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Health Technology Clinical Committee Public Meeting

March 18, 2016

Chris Standaert: The phone is limited. So, we're on our micro technology over there so that people on the phone can hear, and if there are issues with communications, someone will have to make that clear so we can make sure everybody has access, as appropriate. We will start with Josh's program updates.

Josh Morse: OK. Thanks, Chris. So, as Chris pointed out, there are a couple things different. The video camera, I understand, will be turned on for the second topic today and not for the morning topic. There is a new communication system. It seems to be working well. There are some functions on it, I don't know that we'll need them but apparently you can mute yourself and some other things, but we would prefer that everything is recorded. So, as a reminder, it's really helpful for the transcriptionist if we state our names, at least early in the meeting so that the person who does listen to this recording and then types it up can identify voices further. There have been some challenges with that lately. So, if we could please state our names before we speak, that would be helpful.

So, I think the slide is up, I guess, behind me, but I'll go from the paper here. So, today's topics are extracorporeal membrane oxygenation this morning, and this afternoon is the re-review of spinal injections.

Chris Standaert: Do we have other screens down... is there a screen down there we can use or there is none.

Christine Masters: They folded them up temporarily while they're trying to correct the audio for the telephone.

Chris Standaert: OK.

Josh Morse: Thank you, Christine. So, the first topic is abbreviated as ECMO. It's a new topic. It was selected by the Health Care Authority directors for

review last year, and that was part of the selection cycle last year. The spinal injections re-review, this was originally a topic that was before the committee in 2011. It was selected for re-review last year based on new literature, which is in the report, along with other literature that has since been published, and it was based on the... the selection was based on that new literature and on some safety concerns that were, at the time, being put out by the Food and Drug Administration.

So, following this meeting, your next meeting is scheduled for May 20th, and the topics scheduled for that meeting, at the moment, are bronchial thermoplasty for asthma and injections, autologous blood injections and platelet rich plasma injections. We have been working on beginning the projects for the fall for November, and right now, we are in the process of working a fecal microbiota plantation topic, and the negative pressure wound therapy for home use topic. So, that'll be in November.

So, for participation for those of you who may not be familiar with the program, we have a website and visiting the Health Technology Assessment website, you can see all of the materials that are published for these meetings and meeting materials in preparation for the meetings. We encourage people to join our stakeholder distribution list and the email for that is SHTAP@hca.wa.gov. That is the state Health Technology Assessment Program @ Healthcare Authority. We notify stakeholders of all changes in publications and schedules and things like that at draft comment periods, proposed topics, key questions, etc. Attendance at these meetings, we invite people to attend. These are all open public meetings, and again, all the meeting materials have been posted for a couple weeks in preparation for this meeting. Anybody may present comments to the committee during our open public comment session later on this morning for each topic, and anyone may, of course, nominate technologies for review, and that is it. So, I'll turn it back over to you, Chris. Thank you.

Chris Standaert: So, our first order of business is going to be to approve the minutes and make a final vote on our coverage determinations from the last meeting. So, if we all turn to page... to our packets, our minutes are in there. That's the green page following Josh's presentation. I know people had to review the minutes.

Josh Morse: We got Dr. Odegard's name in there, this time. Sorry about that.

Chris Standaert: I had a question on one question mark, whether that should be a question mark or a period. Did we straighten out if that should be a question mark or period?

- Josh Morse: Where is that?
- Chris Standaert: On page 3. Other than that, I didn't see anything.
- Josh Morse: OK. Thank you. That is an error.
- Chris Standaert: OK. Correct that. If the committee could look through the minutes, and we can have a motion to approve. Second? Comments on the minutes? Are we good? All in favor of approving.
- Josh Morse: It looks like all approve.
- Chris Standaert: All approve. OK. Next, we move on to our coverage determinations from the last meeting. The first of these is the one on Novocure. We received one public comment from Novocure, itself, with the study that they forwarded, which I believe was part of our report. I'm just double checking now. We did not receive any other comments. Anybody have any points they want to bring up on Novocure or our decision? No? There being no comments, do we motion to approve? Second? So, all in favor of approving our... making our decision final, finalizing our decision, approving our prior decision?
- Josh Morse: All approve.
- Chris Standaert: All approved. And our second decision was on cardiac stents. In two circumstances, so cardiac stents for stable angina and cardiac stents considering drug-eluting versus bare metal stents. I don't believe that we received any public comment about our decision.
- Josh Morse: So, this is Josh. There is one staff suggestion on the... on this, for a change. It's in your... you'll see the decision as published based on your determination first. Immediately behind that, those two pages, you'll see a... it says at the bottom, draft proposed staff changes.
- Chris Standaert: Where are you? What page?
- Josh Morse: Page... you'll see, for the cardiac stents decision, there are three pages and then following that, there is another document that looks the same. It's the same first page, but at the bottom it says draft proposed staff changes.
- Chris Standaert: Alright.

Josh Morse: This does not change anything about the meaning. It just changes the order, trying to make more clear. We had some feedback that wasn't written that it wasn't exactly clear how the staff had typed this up. So, we have a suggested change to try and make it more clear.

Chris Standaert: What is the change? Can you help us with that?

Josh Morse: It's the same information. There are some extra words here. I mean, the new one says, I want to make sure, yeah, it says either drug, I mean, if you want to look in your binder you can compare these. We didn't do this and track changes, as you have asked us in the past to not show it that way. You'll see that we say either drug-eluting or bare metal stents are a covered benefit when stents are indicated for treatment, and we added the parenthetical here, this includes stable angina and unstable angina). We added some space and separated that from the second part, which is that... for patients being treated for stable angina, cardiac stents are a covered benefit, and you have conditions on that piece, and we move the conditions up to tie that together.

Chris Standaert: So, one... yes, and you changed it to conditions to include and give our two conditions, but include implies there may be more than the two we gave, just the use of that word, as opposed to, we said are covered for the following, which is fairly direct.

Josh Morse: Yep, we can remove that. Good catch. We can just remove the whole conditions include and put the colon after the benefit with conditions. OK.

Chris Standaert: I don't know what other people think on the first one, the word either doesn't really seem to matter to me either, drug-eluting or bare metal. I don't know if it makes a difference but I'm fine with the word. Do we... putting includes stable angina, unstable angina, I mean, I don't know if we need to say that or not. I don't have an issue with it. I don't know if we need to say it, because we didn't even really talk about unstable angina. We talked about the stents themselves. What do people think? Do we want to change it or leave it the way it was or add the word either?

Michael Souter: That part of it, I think, it doesn't functionally make a difference, as far as I can read it.

Chris Standaert: So, take out the includes stable angina, unstable angina and just add the word either and we're good?

- Josh Morse: So, remove the parenthetical?
- Chris Standaert: Remove the parenthetical.
- Josh Morse: OK.
- Chris Standaert: I don't get to say parenthetical that often. That's a good word. OK. So, with that slight change...
- Josh Morse: So, we're leaving the word either?
- Chris Standaert: We'll leave the word either.
- Josh Morse: OK.
- Chris Standaert: So, with those two slight changes to the amended language, we will revert to our initial statement for the second one, for the cardiac stents and stable angina, and we'll revert to our initial... our original language... are covered for the following.
- Josh Morse: OK. Thank you.
- Chris Standaert: And then we'll add the word either to our cardiac stent condition, yeah? Alright. Comments? Motion to approve? Second? All in favor of approving? We're good. Now, we can move onto ECMO. Alright, nicely on time. So, we will start with the state agency utilization and outcomes, and we'll move onto public comment before getting to our evidence report. There we go. Dr. Hammond is representing the state agency directors.
- Steve Hammond: Good morning. My name is Steve Hammond. I serve as chief medical officer for the Department of Corrections. So extracorporeal membrane oxygenation, also known as ECMO, is a life support technology that provides respiratory and/or circulatory assistance through devices outside the body. It's one of a broader class of technologies termed extracorporeal life support. We have found that in scoping this topic, we needed to be a little more detailed in our terminology. ECMO can be used for extracorporeal gas exchange with or without circulatory support. Sometimes, it's used primarily to oxygenate the blood, and sometimes it is used primarily to clear carbon dioxide from the blood. Also, it can serve to warm the blood, which in some cases provides significant clinical benefit. ECMO can be distinguished from cardio pulmonary bypass in that typically in the ECMO situation, the heart is still beating, whereas with standard cardiopulmonary bypass, the heart is not. So, ECMO

generally will take blood from the venous system, or always does, and returns it either to the venous system when only gas exchange is needed, or to the arterial system when circulatory support is required.

It's a highly invasive procedure that can sustain life and allow recovery from acute illness, or it can be used in interventions, such as lung or heart-lung transplant to address respiratory and circulatory need during that procedure. It is typically used only in situations with a very high mortality risk, typically 50% mortality risk or higher, and it's used when there's judged to be a reasonable chance of recovery of independent respiratory and circulatory function without that support.

So, here is a diagram of an ECMO circuit. I'm going to use a pointer. I'm not sure which screen, do you prefer which screen I point at, Dr. Standaert? I'll point at the one up front. So, here is, in this circuit, the blood outflow comes from a catheter in the right atrium and then it goes through certain processes, including anticoagulation with fluid, as needed. There's a pump function, and then there's a membrane for gas exchange, both oxygenation and Co2 clearance, and then there can be a warming element, and then in this case, it's a return to the arterial circulation to the thoracic aorta. So, it's a complex technology. It's an extremely intensive and invasive treatment. This is a graphic display. I don't know the details of this case, but it appears that the outflow is from the right atrium with return probably to the thoracic aorta. I'm going to say right now that I consulted a little bit with Dr. Bulger on this topic, because I wasn't highly familiar with it. She suggested that this was probably in the setting of open heart surgery. There are some surgical drains here.

Here is another case of what looks like venovenous ECMO through the internal jugular vein. You can see the apparatus is very complex. This is a case that actually is posted on the internet of a 23-year-old Marine who developed an acute respiratory illness and was Lifeflighted from Japan, first to Hawaii and then to an ECMO center in Iowa. There is a testimonial by the Marine after his recovery, and by his physicians and his mother.

So, when we first approached this topic, we had high concerns with respect to safety, efficacy, and cost. So, we'll look at the utilization data. There have not been many cases, and the data are actually presented in a somewhat obscured way because of concern for identifiability of individual cases, but we can get some important information from these data.

This represents utilization in Medicaid and the Public Employees Benefits Plans, the UMP between 2010 and 2014, and what we see is a rising trend in utilization. From what we could determine from diagnosis coding, a little more than half of the cases were for primary pulmonary diagnoses, including lung transplant and then a substantial portion of the remainder were for primary cardiac diagnoses.

