsequent discussion suggesting that in lower risk individuals, we shouldn't rule out stress EKG. So, essentially stress echo and stress EKG as the comparators.

Chris Standaert: I guess the other question I would – the one obvious question in my head is the relative indications of these in individual patients. There's a reason why you can't do a stress echo and a stress EKG in some patients. They can't physically do it. They have to do a chemical thing. So, regardless of the outcome, if you can't – so the indication becomes important to say, because I could see us coming in. Do we cover, you know, PET something or a SPECT something, but if the reason it's being done isn't always the study is better but because the patient can't do the other study. That's helpful to know. So, the indications for the different procedures.

Marie Brown: They can't walk.

Chris Standaert: Yeah, they can't walk, you know. They're ill, they can't walk. They're an amputee, they're whatever.

Craig Blackmore: So, their key question might be, are there specific clinical scenarios in groups of patients in whom one of these tests might be preferable to stress echo due to – I mean, I don't know how to phrase this, but...

Chris Standaert: I guess are there subpopulations where - which would affect the indications for each test? Something like that?

Craig Blackmore: Are there subpopulations where stress echo can't be performed?

Seth Schwartz: But that's already done. That's what exists now.

Craig Blackmore: Yeah. I don't know how to...

Richard Phillips: You know, there are some AHA, ACC guidelines that are exhaustive for different clinical entities, and I'm – the thing I'm having problems with is exactly what this is – is it supposed to take in all those guidelines? Is that – for example they have it for unstable angina, non-STEMI. They have one for STEMI. They have one for stable angina, and gosh they're so prescriptive. I mean, these papers are each 150 pages long, and I'm just trying to figure out what we're – what's the focus here?

Craig Blackmore: Well, it says acute and stable chest pain symptoms, recurrent chest pain subsequent to revascularization, congestive heart failure. Those are the four groups that are described, which those are big groups.

- Chris Standaert: I guess, yeah, but I mean, when you look at these, there are questions about the differential sensitivity and specificity, and there are questions about the applicability to a given patient, and I don't know enough cardiac stuff, but I know in other times if you do tests with high sensitivities in low-risk patients you wind up with lots of false positive things. So, I could see some of these not being indicated in very low-risk patients theoretically. Say you have a low-risk patient, maybe that's when you do the stress echo if they can do it. Maybe that's – I guess – I don't know if that's how that works, but I don't think that's going to come out the way this is written. Does that make sense?
- Michelle Simon: This is a more general question. Is there usually someone like a cardiologist involved in formulating these questions?
- Craig Blackmore: Well, the attempt is always to get the clinical expert involved early and then the vendor in formulating the clinical questions from the scope gets input from clinical experts that they identify. So, our job is not really to, here now, is not to understand the clinical relevance. It's to make sure that we're asking for the information that we'll need, to make a decision, because the clinical expert doesn't know what we need to know. What we need to know is always how, how are we going to draw this line in the sand?
- Seth Schwartz: But I think that this...
- Craig Blackmore: So, hopefully, the clinical relevance is there.
- Seth Schwartz: But I don't think that's totally accurate, Craig. I think knowing what the current standard is and knowing what – if we're trying – because a lot of times what we're trying to figure out is are they asking us to compare the current technology or the technology I'm assessing to the right thing?
- Craig Blackmore: Well, that's true.
- Seth Schwartz: And I think that's what we're trying to offset.
- Kevin Walsh: What's the compare – we need to specify a little bit what are the comparators that we want, I think.