This gives, without detail, the location of these cases. The majority were conducted either at the University of Washington Medical Center and/or Harborview or the Legacy Emmanuel System in Oregon, which serves Southwest Washington. There were a few other facilities in Washington State, and then a couple out of state. There were six centers in Washington State where ECMO is performed.

A little bit more about utilization. You can see the usage extends from 1 to 27 days with an average of 3.5. The cost of the intervention is difficult to determine from administrative data, billing and payment data, but the cost, as best as we can determine, was somewhere between \$1000 and \$5000 per day. In the evidence report, there is an estimate of the cost of ECMO being between \$100,000 and \$500,000 per case. This procedure is carried out in the midst of other intensive care. So, it's difficult to tease out exactly what the cost of the procedure is, but it is costly.

Coverage policy, currently, is mostly covered without conditions, although at the Labor and Industries, prior authorization is required. There is a professional association dedicated to extracorporeal life support, it's called ELSO, and they have developed guidelines and training standards, and I would like to review those just an overview. This is really verbatim from their... and this is in the evidence report, but indications for extracorporeal life support include acute severe heart or lung failure with high mortality risks, despite optimal conventional therapy. ECMO is considered for use in patients at greater than 50% mortality risk and indicated in most circumstances at greater than 80% mortality risk.

There are a number of specific indications listed in the guideline, which is in the evidence report, but a couple of examples are primary or secondary hypoxic respiratory failure or Co2 retention, on mechanical ventilation despite a high plateau pressure. There are also some specific relative contraindications listed in the guidelines. Two examples are conditions incompatible with normal life, if the patient recovers, and chronic organ dysfunction, such as emphysema, cirrhosis, or renal failure.

Also, importantly, the guidelines include some facility and training standards, and one of their standards is that facilities should participate in the ELSO registry. Also, there are a number of specially-trained staff that are required to carry out ECMO and that's addressed in the guideline, as well.

So, looking at the evidence base, the evidence base for effectiveness is weak, and this is not to disparage the research that's been done, but this is not an intervention or a situation that lends itself to tightly-controlled studies, but again, summarizing the evidence for effectiveness, largely repeating what's in the evidence report, there is insufficient evidence to support using ECMO for cardiac support compared to ventricular assist devices. Low quality evidence favors ECMO in appropriately considered case or appropriately selected cases of respiratory failure compared to optimized conventional mechanical ventilation. It is insufficient to support bridge to transplant, as compared to cardiopulmonary bypass, and low quality evidence suggests that extracorporeal CPR, cardiopulmonary resuscitation using ECMO is non-inferior to conventional CPR.

The evidence report notes that there are significant risk of harms related to this procedure, the most common being bleeding and limb ischemia, but these harms must be weighed against the setting in which ECMO is applied and in which there is an extremely high mortality risk, and the high cost, again, estimated to be between \$100,000 and \$500,000 per case, must be weighed against the prospect of full or near full recovery in patients with potential for substantial life expectancy with good function.

So, trying to put this together, and I will say that given the state of the evidence, I also did consult with Dr. Bulger. I ran this by her and she made a couple of suggestions. So, I used expert opinion, as well as the evidence reviewed in the report, but we suggest that ECMO be covered with conditions and suggested these conditions that are listed. I'll go ahead and read them; in appropriately selected cases of respiratory failure with or without potentially reversible circulatory failure or shock or in the perioperative period for lung and heart transplants, or as a bridge to ventricular assist device. Dr. Bulger pointed out that sometimes these devices are not immediately available, and ECMO can be used as a bridge until one can be obtained. For extracorporeal CPR, for in-hospital cardiac arrest, or for extracorporeal CPR in the setting of accidental deep hypothermia. This is using the warming function of ECMO, the warming... that potential feature, and then only at facilities participating in the ELSO registry. From the evidence report, it appeared that coverage in the setting of cardiac support in lieu of a ventricular assist device or for

extracorporeal CPR for cardiac arrest outside the hospital setting other than accidental deep hypothermia, is not warranted. Finally, given the state of the current evidence that we continue to monitor evidence for any re-review that may be warranted in the future.

Chris Standaert: Thank you. Questions?

Kevin Walsh: How did you... what evidence did you use to distinguish between in-hospital and out of hospital cardiac arrest? I don't remember seeing anything that distinguished that in the evidence report.

Steve Hammond: Yes, and I'd invite Dr. Bulger to comment if she wishes to, but the eCPR studies that were done that appeared to be used... be looking at out of hospital arrest showed comparable results with... between ECMO and conventional CPR, but in-hospital, ECMO is more readily available and so may be more effective. So, again, this is a decision that the committee can ponder, but it seemed to make sense, and I have to admit that I don't have strong evidence aside from that, that was reported, to support that.

Chris Standaert: Other questions for Dr. Hammond? Yeah, question?

Carson Odegard: On your bar chart, you know, I assume this is involving technology that is very, very complex, but since 2010, had there been more centers included in Washington State since that time? You mentioned six centers but in 2010. Were there still six centers at that time?

Steve Hammond: The number of cases in 2010 was fewer than six. So, it's, I... I don't know, at that precision of detail, when... there were a couple of centers that had only one case, I believe, and so... and I couldn't tell you what year those were. Sorry.

Carson Odegard: OK. And then one more question, on your pie chart, the other category, would we assume that the others would be the hypothermia cases, or?

Steve Hammond: Uh, no. Those were actually poisonings.

Carson Odegard: Poisonings, OK.

Steve Hammond: But they... they were going from the primary diagnosis for the hospitalization. So, the, we're not sure exactly what the indication was, but presumably it was respiratory failure.

Carson Odegard: OK. Thank you.

- Chris Standaert: Dr. Yen?
- Tony Yen: Two questions for you. The first question is, these agency recommendations, are they for age 17 and greater?
- Steve Hammond: Yes.
- Tony Yen: OK. And the second question, for the first bullet point with the coverage with conditions, can you just give me an example of an appropriate case with respiratory failure without potentially reversible circulatory failure or shock? I just want to have a scenario.
- Steve Hammond: Yes. Well, in some cases the cardiac function is relatively intact, but there is respiratory failure. So, that's...
- Tony Yen: Right, but what I was looking for was a scenario where there is a case of respiratory failure without, sorry, with potentially, sorry, without potentially reversible circulatory shock. I'm sorry. I guess, is it without... I apologize. Is it without having a reversibility of the shock or without circulatory shock?
- Steve Hammond: OK. No. What I meant to say is it's in appropriately selected cases of respiratory failure where cardiac failure is not an issue.
- Tony Yen: OK.
- Steve Hammond: Or in cases with respiratory failure when there is a potentially reversible circulatory failure.
- Tony Yen: OK. Thank you, for letting me understand that.
- Steve Hammond: Sure. Thank you for asking the question.
- Louise Kaplan: I just want to go back to the questions that Carson was asking about. So, in chart one and two, in chart one you give percentage of distribution of the cases, and in chart two if I add it up, there have been 36 cases between 2010 and 2014. So, chart one is effectively saying, of those 36, about half occurred in 2014? Is that the correct way of reading this?
- Steve Hammond: Yes, 52.8%.
- Louise Kaplan: I was just trying to figure that out.
- Chris Standaert: Other questions? No? I'm going to take the opportunity to...

- Michael Souter: One, one last one, sorry.
- Chris Standaert: Yeah.
- Michael Souter: Again, just to be absolutely clear, and this is... the utilization by date, again, that refers to presumably the adult population rather than the pediatric data on hand.
- Steve Hammond: Yes, and it's... it's greater than 17 years old. So, it's really 18 and older.
- Michael Souter: OK. And again, do you have any insight into the... with that utilization data, can that be parsed into the diagnostic categories that they fit into, or are there indications for other, you know, if you think about, um, those, that utilization data in the... with the lens of, you know, your slide on the, on the chart two, you know? I'm interested in basically whether there's a difference in the range experienced by cardiac cases versus pulmonary cases, for example.
- Steve Hammond: You mean age range, or, I'm?
- Chris Standaert: I think he's getting it there, but three-quarters of them done in 2013, 2014 and what kind of conditions are they? Is that what you're getting at?
- Michael Souter: Well, I'm... I'm thinking about the, again, it's utilization data. I mean, is there a difference there that, you know, between, you know, the cardiac group only requires one day? Is there a quick bridge, or is there, you know, the, the pulmonary data? Essentially, is there a difference in utilization depending upon the diagnostic category?
- Steve Hammond: Oh, so you're referring to the duration...
- Michael Souter: Yes.
- Steve Hammond: ...of the ECMO? And I am sorry. I don't have that level of detail, and Chris, I don't know if you have that readily available? No?
- Christine Masters: One of the things we need to be careful about is that there are so few cases and so few facilities that they go to that we not be readily able to identify those individuals. That's why it's kind of put into percentages on one, counts on the other. I can get that information for you. I have that, but that, that would be the concern here with PHI.

Chris Standaert: Questions? I'm going to take the opportunity to introduce our clinical expert, Dr. Eileen Bulger, a professor of surgery at the University of Washington and chief of trauma at Harborview Medical Center, and we appreciate you being here. We appreciate your help. This is a complex technical issue, and we're going to need your expertise at various points, I suspect. I had wanted to give Dr. Hammond a chance to respond to where he derived these from. That's really what the... what we need at that point.

Eileen Bulger: But I can answer a couple of the questions, I think, that were raised. One was around the question of in-hospital CPR, and that's really around two groups of patients, one is the massive pulmonary embolus that happens occasionally in the hospital, particularly in trauma centers after trauma, and there is again not great data in the literature but lots of reports of people being rescued from massive pulmonary embolus if you can bridge them on ECMO and then do a catheter directed thrombolysis. So, that would be one indication of, you know, potential in-hospital cardiac arrest that would be a candidate for this technology. Another would be the patient in the catheterization lab with refractory ventricular fibrillation. Those, again, are patients that are often bridged on ECMO to another more invasive cardiac procedure, like a VAD or some other support system, but those would be the two main cases of really in-hospital ongoing CPR, what you might want to think about the use of this technology.

Chris Standaert: Other questions or comments? We can certainly come back to them. We are on time for public comments.

Josh Morse: Do we have anybody signed up?

Chris Standaert: Do we have anybody signed up in the room? So, this is the opportunity for the public to address the committee and make their thoughts or express their thoughts or considerations on this technology. There is nobody signed up and nobody presubmitted a presentation. If there is somebody in the room who wants to speak, they can. Otherwise, we'll go to the phones and ask if there is somebody on the phone who wants to address the committee.

For people on the phone, you have now been unmuted, and we can hear you, assuming you've unmuted yourself. So, if any of you want to address the committee, please identify yourself so we can do so. Hearing no one, we don't have any public comment, it seems. So, we will move on. We're going to move on to our evidence report from ICER. I'll try to get my slides in line here.

Elizabeth Russo: Hello. Let's see. Is this on? Yes? OK. So, good morning. I'm Elizabeth Russo. Thank you for the opportunity to present this review of the evidence.

ECMO, as you've heard...

Chris Standaert: Can you lower the mic a little bit so we can...

Elizabeth Russo: Is that any better?

Chris Standaert: That's better.

Elizabeth Russo: OK. Thank you. So, as you've heard, ECMO is a form of life support. Sorry. Let me just get to the right slide, is a form of life support that provides cardiopulmonary assistance outside of the body for reversible indications. It is used to support lung function for severe respiratory failure or heart function for severe cardiac failure, and it has been a well-established treatment for infants with lung and heart failure, but early studies of ECMO in adults showed poor survival rates.

In 1979, Zapol's study of adults and respiratory failure treated with ECMO compared to mechanical ventilation found similar low survival rates in both groups, and this effectively suspended a lot of the enthusiasm for adult ECMO, but since 2000, there have been technological advancements that have improved the safety of the device and broadened its application and some of these advancements include heparin-coated cannulae, new oxygenators, more efficient pumps, a smaller size such that fewer specialty staff are required to operate the apparatus, and although it's not a technological advancement, the 2009 H1N1 pandemic increased the demand for ECMO for adults with respiratory failure that was presumably reversible. So, this changed the ECMO landscape.

ECMO, itself, is comprised of different circuitry, including venovenous ECMO, (VV) ECMO for pulmonary support where the blood is externally oxygenated. Veno-arterial ECMO where the blood is externally oxygenated but also augmented, the blood... it augments the blood pressure to support cardiac failure in addition to pulmonary failure. There is also a category of other external gas exchanges that do not have the pump function but still remove carbon dioxide. So, extracorporeal carbon dioxide removal. They provide ventilatory support and are referred by a diverse nomenclature, including ECCO2-4, pECLA for

pumpless extracorporeal lung assist, and iLA, the interventional lung assist, and this review examines all three types of circuits.

OK. So, this is a depiction of ECMO circuitry, similar to what you've seen in the prior presentation. On the left, we have the femoral artery removing, let's see. I want to make sure I say it right. We have the femoral vein, yes. It's the femoral vein removing blood, deoxygenated blood going through the pump oxygenator and returning to the femoral artery where it is bypassing much of the lung's role in circulating the blood. Whereas, on the right, VV-ECMO is removing blood from the internal jugular vein back through the oxygenator and returning it to the femoral vein where the blood is responsible for circulating that newly-oxygenated blood. Often, another additional cannula is inserted in the lower extremity to support oxygenation of the lower extremity, if it's being bypassed from this blood circuit.

The key questions that we examined in this review are: 1.) What is the comparative clinical effectiveness of ECMO versus conventional treatment strategies in adults. 2.) What are the rates of adverse events and other potential harms associated with ECMO compared to other treatment strategies. 3.) What is the differential effectiveness and safety of ECMO according to sociodemographic and clinical subgroups? Some of them are named in more specifics on that slide. 4.) What are the costs and potential cost-effectiveness of ECMO relative to conventional treatment strategies? Sometimes I can't advance the slide, I'm sorry. OK.

The project scope focused on the population of adult patients with severe respiratory and/or cardiac failure. The intervention included venovenous or VV-ECMO, venoarterial, or VA-ECMO, as well as the pumpless extracorporeal ECCO devices.

The comparators included conventional intensive care management with endotracheal intubation and ventilation, ventricular assist devices (the VADs), and cardiopulmonary bypass used in the operating room setting.

The outcomes of interest included these you see here: All-cause mortality, length of hospital stay, survival to discharge, disability, device-related complications, health-related quality of life, and cost/cost-effectiveness.

We limited the timing of... the timeframe of the literature review from the year 2000 to account for the technological advancements we discussed earlier, and the study designs included randomized control

trials, observational studies, both comparative cohort and case control trials, and case series of more than 150 patients. We also used the USPSTF criteria to assign quality ratings to the publications we examined and discuss here the good quality studies only.

I'm sorry about this slow slide. There we go. So, initially, we identified 3600 references after title abstract screening, 274 remained, and after a full text review, 97 remained, of which 2 were RCTs (randomized control trials), 41 were comparative cohort trial publications, and 54 were case series.

Overall, this growing evidence base is made up mostly of comparative studies, which have diverse patient population, disease entities, different settings, different technologies were used, and all of these factors limit the generalizability within and across the studies. There were differences in standards of care. Again, the device technologies differed. Clinical decision making about how to identify eligible patients for ECMO differed. Patient characteristics differed, and there are some inherent challenges with retrospective study designs, which were the case in several of these studies. There were two RCTs, both of good quality and as has been mentioned in the prior discussion, there are ethical concerns with holding the controlled population to a very rigorous prescribed treatment regimen. So, there are definitely challenges with RCT trial design in this intensive care setting, but we will discuss these two RCTs; 16 of the 41 comparative studies were of good quality, and we will discuss those, as well.

I think if I point here. OK. Key question one asked, what is the comparative clinical effectiveness of ECMO versus conventional treatment strategies in adults, and this is a chart that divides the evidence into four different clinical indications. The first is for cardiac support, ECMO used for cardiac support. The second ECMO used in pulmonary support. The third ECMO is used as a perioperative bridge to transplant, either lung or heart transplant. The last is ECMO used for extracorporeal CPR, cardiopulmonary resuscitation.

The strength of evidence for these indications is highlighted in yellow, and all of the indications, except for pulmonary support, had a low strength of evidence because of the limited evidence base. ECMO for pulmonary support was given moderate strength of evidence because again, the bulk of the evidence we reviewed was for this clinical indication, and we will present these findings by clinical indication.

So, first ECMO for cardiac support. There was only one study of good quality that compared ECMO to miniaturized percutaneous ventricular assist device, or mini-VAD. It used a retrospective chart review of 79 adults who were hospitalized with cardiogenic shock, and in this study, ECMO showed no benefit for any of the following: Weaning from mechanical support, in-hospital survival, and bridging to long-term support or transplant.

And now, transitioning to ECMO for pulmonary support, there were two RCTs and six observational studies of good quality that compared mechanical ventilation to VV-ECMO or VA-ECMO or ECCO, and the first, Bein et al, was an RCT set in Germany and Austria in 2007 to 2010 where 79 adults with ARDS received either AV-ECCO or conventional low tidal volume ventilation, and there was, at 60 days of follow up, no statistical difference in the following outcomes: Mortality, organ failure, days without ventilation, length of hospital or ICU stay between the two groups.

The next RCT is the CESAR trial by Peek, et al, which you have likely heard a lot about. This is a trial that was set in the U.K. in 2001 to 2006 where 180 adults with respiratory failure received either VV-ECMO at one treatment site or conventional low tidal volume ventilation at a number of other hospitals where sort of best clinical practice was executed in that center. There was no mandated management protocol for the conventional treatment group whereas those that were transferred to the ECMO hospital had uniform institutional protocols. The authors of this study point out, this is... this is definitely a limitation in the study design, but the authors point out that this “pragmatic” RCT design was essential in order to be able to do the study and, in fact, if they had tried to prescribe the best practice for the conventional arm, it would have prevented those clinicians from accessing whatever new developments came on the scene in the time of the trials. So, this is a limitation. It falls short of the gold standard of an RCT but sort of given the clinical setting, the clinical realities, and the ethical challenges, this remains one of our good quality studies. So, at six months of follow up, their primary outcome, a composite outcome, showed less mortality and severe disability with ECMO compared to the conventional treatment arm. This outcome, when it was separated as just mortality or just severe disability, did not show a difference, but the composite outcome, which was their primary endpoint, did show an outcome difference. There was also longer median hospital stay with the ECMO patients, and it’s not clear how this accounts for mortality differences.

So, of the six observational studies that were of good quality that examined this clinical indication, four found lower in-hospital mortality for the ECMO treated patients than the comparator groups. Four studies reported on the length of hospitalization and found comparable or longer hospital stays with ECMO. There remains an inconclusive impact on morbidity, disability, and quality of life, although there was a trend towards improvement in the CESAR trial that examined quality of life, but all of those indicators did not reach statistical significance. So, just to kind of recap the pulmonary support clinical indication, neither RCT showed an independent mortality benefit for ECMO.

So, moving on to ECMO as a bridge to transplant. There were three observational studies of perioperative ECMO as a bridge to heart or lung transplant compared to not using ECMO or using cardiopulmonary bypass. The ECMO recipients had similar or higher mortality post-discharge and the in-hospital mortality data was inconsistent. ECMO was associated with decreased hospital stay, but this too may have been skewed by higher mortality. Disability, health-related quality of life, and other functional outcomes were not examined in these studies.

So, the fourth indication, ECMO for a cardiopulmonary resuscitation, was described in five observational studies, whereas the previous studies were set in North America and Europe, these five studies were all set in East Asia. These studies used retrospectively analyzed data and found inconsistent results on mortality. Four of the five reported improvement for in or out of hospital cardiac arrest that then waned after later follow up in three of the studies, and the one study that reported follow up at two years reported a sustained mortality benefit.

There was no significant difference in the length of hospitalization in the one study, which examined length of stay. Lin, et al, reported better neurological outcomes within the ECPR group at discharge, and again, this difference disappeared at three months. Sakamoto reported better neurological outcomes up to six months of follow up.

The second key question asks about rates of adverse events and other potential harms associated with ECMO compared to conventional treatment strategies and the major three harms that emerged from the literature review were, as you've heard already, bleeding, limb ischemia, and cannulation site complications. The bleeding is most attributed to the anticoagulation needed for the externally circulating blood. Limb ischemia results from the cannulation set up, and the cannulation site complications are as they would be for any type of invasive procedure involving cannulation. So, the strength of evidence for these harms is

shaded in yellow. The evidence base is consistent and of moderate to high strength to evaluate these harms. So, more broadly, the description in the literature of all types of harms associated with ECMO is limited by several factors that are listed on this including that harms, in general, are under reported in most studies. There aren't usually ratings of the severity of the complication. Most studies are under powered to detect differences between the two arms or the comparator group does not report complications. There is high variability in how the available estimates correlate between adverse events and the duration of follow up, and there is insufficient evidence to evaluate whether complications differ by indication or by type of ECMO.

So, the chart on this slide and the next summarize the harms by clinical indication. The most common harms, again, are bleeding, limb ischemia, and cannulation site complications on the three most columns, and the broad range of all complications has a broad range of incidence, which is typical for studies that report all types of complications. The bleeding harm ranges from 2.5 to 25%, limb ischemia from 2.5 to 7.5%, and the cannulation site complication from 1 to 23%, and this is the continuation of that chart showing bridge to transplant and CPR, and these are nine comparative studies that described complications.