- Seth Schwartz: I just want to make sure that we're looking at the right comparators.
- Joann Elmore: Gold standard cath.
- Craig Blackmore: Yeah, and this one's this one's really...
- Joann Elmore: Well, the gold standard here is cath, to define accuracy.
- Craig Blackmore: No, is the gold standard cath? Cath is anatomic. This is perfusion.
- Chris Standaert: What we're going to have to do at the end is define which patients can get which of these tests. That's what we're going to have to do. So, what I'm going to want to know is the differential use of these tests in different patient groups, so I know which ones you need to use them in, which ones they are inappropriate in, and which ones you, you know, what do you do when you can't do one or the other tests on a patient?
- Kevin Walsh: And that's what Richard was alluding to about how complicated it gets, how quickly.
- Seth Schwartz: And along the other lines, what are the other tests? We're saying stress echo is one, and I guess the question is, are there other – are there other tests you might use in these subpopulations, because if that's the question, if there are other tests, we should say in stress echo or X or Y or Z.
- Craig Blackmore: I think the point is, a lot of people get a lot of tests.
- Richard Phillips: Yeah.
- Craig Blackmore: And probably people get every possible test a lot of the time, and how are we going to address that is the challenge.
- Richard Phillips: I think that's really the question. Utilization may be an issue, like in the Emergency Room. These patients who come in with chest pain, they oftentimes get a nuclear medicine scan, and they also get an echo, because you really need an echo. You need to see the structural integrity of the heart, what's on the inside of it, and what's going on. You know, the nuclear medicine has become a standard, moreso than the stress – what do they use as the

standard? The stress echo or dobutamine echo. Some people get that because of exercise things.

Craig Blackmore: Actually, there's different camps, I think it's...

Richard Phillips: I think all these things are defined in those guidelines from the AHA/ACC, those tomes of information. I guess I'm trying to figure out where we're...

Michelle Simon: But maybe we're just trying to look at this one intervention and when the appropriate time to do this, nuclear study, is and not all the different possible studies and what the right populations are for those? Is that right?

Craig Blackmore: Gary, what do you want to know?

Marie Brown: What's the problem?

Chris Standaert: Yeah, what's the problem?

Gary Franklin: Well, the draft question one frames it, doesn't it?

Joann Elmore: Well, it frames too much. Draft question one should really just be accuracy. Let's start with simple, what is the accuracy of each of these different modalities? But then to define accuracy, you need to know what is your gold standard definition?

Chris Standaert: Right, but you also need the differential accuracy and why would you do one versus the other. That's what you really need.

Joann Elmore: And then you get it accuracy based upon patient characteristics, are they obese, can they not walk?

Kevin Walsh: That's where you're going to get the subset stuff.

Chris Standaert: Yeah, you have to know who...

Kevin Walsh: And it is – it is – I mean that does sound germane to ask the basic question first.

Joann Elmore: I would want to start with that and then I would ask each predictor.

- Kevin Walsh: And then you start to look at subgroups, which is where you get the people that have already had a stent...
- Joann Elmore: Subgroups that affect accuracy.
- Kevin Walsh: ...and the people that have unstable angina to see if you can tease out differences in those subgroups.
- Marie Brown: It seems really basic, but why would we want to know the accuracy. I mean, is there not data about the accuracy of these tests?
- Chris Standaert: I guess, is it not established is your question.
- Marie Brown: Yeah.
- Gary Franklin: We figured out which advanced imaging tests should be reviewed by the agencies. We had trouble figuring out what to do with these tests and with abdominal and pelvic CT. So, this is coming to you because we really didn't know what to do with this one, but we are spending quite a bit of money on it, and we hoped that you could provide some guidance as to when these tests should be done, what kind of a checklist would you come up with for conditions.
- Craig Blackmore: Yeah, so I was the one who said you can't do this. Actually, it's not possible. Throw it back here to HTCC and you're telling me [inaudible].
- Joann Elmore: Better to discuss it here than nine months from now after they've done a review.
- Richard Phillips: I think the testing is going to be different whether the patient comes through the intensive care unit, whether they come through the Emergency Room, whether it's an outpatient and, you know, you have to send him over to an outpatient center, whatever it is. So, you know, the clinical scenario really is important here, and I guess, from my perspective looking at what the agency wants is which group is causing the most angst for you guys?
- Craig Blackmore: So, I think that's a really good point. I mean, what – what I'm hearing is that the agency directors want us to give them a list of

the accepted indications for these tests and the accepted indications – acceptable indications for these tests are going to be all over the map and not something that we can conjure up, but if there was one specific scenario that they were worried about like the ED with acute chest pain or like chronic stable angina or like something else...