Key question three address the differential effectiveness and safety of ECMO, according to sociodemographic in clinical subgroups and the three major groups identified in the literature review were age, gender, and dialysis status. The evidence was limited for its treatment in all subgroups and highlighted in yellow we show low strength of evidence for all three of these.

There is insufficient evidence on differential effectiveness for ECMO use according to race, ethnicity, disease severity, setting, time of initiation, duration of time on ECMO. Regarding age, the CESAR trial found no difference between the treatment groups, between ECMO or conventional ventilation and treatment by age group, and the evidence is inconsistent to determine whether age is an independent predictor of survival.

Regarding gender, neither RCT evaluated the role of gender on ECMO related outcomes, but four of the five comparative cohort studies that did, did not find gender to be an independent predictor of ECMO. Renal replacement therapy, or dialysis status, was found by Tsai not to be a predictor of survival to discharge for the ARDS patients who received ECMO. However, the ELSO registry data, which you've been introduced to... ELSO is this voluntary... it's an organization that collects data from

centers that use ECMO who voluntarily sign up and report their use of ECMO, and they publish case series of outcomes. So, their registry data showed that RRT and dialysis are associated with high mortality among ECMO recipients.

Key question four addresses the costs and potential cost-effectiveness of ECMO relative to conventional treatment strategies. The cost-effectiveness data for ECMO is limited to two studies in non-U.S. settings giving low strength of evidence assessment shown highlighted in yellow. So, these two, again non-U.S. based studies, where costs are often lower than in the U.S., described first in the CESAR trial, cost-effectiveness of VV-ECMO in adults with respiratory failure. They found a mean cost per patient of \$65,000 more than in the conventional treatment arm in 2005 U.S. dollars. At six months, the cost-effectiveness exceeded 2 million dollars per QALY gained, and when that was extrapolated over a lifetime, which there are some implicit assumptions with doing, that cost decreased to \$31,000 per QALY gained. In Canada, St. Onge described cost-effectiveness of VA-ECMO in adults with cardiac arrest, or cardiotoxic induced shock, and described an incremental cost per life year of \$7000 in 2013 Canadian dollars, assuming 100% survival for cardiac arrest and 83% survival for severe shock, and when lower survival estimates were used, the incremental costs per life year changed to \$34,000.

Some U.S. studies that were not of the same quality described first charges by Maxwell and then costs by Sauer. So, Maxwell described resource use trends in the U.S. for critically ill adults treated with ECMO using the nationwide inpatient sample database. They described average charges per admission of \$344,000 with a mean total cost increase from under \$200,000 per patient to almost \$500,000 per patient, and I'm sorry. I said cost, but I should have said charge. The total charges were highest for patients with heart transplant, \$700,000, and lowest for patients with postcardiotomy indications. Sauer used the same database with some different statistical methods over a similar time period, and estimates cost as median costs per patient of \$120,000, and part of the reason there is differences in these two monetary values is one is using charges, one is using costs. There are different statistical methods and ICD-9 codes may have changed between the two studies.

So, having presented the clinical effectiveness and cost-effectiveness review, we will integrate that assessment in the integrated rating matrix, which plots clinical effectiveness on the Y-axis, comparative value across the X-axis, and given that the evidence base is either insufficient to make a proper comparison or demonstrate comparable health benefit, the

ratings mapped to this C row at best. These evidence ratings reflect a value judgment based on the available evidence. Overall, there was no consistent benefit on survival, days in hospital, or disability, and no consistent evidence that harms differed from conventional management. For cardiac support, comparing ECMO to mini-VAD, we assigned a rating of insufficient evidence and low value. For pulmonary support, comparing ECMO to mechanical ventilation, we assign a rating of C+/C because the majority of the studies showed reduced mortality with ECMO over the short term. As a bridge to transplant, ECMO versus cardiopulmonary bypass was assigned a rating of insufficient evidence and low value, because of the inconsistency across studies. For cardiopulmonary resuscitation, we assigned a rating of C, because the benefit/harm tradeoffs appeared similar and relatively consistent across studies. So, ECMO appears to introduce substantial incremental hospital costs compared to alternative means of cardiac or respiratory support. We consider ECMO to represent a low value in all indications, albeit that ECMO has a clinical role to play in certain clinical settings; however, the evidence base is not sufficient to support a broader conclusion.

The clinical practice guidelines, some of them you've already heard about, including ELSO, the Extracorporeal Life Support Organization, which again is this voluntary consortium of centers that use ECMO. ELSO recommends acute heart/lung failure be the primary indication for using ECMO when there is a high anticipated mortality risk, that it should be used in tertiary centers with tertiary level adult ICUs in centers that can support a number of cases a year, that participate in the registry, and that training and certification be sufficient to support this highly skilled technique.

The American Heart Association believes that ECPR may be considered when time without blood flow is brief and cardiac arrest is reversible or pending heart transplant or revascularization in patients who are younger than 75. The American Thoracic Society suggests that ECMO should be applied selectively by experienced, well-supported centers to patients with disease that is not responsive to other therapies. NICE, which is the National Institute for Health and Care Excellence in the U.K. find adequate evidence for both cardiac and pulmonary use of ECMO when patients are likely to recover spontaneously, as opposed to situations where the life expectancy may not extend beyond six months regardless of the treatment.

So, payer coverage policies, we did not identify any national or local coverage determinations for ECMO in adults from the centers for Medicare and Medicaid services. AETNA covers ECMO for adults at high

risk of death with reversible causes of respiratory or cardiac failure, unresponsive to other measures. Premera and the Regence group cover ECMO for treatment of cardiac or respiratory failure that is potentially reversible or as a bridge to heart or lung transplant.

There are several ongoing trials. The most exciting of which is this one that I'm really interested to see what it shows. It's called the EOLIA trial, the extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. It's being conducted in France. Its estimated primary completion date is just recently, February 2016, with an estimated enrollment of 331 patients followed for at least 90 days who were randomized to either receive vv-ECMO or standardized ARDS management in the comparator arm, and the primary outcome measure is all-cause mortality on day 60.

So, that is the conclusion of our evidence review. I'm happy to try to address questions.

Chris Standaert: Thank you, Dr. Russo.

Elizabeth Russo: Yep.

Chris Standaert: I know there's a... we need to give the committee an opportunity to ask you questions about your report and presentation.

Kevin Walsh: Can we go back to slide 38, please? Can you go over, again, why pulmonary support is given comparable or better rating?

Elizabeth Russo: As opposed to?

Kevin Walsh: Insufficient or comparable?

Elizabeth Russo: So, again, this is a judgment call, and I think it's open to interpretation. I... so the question is, why comparable or better versus insufficient?

Kevin Walsh: Yes.

Elizabeth Russo: OK. It's hard for me to nuance the answer, partially because I think when you look at all the evidence and you think how hard all these researchers are trying, you want to give some benefit of the doubt. So, I think there's, there's something about that, and there, the, the peak CESAR trial did show improved mortality benefit, albeit in a composite outcome. So, if that is sort of the highest level of evidence, and it's supported

somewhat by some of the comparative studies, it swayed us towards comparable or better.

Kevin Walsh: So, I want to go back to, uh, Page ES19 in the study, in the report.

Elizabeth Russo: OK.

Kevin Walsh: Which says that neither RCT showed an independent mortality benefit for ECMO.

Elizabeth Russo: That's right.

Kevin Walsh: And that while Peek described a comparative outcome, which was improved for ECMO patients, the study was not powered to detect differences in survival alone and indeed did not.

Elizabeth Russo: That's right.

Kevin Walsh: I'm struggling with that statement and your interpretation that it shows benefit.

Elizabeth Russo: So, it did show a benefit for the composite outcome, which includes mortality. You're saying, you're saying exactly the same, I mean, what you're saying is exactly true. So, it didn't show an independent mortality benefit, but it did show a mortality and severe disability benefit. So, it's whether or not you determine that composite outcome to be... to sway you towards comparable or better, or if you are more purist and want to parse it separately.

Chris Standaert: Yeah, Dr. Schwartz?

Seth Schwartz: Yeah, this is Seth. So, a follow up to that question, I think back on slide 17, looking at the Bein trial, I'm curious, it's... there were no statistically significant differences, but that seems like a relatively small trial. So, I'm curious... it sounds like it might have been under powered. So, if it was under powered, what was the raw data at least? What was the?

Elizabeth Russo: You mean the numbers?

Seth Schwartz: Yeah, the numbers. Do we have that?

Elizabeth Russo: OK. So, the... and the numbers are presented in, do you want me to show it to you on ... I think I have it on a slide. Do you want to see it here?

- Seth Schwartz: Yeah.
- Elizabeth Russo: OK. I think it's an additional slide. Of course, it's too small to see. Let's see.
- Chris Standaert: The slide is in the binder, yeah, in the back.
- Elizabeth Russo: It's also in the back. That's true, it is in the back, and I have it printed here, too. So, um, the primary outcome, so... this is another interesting thing. So, in Bein et al, the primary outcome was days without assisted ventilation. It was not mortality. So, it was... the trial was designed to look primarily at how many days patients could be off the ventilator. So, those top outcomes are all discussing that, but the in-hospital mortality was 17.5% versus 15.5%, very similar. And you are correct that even the primary outcome did not reach significance either, so.
- Gregory Brown: Can we clarify what the primary outcome was for the CESAR one again? It was combined?
- Elizabeth Russo: CESAR was the composite outcome of mortality plus severe disability.
- Gregory Brown: So, as the primary outcome, that would be, then, what was used to power the study.
- Elizabeth Russo: Yes.
- Chris Standaert: Dr. McCulloch.
- David McCulloch: David McCulloch, and this is... slide 29, and this may be a question for the clinical expert. It just jumped out at me as being not what I would have expected to say that, you know, limited and conflicting evidence suggests that older age predicts survival and positive neurological outcome. Is that because the conditions result in the patients being given ECMO are different than in younger... because I... I just... I, I would have thought in general, younger patients would do better than old. It's hard to know the older patients predicted survival. Would you mind commenting?
- Eileen Bulger: Yeah. So, I just think there's insufficient evidence with age.
- David McCulloch: OK.
- Eileen Bulger: I mean, nobody's really looked at older patients. Most people don't put very old patients on, because again...

- David McCulloch: Right.
- Eileen Bulger: ...it has to be a reversible condition.
- David McCulloch: Right.
- Eileen Bulger: Most of the people you would consider putting on are relatively young people with a reversible viral pneumonia, or...
- David McCulloch: OK.
- Eileen Bulger: ...you know, other issue of reversible ARDS. So, I don't think there's just not enough data to answer that question.
- Elizabeth Russo: And I should say that I think the wording of this is misleading. I think it's meant to be much more neutral. I mean, you could say survival or you could say mortality, if you think of survival being the inverse of mortality, but you're absolutely right. All of the case series suggest that younger patients do better.
- Louise Kaplan: A question about... on some of the key question summary slides, you have the column risk of bias.
- Elizabeth Russo: Yeah.
- Louise Kaplan: So, there are different types of bias. So, what type of risk... what type of bias are we considering?
- Elizabeth Russo: Mostly study design.
- Louise Kaplan: OK.
- Chris Standaert: And I had a question on the risks and harms. And what I'm trying to wrap my head around is a comparative risk. I mean, I assume these are done in people where the risk of not intervening with some type of critical care intervention is death. So, something is going to happen to most of these people, and I understand the risks you present, but I'm curious about them and realize that the randomized trials are tricky, but in terms of relative complications for intervening in people with severe illness with pending death from cardiac or respiratory failure with critical care interventions, are these out of line with the risks of other approaches that may be taken?

- Elizabeth Russo: That's, I mean, that's an incredibly good point, especially if... so, limb ischemia is a complication, but if the patient dies do we know if the patient had limb ischemia? Maybe not. So, there is... so basically... so, it's a fraught issue.
- Chris Standaert: So, you don't have data on sort of general complication rates of treatment of...
- Elizabeth Russo: Of critical care?
- Chris Standaert: ...severe cardiac or pulmonary illness in the ICU and what...
- Elizabeth Russo: Only in as much as it would have been reported in the studies. So, if they reported differences between bleeding complications in the two arms, that's where that data comes from in this report.
- Michael Souter: I just want to, sorry. OK. This is Mike Souter again. I want to go back to the Bein study again. My impression on reading that Bein study was that, in fact, the study was limited. They did actually have a different target study population number, and they were kind of closed down by their data safety monitoring board who decided that they weren't actually making enough progress. So, they limited the study, period, which limited their ability to get to their population required to attain decent power. Is that true?
- Elizabeth Russo: I'd have to re-read the same section, and I don't know if, Patty, you remember? OK.
- Seth Schwartz: This is Seth again, I'm trying to wrap my head around the outcome measure for the CESAR study, and maybe you can help me with this a little bit. So, they're looking at a composite... no, they're not looking at mortality. They're looking at some composite of length of hospital stay and mortality?
- Elizabeth Russo: No, survive, like, mortality plus severe disability.
- Seth Schwartz: Plus severe disability, that's the composite is... for this?
- Elizabeth Russo: Mm-hmm.
- Seth Schwartz: OK. So, it seems like they did not find a significant difference in terms of survival, but patients... but the length of stay in the hospital was significantly longer. So, just to understand the setting, am I seeing that people are basically... they're on ECMO for longer but then still die?

Elizabeth Russo: Well...

Seth Schwartz: In other words, ECMO is keeping them...

Elizabeth Russo: ...I don't think the length of stay...

Seth Schwartz: ...alive for additional days, but they're still not, they're still dying in the hospital. That seems like it's not... it may look like they're living longer, but it still may not change what the outcome really is. So, I'm just trying to understand what's actually happening to those patients.

Elizabeth Russo: I agree that the length of stay outcome is confusing to interpret, because it's not clear whether it means that you kept somebody on ECMO for longer but then their ultimate survival was not changed? I did not see that outcome try to tease apart the mortality and length of stay. Those two outcomes I did not see any attempt to interpret one from the other, but I don't think length of stay means length on ECMO either. So, somebody could have been on ECMO for less, you know, fewer days than they were in the hospital, most likely.

Seth Schwartz: No. I understand. I guess I'm just trying to see...

Elizabeth Russo: Yeah.

Seth Schwartz: ...is ECMO simply prolonging the inevitable in those patients.

Elizabeth Russo: That's exactly the question.

Seth Schwartz: Yeah.

Elizabeth Russo: Yeah.

Seth Schwartz: And it's not clear from this data. Is that...

Elizabeth Russo: Well, I mean...

Seth Schwartz: ...not clear?

Elizabeth Russo: ...by six months there was, there was an improvement in survival plus severe disability. When you take away one or the other, that difference goes away.

Michael Souter: I think this is an important thing to understand, though, and I'm sure that, you know, Dr. Bulger will chime in on this, as well. I can see your

hand up, but I think, you have to be very careful about using mortality on its own as a discriminator, particularly in critical care studies when there may be secondary decisions to limit care based on what the discernible quality of life or functional status for the patient may be. In other words, there may be decisions made either by physicians or families or a component of both to actually intervene in someone's hospital stay and say OK, well actually we're going to limit care now based on that. That's one of the things that's always very difficult to assess in any critical care study, how much is withdrawal of care a facet in that particular component. So, it's not an unusual approach to actually combine mortality associated with, you know, severe disability numbers in there because that does give you a sense of what's truly important at the end of the day to families, but Dr. Bulger had her hand up. So, she obviously wants to comment.

Chris Standaert: Do you want to comment on the study? Is that what?

Eileen Bulger: Yeah. I would appreciate the chance to comment. I think I would absolutely echo what you just said and that is that the most clinically relevant endpoint is not surviving to hospital discharge, which is most previous studies have been based on. It's surviving with functional neurologic outcome. So, the fact that they looked at that at six months and showed a significant improvement is really important, and I don't have the numbers to break it out and show survival alone. It's not powered that way, but I think from a clinical perspective, if you're looking at, you know, what therapy am I going to choose for my patient or my family member, it makes a big difference to know that there is a potential improvement in not only survival, but clinical function, neurological function six months later. So, I think it's a very relevant endpoint. The Bein Study, I think is under powered. I think it also does not look at ECMO really. It looks at extracorporeal Co2 removal, which is not what most people in the U.S. are using. So, it's not a totally great comparator either. So, I don't put much stock in that trial. So, in my mind, the really only strong randomized evidence we have is the CESAR trial, and it is only one trial, but it is, I think, what is probably tilting that estimate to more favorable on the rating scales.

Elizabeth Russo: The other thing that I should just maybe mention is that when they did look at the mortality by itself, it was in the same direction. So, fewer people died in the ECMO group than, I mean, obviously, but it's not like the relationship became a different direction when they separated out the... it's just that the confidence intervals overlap, and just as you've said that they wanted to have a meaningful outcome. So, it didn't have people surviving in a way that was undesirable.

- Chris Standaert: It looks like on that slide...
- Kevin Walsh: So...
- Elizabeth Russo: I thought he was going to say something.
- Kevin Walsh: Go ahead.
- Chris Standaert: OK. It looks like on the slide you have up there, you have that death or severe disability at 37 for ECMO versus 53 for ventilation with a $p=0.03$, and then death and mortality alone is 37 versus 45 with a $p=0.07$. So, as a trend, is it not valid? Is it under powered? It all sort of bounces around in there?
- Kevin Walsh: Help me understand the difference between the... the differences between ECMO and ventilation for the severe... for death or severe disability, which is 37% for ECMO, 53 for ventilation, and then when you get down to overall health status, which is a patient reported number, the difference between ECMO and ventilation is almost gone. So, does that mean that clinicians are determining less disability than patients are?
- Chris Standaert: Those are the people who are still alive. So, you have to, I assume, they're a composite of or a reflection of that and mixed with the mortality data winds up with some statistical significance.
- Patty Synnott: If I could just follow up on the question about the Bein study, it's exactly as the panel members said. The enrollment was restricted after an interim analysis by the data safety monitoring committee determined that it was not likely to reach distinguishable differences.
- Michael Souter: That's always a speculative gamble, I think.
- Chris Standaert: Is it terminated because... usually when you terminate a study it's because you decide that you have a clear benefit or a clear harm.
- Patty Synnott: They limited enrollment to strictly three years.
- Chris Standaert: To what?
- Patty Synnott: To three years.
- Chris Standaert: OK. Yeah, Louise?

- Louise Kaplan: I just want to touch back on something that Dr. Bulger just commented on and something that you commented on in your slide on the quality of the evidence and you addressed the, uh, variability within and across the studies, and so what I heard Dr. Bulger say is that the CESAR study is the one that uses the technology most comparable to what's used here in the U.S. So, and I noticed that so many of the studies were done in Germany, France, Italy, Taiwan. So, is her statement a reflection of the specificity of the technology that the CESAR study is the one that is most like what is used in the U.S. or are there other countries that use technology that would be comparable, or the same? I don't know how much they vary between countries and what type, and also because this covers such a long period of time how the technology has changed from study to study.
- Elizabeth Russo: Dr. Bulger, you probably can speak to this just as, I mean, better than I can, but I think, I mean, I think this evidence base reflects what has been published, and there just... there's not a lot of U.S. based studies.
- Eileen Bulger: Yeah. I think the challenge is, as you allude to, is the technology is sort of rapidly evolving, and the most comparable would be anything that's got... that's an extracorporeal membrane oxygenation system with a pump, so not the extracorporeal Co2 removal systems, which most people in the U.S. are not using, but the important thing to recognize is, it is rapidly evolving, and that's why you're seeing increased use because of safety, like the harm data that we talked about, the heparin bonded circuits that allow you to use lower levels of anticoagulation that you did in the past, which reduces the bleeding risk. The limb perfusion issue has been recognized, and so now everybody puts in a perfusion catheter into the limb if they put in a femoral arterial line. So, the limb gets its own perfusion. So, a lot of those safety things that have been reported in the studies, I think people have adapted the technology to, and have improved the safety. So, with improving safety profile, stronger data in adults that there is potential benefit, then there is increased clinical adoption of the technology, and that's... I think that's what's being reflected in the ELSO data, as well.
- Carson Odegard: Yeah, I have a question on slide 34 and 35. The Maxwell study looked at data over an 11-year period and stated that the costs had risen from \$2000 to \$5000 per patient, average about \$350,000 a patient. Yet, the CESAR trial states that the costs, the average costs or mean cost, is \$65,000 more than the conventional treatment. So, are we to assume that the conventional treatment is somewhat comparable to, you know, minus \$65,000 on average than ECMO, or how do you, when you have such a wide, you know, difference in costs, how do you, how did they come up with the \$65,000 higher costs than conventional treatment?

Elizabeth Russo: In order to answer your question, I would have to kind of reread the methods for how Peak study generated their data. I agree that it's not satisfying to have these numbers that are desperate, but, I mean, I can try to rearticulate what their methods were, or maybe if Patty could help me do that.

Chris Standaert: We'll take a break in a few minutes and if...

Elizabeth Russo: OK.

Chris Standaert: ...you could look at it during the break...