Chris Standaert: Right, like by diagnosis, like the tests by...

Craig Blackmore: ...by clinical scenario.

Chris Standaert: Yeah, then that would be preferred.

Craig Blackmore: What clinical scenario do the director, or maybe there's more than one that's driving this, and maybe that's what is tried in this population, which is basically everybody. Or maybe that is what they're trying to get at here. Patients with acute or stable chest pain symptoms, those with current chest pain, and patients with congestive heart failure, but those are still huge groups.

Daniel Ollendorf: If I can interject for a second. So, unfortunately, we sent some thoughts on revised key questions to Josh, but there hasn't been enough time to actually look at them based on some recent clinical input that we got, so we asked some of the same questions of our clinical experts. What are the general uses of this test? Where are areas you think there is potential overuse or inappropriate use, etc.? So, we actually broke key question one into three separate questions. One focused on diagnostic accuracy for obstructive CAD, one focused on prognostic information to guide treatment decisions, and the third question focused on postprocedure or postevent serial monitoring, which is another area where the tests are used.

Craig Blackmore: I like the last one, in particular. The first one, we can't look at the diagnostic accuracy for obstructive coronary artery disease. It's not – we can't – that's not actionable to this committee. We can't say, okay, it's accurate, we fund it. We have to know in a clinical – in a specific clinical scenario, is it useful compared to other tests?

Daniel Ollendorf: I'm sorry. That key question one still does include diagnostic accuracy, as well as impact on patient outcome, so we can word it...

- Craig Blackmore: But it still – it still has to be in a specific clinical scenario. Otherwise, we end up with...
- Chris Standaert: The problem is, if you come back and tell me PET scan has a sensitivity of this and specificity of that and SPECT has this and that, and this is this and that, that's all well and good, which patient should get which one? Are there circumstances where one patient needs one because they can't have the other? That's what I would need to know.
- Michael Souter: Well, that comes down to question three, then, which is the differential effectiveness and safety of the tests of interest.
- Daniel Ollendorf: But I think more to the point of what we're talking about, so we need to segment out patients with acute chest pain, outpatients with stable chest pain symptoms is one potential split for example.
- Craig Blackmore: We're going to be asked to list conditions where we pay for SPECT. So, that means we need to know specifically in this situation how does it do, and it may be that there are a thousand different situations, so what we should do is narrow it to the ones we're most worried about that are common and expensive, and that – these guys have to help with that.
- Daniel Ollendorf: What we've heard from our clinical experts, in any event, is that by far the largest indication is investigation of acute chest pain of unknown origin.
- Richard Phillips: There you go.
- Craig Blackmore: Right, that's how...
- Daniel Ollendorf: Or chest pain of unknown origin, whether acute or stable.
- Craig Blackmore: In chest pain of unknown origin, that's a clinical scenario we can get a handle on, and we can say should we fund it in that situation? Does it work? Does it improve outcome? Does it do this and that?
- Chris Standaert: Yeah, but I would ask those guys if that's what they're worried about. If they can't break that out by the utilization or they're not

concerned about that, your expert may be concerned about it, but they may not be.

Craig Blackmore: And we're much better off with an in-depth look at that topic than a scan of 50 topics, none of which have good evidence, which never happens.

Marie Brown: So, we need your input medical directors.

Gary Franklin: The agency has to clear this a little more.

Michael Souter: Well, and also still the question of are they concerned about combinations? If they're worried about overuse?

Craig Blackmore: Well, I think they are.

Michael Souter: So that, I don't really see that outlined as being a comparator in there anywhere.

Craig Blackmore: I mean, it says relative combination.

Michael Souter: Yeah, but that's – I think that needs to be called out more clearly in terms of which is more effective looking at one modality, looking at combination modalities in those circumstances, just so we can see that the combination [inaudible].

Craig Blackmore: Incremental benefit of the second test...

Michael Souter: Exactly.