Elizabeth Russo: Sure, yeah.

Chris Standaert: ...and answer his question when we start, that'd be great. I have one other question on hypothermia, so the agency directors called that hypothermia as a discrete thing, and you didn't talk about hypothermia. Is that tied into the CPR issues, or is there a whole separate indication for ECMO using the warming feature as a treatment of hypothermia that you either didn't capture in your data or didn't go looking for. I'm just trying to figure out if that was...

Elizabeth Russo: No, you're...

Chris Standaert: ...was that within the scope of what you were looking for or was that not in...

Elizabeth Russo: ...I mean, it would have been...

Chris Standaert: ...the scope?

Elizabeth Russo: ...captured if, you know, the search terms included extracorporeal... any of those extracorporeal devices, but we did not use hypothermia as a search term. We did not exclude studies because of, you know, because they addressed hypothermia. We were looking at any indication.

Chris Standaert: Specifically for cardiac or pulmonary arrest, or?

Elizabeth Russo: Well, the... the patients had to have respiratory or cardiac arrest, but that would still, I mean, if you had... if they had hypothermia they could still have respiratory or cardiac arrest, but it's true that these studies did not, maybe they weren't, that wasn't the focus of the studies, and it wasn't parsed out. I don't know, Patty. Do you have anything else to add to that regarding the search strategy?

- Patty Synnott: I would just say that we encountered it more in case reports than specifically called out in the comparative literature.
- Eileen Bulger: I would comment that it's basically replacing cardiopulmonary bypass, which traditionally has been used for active rewarming, which, this is must faster to institute and much safer to institute with the risks. So, clinically, we've just... people have just adopted it for that use, because other, your other alternative is cardiopulmonary bypass, but there's not great studies. There's just case reports, I think.
- Chris Standaert: Yeah, and my, and my question is rewarming when we're using ECMO within the scope of our evidence base and our decision or if we're strictly looking at cardiac or respiratory failure. Then we wouldn't be addressing strictly using it as a rewarming measure for hypothermia.
- Elizabeth Russo: It's a good distinction. We did not make that distinction. So, you'd have to decide.
- Louise Kaplan: In line with that, there were the three cases that were poisonings. So, where did the poisonings fit in? That was that other category. So, where does poisoning fit in?
- Chris Standaert: Well, if it led to cardiac or respiratory failure, maybe that's it. I don't know if the ECMO was used as a cleanse, like a dialysis or a cleansing-like device I wouldn't think. I guess one would assume they developed cardio or respiratory distress. No. That's a good question. Other questions? We certainly can come back and act... ask Dr. Russo more.
- Carson Odegard: One other clarification, just on 41 you said the American Thoracic Society was 1997 and...
- Elizabeth Russo: Was what?
- Carson Odegard: ...1997 is the date you have listed and just in light of our recent discussion about changes in technology, that's really the most recent guideline that they have?
- Elizabeth Russo: I'll double check.
- Carson Odegard: OK.
- Elizabeth Russo: But that's what I have, yeah.
- Joann Elmore: Do you want me to ask my question after the break?

Chris Standaert: No. You can ask your question.

Joann Elmore: OK. Is this on? OK. So, we have two RCTs. One, we've decided the Bein is technologically not relevant and they've stopped it and it was underpowered. So, that leaves us with the CESAR trial. And it's an interesting study design, pragmatic clinical trial. It had to be, and I doubt there's an answer to this question, but it's the following. All of the ECMO was done at a really good center. They flew people, the patients there, and there were over 100 outlying hospitals and centers that had IRB and that... you know, they tried to enroll their patients and then they would call a central group and if a patient at one of these sites was eligible, then they would randomize. You either were stuck at your little hospital or we're flying you here to the specialty place, and they did carefully describe how, well, we did use different doctors to take care of the regular ICU patients at this really good centralized hospital that does ECMO, but here's my question. When you have a specialized center that has ECMO that really knows how to do it, they've got great docs, great specialty, and so do we have data for this one hospital, and I'm thinking of, you know, Dartmouth Atlas, variation in quality among hospitals. Do we know, for example, for the year before, the outcomes of patients in the ICU at that hospital versus these hundred other hospitals, because what amount of the differences that were found in the ECMO patients is because of the hospital itself not the ECMO?

Elizabeth Russo: So, I mean that is such a great question, and I was just reading a Health Technology Assessment that they produced. So, where they kind of, they articulated their reasoning for the study design in more detail, and one of the things that they did to try to address this question was say that kind of like the suggestion that the three cardiothoracic surgeons at that center who were sort of zealots for ECMO would have provided superlative conventional intensive care compared to the intensivists in the other hospitals is flawed. That, in fact, they are ECMO specialists and might have even introduced some kind of conflict of interest for that same center to be providing care in both arms, and that there are so many nuances in decision making and so much decision making within conventional care that to sort of short change the clinical expertise of those other intensivists, wouldn't actually be helpful. And I guess there was some background study, which I don't know the details of that background study, but they said that it has not been shown that cardiothoracic surgeons provide better intensive care than noncardiothoracic surgeon. So, I guess that speaks to that issue a little bit.

- Michael Souter: I would also offer the observation, because these are U.K. centers. So, therefore, I'm a little bit, I do have some limited insight into that, but most I see in the U.K. actually come under very close scrutiny as to their objective levels of performance. I would say much more so than our centers regulated in the U.S., that there's a lot more scrutiny of performance with regards to objective criterion and a lot more, I think being called to account should your center vary by what would be nationally accepted standards. So, I would say that, you know, the idea that you would have one super center versus other kind of, you know, centers of let's just say adequacy, it would be less... less likely I think, just from my perspectives on the provision of intensive care in the U.K.
- Elizabeth Russo: There is one other thing that I should offer, which is that transferring patients who are critically ill is not an insignificant practice. In fact, several of the patients died on transfer or prior to even getting ECMO at the referral hospital. So, the idea that the intensive care should be centralized has costs in morbidities and mortalities associated with it, as well.
- Michael Souter: And that's not an unusual, you know, methodology of providing care in countries across the world. There's many centers where they want to focus their ability to deliver care in adequate treatment centers where they will make that decision to transport patients to that center rather than to duplicate services across the country and it is, again, fairly common to transfer patients to ICU facilities across the U.K. where the study was performed.
- David McCulloch: I understand all that, but in, in terms of that study, if patients were randomly assigned to be flown to the ECMO site but died before they got there were they included as an intention to treat analysis?
- Elizabeth Russo: They were, and I think only three-quarters of the ECMO patients actually got ECMO because of that in part.
- David McCulloch: Good.
- Carson Odegard: I ask a comment from our expert and that is, is... I know there is a concern that there wasn't a big difference in quality of life at six months. My limited experience in orthopedics says that six months is not a good... patients continue to improve significantly even out to a year and beyond. So, that may explain some of the difference? Yes or no?
- Eileen Bulger: Yeah, I would agree with that. I mean, sort of subjective survey assessments of quality of life, that takes a long time, but these patients

are the sickest of the, you know, patients in your ICU, right, with an 80% mortality. So, the fact that they're home and neurologically functioning at six months, I think is great, and it probably does take longer if you want to see real differences in their, you know, quality of life scales on surveys.

Chris Standaert: Other questions? We can come back and ask Dr. Russo more. So, if you look at Dr. Odegard's question during the break, that'd be great, and we'll take our 15 minutes, and we'll come back at 10:05, and we'll keep going.

If the committee could come back, we can get started. It looks like our phone lines are hooked up. Actually, let's finish this, then we can bring this up. Alright. We're going to get going. We have everybody here. Alright, so now is the committee's time. So, we get to discuss our evidence and decide what we want to do with it and go through our voting process. We still have the vendor. We still have Dr. Bulger, our clinical expert. So, we'll start with, did you look through the answer to Dr. Odegard's question. If you could just repeat the question and remind people what you're looking for.

Elizabeth Russo: So, we just looked back at the CESAR trial to figure out where they came up with the \$65,000 figure, and it... there was a study that was done at the same time as the CESAR trial that looked at costs in critical care units, including ECMO centers. It was a large multicenter study of critical care unit expenditure and case mix, and they based... so the CESAR trial based its costs on that study, waiting according to the number of organ systems supported on that day and they showed all different sort of categories of costs in the ECMO group versus the control group, and the biggest differences in costs between them come from air travel and costs associated with the number of organs supported, and unpaid caregiver support. There is some mention of caregiver burden. So, that kind of ties together also, other hospital stay costs and staff charges. So, the difference is made up mostly of those category of charges, and their emphasis is that that is a big difference, whereas maybe in this country that doesn't seem like a big difference, but in the U.K., it was twice as expensive.

Carson Odegard: OK. Great. Thank you. I appreciate it.

Chris Standaert: OK. Now, we have to figure out how we discuss this and under what terms we might discuss it or what categories, but we can start with people having general ideas or impressions and want to tell us where

they think we may be lying at the moment. Would it help to get people thinking and talking? Opening thoughts from someone?

Tony Yen: Comment. I'm interested to hear from our clinical expert over here. I'm still trying to understand the use of ECMO even with the CESAR trial of how that can be effective. I just... and perhaps I'm not reading the literature very well, but if the clinical expert could just give me a little more guidance about, you know, how is ECMO more effective than standard care. I really would appreciate that.

Eileen Bulger: So, for the respiratory failure population, in particular; so, I think you have to separate them out, the respiratory failure and the cardiac failure population, but for the respiratory failure population, which is what the CESAR trial was looking at, these are patients with advanced hypoxic respiratory failure, bad ARDS, which can be due to a lot of different etiologies, right, infectious, posttraumatic, postsurgical, all kinds of things. The ELSO guidelines, you know, they say consider it at 50% mortality but do it at 80%, that's what we're looking at. We're looking at patients in the ICU who have failed all of our conventional therapy. So, we've gone through evidence based things, like low tidal volume ventilation, proning, neuromuscular blockade, you know, and these patients are still profoundly hypoxic. So, you have a choice. Either they die or you try this therapy, and you have to decide, you know, is this the right patient to try this therapy or not, and I think that's where patient selection is absolutely critical. You have to have a condition where you think its reversible, where you think the patient has a meaningful chance of recovery, and those are really clinical decisions to make, but those are the patients that we're talking about. We're talking about people who you don't have something for. We compare it to conventional therapy, right, but conventional therapy is failing them. That's the criteria. So, in our institution, the criteria is failure of institutional respiratory failure pathway. So, you've gone down all these other things. You are failing. And then we have to decide, do you have contraindications, are you a good candidate, is it worth that, you know, trial of this approach, but that, does that, does that answer your question? That's the group we're looking at.

Tony Yen: It does answer my question a bit, but I guess what I'm trying to find out is does the literature really support that ECMO is really that much more superior than standard therapy? I guess that's where I'm still trying to, you know, come to that understanding. I think we have two RCTs over here, the Bein trial you said that was not as applicable to what we do here in the U.S. The CESAR trial, it seems like that, that's probably the

one RCT that we have available that really gives us guidance in the here and now. Am I right?

Eileen Bulger: I think that's the one RCT and then we've all talked about what the limitations of doing RCT in this patient population is, but if you look at the observational data, as well, it also trends in that same direction, you know, data that came... she presented, you know, a series of those studies, but data out of the H1N1 epidemic, not randomized, retrospective, you know, looking at centers that had ECMO, didn't have ECMO and that sort of thing, dramatic differences in survival. So, you know, I think that the observational data is very supportive of the one RCT we have, and I acknowledge we only have one RCT, and it's not a perfect study, but, but that's the challenge of this field, I think.

David McCulloch: This is David McCulloch, again, and I talked to Dr. Bulger briefly at the break, but I wanted to do this publicly. RCTs are absolutely the gold standard when looking... when they can be designed properly when looking at different outcomes and all that, but in a rapidly evolving field with this, we... we could get a lot of information on safety and harms and all that from the growing registry data. My sense is that there are hundreds of patients per year now being tried on this and now they're using different catheter or different heparinization and different ways of limb salvage that I just wish we merely had access to a sense of over the past four or five years and where things are headed how many hundreds of patients are being given ECMO under different circumstances and how... how they're doing in terms of those kind of at least safety and harms, because my sense is the data that we have in the literature given how long it takes to even collect enough patients and randomize them. We're not looking technologies of five years ago and that may not be comparable to what's actually going on now. So, again, my question both to Josh and others here are, it seems like we quite often in this committee are in this situation of knowing that there may well be additionally useful data, at least in the safety and harms realm, that we just don't ever get, and is that because it's being hidden or it is public but the evidence vendor hasn't been tasked with looking at it and evaluating it. I just, so.

Josh Morse: I don't know, but I think it's a good question for the vendor about what evidence they were able to access.

Chris Standaert: Is there published registry data or did you...

Elizabeth Russo: Yes, there's case series, yeah.

- Chris Standaert: From the registry, or?
- Elizabeth Russo: Yeah. So one slide discussed it that the RT findings were different from the observational study about... so, the dialysis seems to be correlated with poor outcomes, and that was not observed in the observational study. So, those case series present harms and outcomes.
- David McCulloch: Yeah, well I mean, I wish that would have been presented in a little more detail. I just would love to know how many patients in the U.S.A. at the Center of Excellence that are part of the ELSO registry were treated with ECMO in 2010, 2011, 2012, 2013, because my guess is it's hundreds and that, that things are improving and changing, and I, I just would love to get a sense of that. I'm not...
- Elizabeth Russo: Yeah, I will say I did just look at the ELSO site and it has, I think, 300 centers in the whole world, and it has 600 cases. So, I don't know if it's hundreds that would be from the U.S., just for frame of reference.
- David McCulloch: Yeah, I just, well, that's helpful to know. I just...
- Elizabeth Russo: And that's international.
- David McCulloch: Yeah. Hmm.
- Chris Standaert: Kevin.
- Gregory Brown: I heard something also that we were looking at harms of bleeding, risks, and limb perfusion and our expert addressed that both of those are being dealt with by a different heparinization over the catheters and also a separate infusion catheter into an extremity, and so I guess, for lack of a better term, what national experience, or other experience, does that significantly change the rates of these complications?
- Eileen Bulger: Yeah. So, again, the data is not keeping up with us, right? So, you know, the changes in the circuit designs are relatively new and that has led to several case series publications of the ability to use lower levels of anticoagulation and in many cases, no anticoagulation, systemic anticoagulation for long periods of time in people who have a high bleeding risk, which is why it is now being considered in trauma patients. It didn't used to be considered in trauma patients at all, but at the trauma meetings that I go to, there's talks every year about the increasing use of it in that population for bad respiratory failure after injury, because the bleeding risks have gone down, but I think the data hasn't kept up yet, and it's case series, publications of, you know, we did

it in 20 trauma patients and they didn't bleed so much, and that was good, but I don't have strong data to support what I'm telling you, but clinically we're... we're encouraged by the fact that we are able to use lower levels of anticoagulation. And I think the limb perfusion issue, now that people are routinely putting that limb perfusion catheter, and I think those numbers will also go down.

Gregory Brown: The other thing I thought I heard you say was that this isn't a question of do we use conventional or do we use ECMO, we only use ECMO after conventional has failed.

Eileen Bulger: Right. That is the current strategy. Now, the French trial that you referred to is really interesting, because it's looking at earlier intervention in a patient with ARDS with ECMO rather than waiting until you've failed most conventional therapy. So, that... the results of that study, I think, you know, we're still waiting to see and if that shows benefit, that would change the landscape a lot, but right now, it's a rescue therapy basically, or a bridge to something else in the cardiac world, or a bridge to transplant. So, it is really something that's considered when you've gotten to the end of the line of conventional therapy.

Carson Odegard: I should have probably addressed this a little earlier to Dr. Bulger, but could you give us just kind of a, just kind of an idea of when we look at these diagrams of how this works and then you compare it to what the internet picture looks like, it looks a little disturbing and...

Eileen Bulger: Yeah, I caution...

Carson Odegard: ...is that what it looks like now, or, or?

Eileen Bulger: ...so, so the picture he showed is a post-cardiac surgery patient, and that's a central cannulation, which is, which is the cannulas you use for cardiopulmonary bypass and they use it not uncommonly if they can't come off bypass and they need to get out of the ICU and they just use the same cannulas and they connect it to the ECMO circuit. So, that is the most invasive form. It's, you know, it's the open into the heart cannulas. The vast majority of the cases we're talking about are percutaneous access using a Seldinger technique to the vessels of the groin or the IJ and for the respiratory failure patients, there is now a dual-lumen cannula that you can use in the IJ so you only have one cannulation site, and those patients get a cannula in the IJ that runs both in and out. It's pretty impressive. So, you know, it's basically percutaneous access to the IJ. It can be done at the bedside in the ICU.

- Carson Odegard: Oh, great. Thank you. I appreciate it.
- Chris Standaert: We had some answers to Dr. Souter's question earlier about utilization, too. That might be helpful.
- Elizabeth Russo: I had two points I wanted to give. One was what had the longest stay, and there was really a balance between both the cardiac and the respiratory pulmonary areas for longer stays. They were five days, seven days, and eight days between all of them. There was a market increase in the cardiac utilization in the last year of the study, and I'll let the clinical expert tell you why there was.
- Eileen Bulger: Yeah. So, we were talking a little bit at the break about that. I think the Washington data is a little bit skewed based on the centers that are currently using ECMO, which are largely the big cardiac centers. So, the growth in respiratory failure, we haven't see dramatically in this state, yet, but I think, you know, with Harborview's program and a lot of the patients that are currently going down to Portland and Oregon will be coming to us instead. I mean, I get about two calls a month from someone in the state of Washington with a patient in the ICU who they think might need ECMO and wanting to transfer them. So, that doesn't mean they all need ECMO. They need to come to a regional center and be evaluated and, you know, treated, but I think that the growth and respiratory failure is a little behind in Washington than it is in the rest of the country just because of the centers that have been involved.
- Chris Standaert: Go ahead, Kevin.
- Kevin Walsh: I would propose that we look back at Dr. Russo's slide 15 the way that the effectiveness question is broken down and that that might be a reasonable way for us to discuss these.
- Chris Standaert: Yeah. She has it broken down into four categories. We have cardiac support or cardiac failure, pulmonary support, bridge to transplant, and extracorporeal CPR are the four categories she gave us, and that seems quite reasonable to run through them under that structure. That's the way our data is presented and dissected for us.
- Gregory Brown: Do we want to add a fifth for hypothermia, since, or...
- Kevin Walsh: Based on what?
- Chris Standaert: We can add a fifth. There may be some, or yeah. We can certainly add it and talk about it and see whether we think there's anything there. Yeah?

- Gregory Brown: Yeah, are we simply defining it as another form of cardiopulmonary failure?
- Kevin Walsh: It was... the only reason we're discussing hypothermia is because it was brought up in the state presentation. There is no... we didn't see any evidence that looked at hypothermia specifically.
- Chris Standaert: Hypothermia as a warming function in the setting of intact cardiac and pulmonary function and acute hypothermia is very different from the rest of this, but I don't know that we got any data on it.
- Michael Souter: Then I would really suggest that we stay away from considering hypothermia from the point of view that we're really talking about the use of ECMO in active cardiopulmonary support in those patients with either established cardiac or pulmonary disease, what are you using it for in hypothermia as an alternative to cardiopulmonary bypass, which is, you know? So, that's an indication in its own right. You're going to either put the patient under bypass, or you may use ECMO. I think it's really... that's, you know, kind of peripheral to our determination here, which is how should you use ECMO if at all in the context of treating cardiac and pulmonary disease.
- Eileen Bulger: I would comment that those hypothermia patients that I'm talking about are, you know, deep hypothermia exposure patients who do have cardiac instability that may have CPR. So, if you made some blanket exclusion for ECPR, for example, that could impact that population of patients who are really being treated for their hypothermia as the cause of their cardiac instability.
- Chris Standaert: OK. That being said, why don't we look at our categories? So, we'll keep under our four categories. So, cardiac support, can somebody give me some idea where they think our evidence lies?
- Gregory Brown: Rather than slide 15, do we want slide 38, which is the evidence ratings? It's the same four categories, but...
- Chris Standaert: We can talk about the rating. We can talk about specific things in the evidence, things that strike you. What do you think? What do you think of the evidence on cardiac support? They rate it as insufficient, but our job is to go through what we think of what we have.
- Gregory Brown: No RCTs on it is my understanding for that. So, um, I would agree that there's insufficient evidence, just to make a determination on that.

Chris Standaert: Because we have no RCT or because the study we have... that they gave us, what, a retrospective chart review. So, we have some evidence they gave us.

Michelle Simon: But the evidence that they did find was really no difference, so.

Elizabeth Russo: Can I comment, or? I think the reason that... the evidence is comparing it to VAD, and we're not suggesting that it should replace VAD. The problem is that VADs are not accessible quickly in every place. In fact, they're only accessible in this state in, you know, one or two places. So, it's used as a bridge to VAD in that situation. So, I would think about it a little bit differently.

Chris Standaert: We have this other problem that we don't really have data on this sort of... there's no other option stage, right? So, you're... everything else is failing and your patient is failing and you try it in cardiac failure. Is that what I'm... but we don't have data.