Craig Blackmore: ...and third test.

Chris Standaert: Right, is there incremental benefit of doing more than one test and, if so, in whom?

Richard Phillips: And that, well that's going to be diagnosis related, too.

Craig Blackmore: Yeah, again, in this clinical situation.

Richard Phillips: The other thing I'm a little concerned about is the comparators. If, for example, they use stress echo as the comparator if they say no to this, then what that leaves us with is that well the stress

echo is what we're going to pay for, and it isn't even used anymore, I mean really.

Chris Standaert: Stress echo?

Richard Phillips: Well, I mean it's used, but I would venture to say that 90% of the time, they're going to be doing something other than the stress echo.

Group: No.

Seth Schwartz: Not where I live.

Richard Phillips: Well if anything comes through the Emergency Room. That's where I'm talking about.

Seth Schwartz: Stress echo.

Richard Phillips: I think you're wrong.

Seth Schwartz: What do you think they're doing?

Richard Phillips: They do a lot of nuclear medicine scans and they do echos.

Kevin Walsh: I think it depends on the community that you're in.

Michelle Simon: Yeah, and the system.

Craig Blackmore: We do stress echo – or echo – it might not be stress depending on [inaudible]...

Richard Phillips: See, that's different than stress echo. I'm talking about maybe – maybe that's a good question. Exercise echo is what I was thinking when they said stress echo, but they might do a dobutamine echo. I agree with that, but they don't do an exercise.

Chris Standaert: But those are different tests. A dobutamine echo is different than a [inaudible].

Richard Phillips: Probably, they'll just do like a Cardiolute study or something like that, whatever happens to be – I would venture 90% comes

through the Emergency Room gets the nuclear medicine as the standard.

Kevin Walsh: But is that – is that the overwhelming percentage of people that get studied are people that come through the Emergency Room, or is it – compared to people who get sent out of a provider's office?

Richard Phillips: I don't know.

Craig Blackmore: And that's two different groups. That's two different clinical questions. Should we fund it here? Should we fund it here? Is this helpful?

Daniel Ollendorf: Yes, thank you.

Joann Elmore: When is this one slated for discussion? When is this one slated to be?

Daniel Ollendorf: September.

Gary Franklin: We have also requested that the program [inaudible].

Craig Blackmore: Well, that sounds good.

Seth Schwartz: It seems to me when you're talking about key questions, you should have something specific like you just mentioned, which is, you know, what is the evidence of benefit for these things over the current standard of care or whatever those comparators are in patients with undiagnosed chest pain or acute chest pain or...

Kevin Walsh: That's a good point.

Seth Schwartz: That should be what our key question is, and if there's another condition we want to look at, that should be another key question. That's the kind of specificity that we need to have an assessment of the data that is actually meaningful to us.

Craig Blackmore: It's what it should be.

Joann Elmore: And I have one other request of the vendor, since you're still here. Our group really likes primary data and if there are a lot of holes

in the data, we're not that enthusiastic about simulation modeling. It's not helpful to spend a lot of time on it.

Marie Brown: Do you mean systematic reviews, or?

Joann Elmore: No.

Marie Brown: Simulation models.

Joann Elmore: We like the primary data. We don't like reviews of reviews and if there's a lot of missing data and assumptions and models, the models junk in junk out, so.

Craig Blackmore: I mean, I think the models are great, but we have to have the data.

Joann Elmore: Right.

Craig Blackmore: The first thing is the data and then the modeling is second. So, we want the – the raw data from the important trials, whatever they are.

Seth Schwartz: And I think along those lines, I mean, there may be situations like the hyperbaric oxygen treatment where there is so much data that they elect to use systematic reviews, and I'm not, I mean, I have issues with that, of course, but at the very least, if they're going to use systematic reviews, they need to bring the primary trials here so then if we want to delve in it.

Craig Blackmore: We talked to the team earlier about that, as well. Okay, we have one more.

Kevin Walsh: So, this is the first time, is this the first time we've done a re-review? So, can you kind of lay out the premise of this? I mean, do we start de novo, as if we've never studied this before or do we start with our previous determination and look at the new literature to see if it makes a difference in our thinking about our decision?

Joann Elmore: It seems the latter.

Michelle Simon: It's the latter. We did that for MRI. We did a re-review on that.

Craig Blackmore: Well, we – no. We considered whether we needed to do a re-review, and the committee said oh, there's not a lot of new evidence, we're not going to go through the formal process. That's different from having a vendor actually look at everything that's happened in the interim and update. So, I assume we will have – well, we'll certainly know what our previous decision was and what it was based on.

Josh Morse: So, at this point our plan is... what the law reads is if there's new evidence that could change the previous determination and we made that judgment and our director selected this based on that, based on new meta-analysis from 2012, the vendor will take the past report and update that report with new evidence from the date of their last search. It turns out the original report was done by Hayes, so they will be revising it at some point. So, we will get a new report that has the old and the new together.

Richard Phillips: Which means we can't change the key questions.

Josh Morse: I would say we could change the key questions if you – probably if the evidence indicated it would be a good way to look at that. So, if we found new – the evidence had new populations or comparators or outcomes that we had left out, that might be a good place to start, but I think you could. These are draft and these are for considerations.

Marie Brown: So, you'd have to be happy with how you define clinical effectiveness last time. I mean, what outcomes were you looking at last time, and do they need to be changed?

Craig Blackmore: Well, I think we could add another outcome and then they would look at everything, not just the most recent?

Josh Morse: We're not rescoping, so they're not going to look. I guess I would have to say...

Chris Standaert: As I recall the data was relatively underwhelming a couple of years ago. So, if there are no new studies, just a new meta-analysis, that's what we'll have. The other thing that would help, it's not just the clinical effectiveness of visco supplementation, but it's these other things. So, it's what are its comparators and then is there a study on corticosteroids or other things. So, even if they're not direct head-to-head comparisons, the comparators

are valid. So, how do the comparators fit into the key question? Are they going to go looking for these other comparators to see if there are effectiveness studies, as well?

Josh Morse: No, I think they would only look for studies where they are compared. So, hyaluronic acid is compared to NSAIDs or – is that what you're asking?

Chris Standaert: Yeah, so, but then if you have a highly effective treatment somewhere out there that you're not even looking for and you have data on hyaluronic acid, but you never found the really – that PT is really effective or steroids are really effective, because nobody – the people who make the drug didn't bother to compare it to the highly effective intervention, for example. Then we wouldn't find it. So, can we look for evidence of effective comparators or is that outside the scope of it?

Craig Blackmore: Well, I mean, it should be – the clinical effectiveness of visco supplementation of the OA compared to standard of care, right?

Chris Standaert: Yeah.

Craig Blackmore: And that gets at it.

Chris Standaert: Yeah, it just doesn't say that, yeah.

Craig Blackmore: So, right, well that's what I'm – we should make sure of.

Michael Souter: There's a lot of comparators there, as well. I mean, were they all useful the last time? I don't remember whether they were useful or not.

Chris Standaert: I don't remember.

Seth Schwartz: So are these comparators as listed not the current standard of care?

Craig Blackmore: NSAIDs, steroids, [inaudible].

Seth Schwartz: We could rephrase this and say standard of care including?

Chris Standaert: I don't think anybody does lavage, but.

Michael Souter: All of that bit the dust.

Chris Standaert: NSAIDs, corticosteroids, PT, pain medications, placebo.

Craig Blackmore: Yeah, I mean, I think that's reasonable.

Craig Blackmore: All done? Yeah, those are all reasonable, yeah.

Michael Souter: I didn't think people did lavage anymore.

Craig Blackmore: They don't.

Chris Standaert: They don't. Lavage and debridement they don't do anymore.

Michael Souter: So, why not just get rid of those?

Chris Standaert: I guess, I agree. I mean, I certainly know people who use this stuff in hips and other joints, too. I don't know if that's part of our scope or not.

Kevin Walsh: I think the last – I'm looking at the decision, and there was a problem with not a lot of functional outcome data. So, we were – it was left more with pain and with functional outcome data to make a decision, and I don't know if this meta-analysis does any better. I'm betting not.

Michael Souter: If it doesn't, then we don't change.

Craig Blackmore: So, what do we – last time what did we say? We covered...

Marie Brown: What were the outcomes?

Craig Blackmore: It covered with conditions.

Kevin Walsh: Yeah, it was covered with conditions. It was, I'm sorry. Patients who have not had adequate response – no, that's not covered.

Seth Schwartz: Pain associated with osteoarthritis of the knee when the following conditions are met: Patients who have not had adequate response to non-pharmacological conservative treatment and simple analgesics is limited to two courses per year, at least four months between courses with documented evidence of clinical

benefit from a prior course of treatment is required for subsequent treatments, so you could get two cycles per year.

Marie Brown: But the question is, was it pain. Is there function? Are they going to look at not only just pain but...

Kevin Walsh: The problem before was that there wasn't much data on functional outcome. So, we were left with pain as almost the only comparator and I doubt that it is going to be any different.

Craig Blackmore: We can ask. We will have to find out.

Josh Morse: They'll of course – they'll look at that. The new meta-analysis contains unpublished studies and more safety.

Joann Elmore: It talks about the risk of the serious adverse events in the meta-analysis.

Michelle Simon: Will they look if there are any new interventions on the market, too, since the last time?

Josh Morse: So, other than?

Michelle Simon: I mean like new products. We've got the Orthovisc, the gel one, other products.

Josh Morse: Yeah, there is a new one. The gel one is a new one. So, they will include the evidence for that.

Craig Blackmore: I guess hearing what Joann just said, I would want to make sure that our safety information included injections into other joints if there was data on adverse.

Josh Morse: Into other joints? So, those other joints are not FDA approved.

Chris Standaert: Right, people do lots of things that aren't FDA approved.

Craig Blackmore: Yeah, I mean sometimes there's a big registry that includes more than just the knee, and I think for safety purposes if that helped us pin down adverse reaction.

Joann Elmore: Meta-analysis was just of the knee though for adverse reactions.

- Josh Morse: Oh, okay. So, expand the search to include...
- Craig Blackmore: For safety.
- Joann Elmore: For adverse reaction.
- Craig Blackmore: Yeah, not for effectiveness, but...
- Josh Morse: Okay.
- Richard Phillips: Also, since that study was done in 2010, will the new study also look at new technologies that might have emerged besides this for us to characterize?
- Josh Morse: Yes, but in the scoping...
- Richard Phillips: Like if there's a new drug, an osteoarthritis drug, I mean, that's what I was wondering.
- Josh Morse: There is platelet-rich plasma, but we elected not to include that, because it's not the standard.
- Chris Standaert: [inaudible].
- Michelle Simon: What is?
- Chris Standaert: Platelet-rich plasma.
- Michelle Simon: Oh, yeah.
- Chris Standaert: You use it for all sorts of stuff.
- Marie Brown: Right now, it's not being covered probably by any insurance.
- Craig Blackmore: Okay, anything else on here that we need to know? What about...
- Chris Standaert: The cost data would be interesting, because you know when we did this, they said the cost was like \$400? We found out our patients get charged \$5,000 for Synvisc 1 in the hospital? So, I would – which would substantially change the cost calculations there. It's like more than a scope almost.
- Joann Elmore: That's why I don't like cost analysis.

- Josh Morse: Well, we're hopeful we'll have good utilization here.
- Craig Blackmore: Okay. Maybe it's not – maybe it's implicit in this or not, but I think I want to make sure we have any information on repeat injections. I think it's probably implied, but multiple courses.
- Chris Standaert: That would be interesting, yeah, multiple courses.
- Craig Blackmore: Because that's part of the deal, right? You get...
- Chris Standaert: Right, more than one.
- Craig Blackmore: Okay, any other business? Alright, thank you all for your hard work, and we are adjourned.