Michael Souter: I mean, I suggest that we think about that with that very discrete set of parameters in hand that, you know, it would seem appropriate when there is no other treatment where you can anticipate successful treatment via different... an alternative methodology, but your sole use of using the ECMO in this circumstance is to permit you the time to be able to get that. So, to some extent that's almost independent of etiology, when we do need to get perhaps trapped too much into categories, but I think if you are using it on the circumstance that it's the thing that's going to allow you to get a more definitive treatment within a short space of time, then that would appear logical to me to support that.

Kevin Walsh: That's the question, though, does it? Does it make a difference? I mean, that's what we're asked to look at, and doesn't...

Michael Souter: The difference then applies to... it comes from a much more... a broader range of considerations in terms of, you know, OK. What does that longer-term treatment then do? I mean, no one, we haven't looked at the data for ECMO then VAD as opposed to ECMO on its own or ECMO or VAD on its own. I mean, that's a considerably larger problem than is actually being asked to deal with at this point in time, and there's a lot more would go into that, and I, for one, would feel extremely uncomfortable at saying we can't use, you know, ECMO in the circumstances of bridging treatment because we actually haven't looked at the outcomes of the larger problem.

Kevin Walsh: When you did a literature search, did you look for that possibility? Did you look at that as a category? You did not exclude it? So, there were no studies.

Michael Souter: Well, apart from say the retrospective one.

Kevin Walsh: Which showed no difference.

Michael Souter: Yeah, which means that you can use it and be, you know, and it wouldn't do any... you're not producing any worse effects than if you went straight onto that. It would still be considered, you know, the treatment of choice in these circumstances, but when you don't have it, then using an ECMO is no worse.

Kevin Walsh: It's not any better either.

Michael Souter: Yeah, but it's better than nothing, which is what we're talking about, having nothing.

Kevin Walsh: But if it's better than nothing, there has to be a benefit. If it's... you're saying that it's better than nothing because doing something is better than nothing, and I'm...

Michael Souter: When the alternative to having nothing is death, that's pretty certain.

Chris Standaert: I think he's saying that if it's equivalent to VAD but VAD is not readily available, then it's equivalent to prolonging life or sustaining the ability to make it to another treatment, as VAD. So, not saying in the absence of nothing else or if you had VAD everywhere readily accessible, perhaps you might view it differently as opposed to saying, it's not better than VAD. It's equivalent to VAD, but if VAD is not uniformly accessible and there are places where you have ECMO but not VAD, then ECMO becomes your, or it's easier... it's something you can institute more emergently, then it becomes an equivalent bridging tool to VAD to get somewhere else.

Kevin Walsh: And where, where is the comparable interpretation coming from that shows no benefit?

Michelle Simon: They're comparing it to mini-VAD in that particular study, that retrospective study.

Kevin Walsh: I'm fearing that there's generalizing going on, and we can generalize, but that's not what the evidence is presenting us.

Michael Souter: I can't agree with that. I think that there's a, you know, there's one retrospective study. It is what it is. It's not a randomized control study. It's not a, you know, an observational cohort. What it is, is just a retrospective chart review which says, OK, when we look at those patients who got put on ECMO versus VAD, you know, the mini-VAD, is the outcome any worse, any better? And they said well, we can't say its any better, but it's no worse. So, if you think about that then logically, if you're making a determination that is acceptable to use, you know, that you want to institute some kind of treatment to allow you to get a VAD into somebody and you don't have a VAD at hand, then I could, I would feel that it's appropriate to use ECMO in those circumstances to buy you the time to get to putting the VAD in. Putting a VAD in is a complicated procedure. It requires a very skilled set of personnel to be able to do that. You've got to have a good cardiothoracic surgeon who is able to do that. Putting in an ECMO catheter is actually, as you heard from Dr. Bulger, is a lot less complicated and so, you know, I am quite comfortable with the idea that you could use a very short-term utilization of ECMO in that circumstance to buy you the time to get to what would be the appropriate therapy.

Chris Standaert: Data from that study, it does say there is, you know, essentially equivalency in terms of bridging to long-term support. There is no benefit. It's not better than VAD, but its equivalent to it. So, again, in a technical setting, it would be, if that's what accessible, that's what's accessible, and your odds of success are just as great as if you had a VAD and you could get it in. Is that my... is that my understanding? What do other people think? It bent a bit into the bridge issue, but we're still on cardiac, so not into the CESAR trial.

Louise Kaplan: I just want to ask a clarification of Dr. Russo. So, on this table, for the study that we're discussing right now, the intervention is ECMO and the control is MP-VAD, but when I'm looking at this, it says the purpose is to compare outcomes associated with the use of Impella and tandem heart short term support devices. So, those are the VAD devices? So, there were two different devices? So, does this break it down to compare the outcomes with both of these devices, or do they aggregate the devices?

Elizabeth Russo: There are some outcomes that are different (inaudible), but if it's not otherwise noted it's the aggregate data.

Louise Kaplan: It's the aggregate data. So, there were 61 with ECMO and 18 with the VAD?

- Tony Yen: Just a question of clarification. It seems like not all ECMO is equivalent, that ECMO for pulmonary replacement versus ECPR is quite a bit different from a technique standpoint. Am I correct?
- Elizabeth Russo: (inaudible)
- Chris Standaert: Can we get the mic to stay on?
- Elizabeth Russo: (inaudible)
- Tony Yen: It appears from a harms standpoint that it would be that the ECPR ECMO has more harms, at least from your clinical experience?
- Eileen Bulger: Well, we... so the data in the literature that you saw when you looked at the harms, yeah. That's higher. It's a much higher risk population, though and most of those are out of hospital cardiac arrest where they're trying to salvage them in Asia primarily from out of hospital cardiac arrest with ECPR programs. I think that's pushing the envelope. I mean, we may get there, but that, that is probably where the highest risks and the worst outcomes are than compared to all the other populations that we're talking about here.
- Chris Standaert: What do you think, Seth?
- Seth Schwartz: I'm struggling a little bit with the cardiac data, as well. I mean, I... we're certainly not seeing anything compelling that ECMO is better than anything else, but I think that as a bridging argument, it's not... it doesn't seem to be worse than other things. I think the... I can't say the data for pulmonary is compelling, but it certainly suggests that there may be a real benefit to patients here and we're also hearing how complicated it is to manage these patients and they don't really have other alternatives. So, I think it may be a little difficult to structure how... well I guess what I'm trying to say is, leaning towards essentially what the recommendations were, which is that there will be coverage with some limitations, and I'm trying to look... conceptually get my head around what those limitations would look like, and I can't say that I have a great understanding of how we're going to clinically define who it's best for based on the data that we have.
- Chris Standaert: Why don't we move on to the respiratory side? We have a study now, right? We have the CESAR study. So, on respiratory failure, is it more convincing, perhaps, than in cardiac, or is there a different role for it, even?

Michael Souter: Well, I think that the role on the cardiac side is in bridging. I don't really think there's a convincing role for it in other circumstances, but in the bridging mold, yes, absolutely. In the... however, in the respiratory side, I think that clearly in the circumstances when you don't have any other modalities of treatment, in other words, you know, you've exhausted all your other alternatives, that the use of... the use of ECMO in these circumstances does confer an advantage in terms of mortality with... when combined with severe disability as an outcome. So, I see a benefit there on the basis of the CESAR trial. You know, it is only one study, but I think it's supported by the trends that you can see when looking at the observational data. So, to me that says that yes, there is a value here in treatment. Now, it doesn't work in everybody, but, you know, few things do work in everybody, especially in the ICU, and you know, many treatments are, you know, put forward on the basis of the ICU on the basis of that they've improved the mortality and are outcome benefits by the order of a few percent, you know, 5-6%. Wow, that's a big thing, because otherwise, the alternative is death. So, I think those things are meaningful in this population. Clearly, to me, I think the difficult thing is to make sure that we actually have identified the population who will benefit, but there needs to be reversibility. There needs to be anticipation of that if you can get somebody over an acute period of dysfunction, they have the possibility of making a huge to moderate recovery.

Chris Standaert: What are you thinking, Michelle?

Michelle Simon: Dr. Souter makes a persuasive argument, I will say. I don't disagree with him. I think the challenge that I have with this is, it's an evolving technology and as our clinical expert stated, you know, the data hasn't caught up necessarily with the evolution, and then the challenge always there is, our charge is to look at evidence and make decisions for the state based on the best evidence, and if we rely on the idea that this theory will evolve and become a reality in the efficacy and the safety and the cost-effectiveness, then we don't need our clinic. I mean, we don't need our committee at all to make those kinds of decisions. So, it's again, the decision to look at the evidence we have and make the decision on that or the, you know, the bird in the hand versus two in the bush kind of thing. So, I like the idea that there is some suggestion here that there is potential for it to be a useful intervention in the bridge scenario to VAD or other long-term treatments. That's persuasive to me. Certainly, there is more evidence for the respiratory conditions, but in general, I'm still struggling with the extreme cost, it seems, and having... trying to figure out the cost-effectiveness of this based on all of the other things the State has to pay for, and what this might preclude the State

from being able to provide for its members, general primary care that goes unfunded, things like that. So, I struggle with those issues.

Chris Standaert: OK, the correlator to the data is not keeping up with the clinical applications, as the clinical applications are not in line with the data, right, or waiting for the data, and that's always the flip side we have to wonder about. Carson, what do you think?

Carson Odegard: Well, that's just one of those situations where you get torn between, you know, the ethical justification of using this type of technology versus the lack of evidence that we've seen in the reports and I'd like to get just kind of a showing of... or an argument or in the cardiac aspect, cardiac support, the use of ECMO or a noncoverage of ECMO, I mean...

Chris Standaert: Argument for non-coverage.

Carson Odegard: For non-coverage, yeah, because, um, if, if there are people leaning that way, I'd like to hear an argument for that.

Chris Standaert: Is anybody leaning that way or want to play devil's advocate and present a perspective?

Kevin Walsh: I would ask if people accept the statement on slide 16, ECMO for cardiac support shows no benefit for the following: Bridging to long-term support/transplant. I mean, it...

Eileen Bulger: Based on what data. I didn't see any data that said that. So, I don't know who drew that conclusion.

Kevin Walsh: I'm sorry.

Chris Standaert: I'm sorry.

Kevin Walsh: You're not a member of the committee and...

Eileen Bulger: I'll be quiet.

Kevin Walsh: ...we're not asking that.

Michael Souter: OK, but I'll ask that though.

Kevin Walsh: I didn't, well I don't have to defend this. It was presented. So, I would ask the people who presented the literature to answer the question.

- Chris Standaert: Well, could you, I guess, one of the issues I would have is a similar question here is the idea that no benefit for bridging. Does that mean no benefit in that people don't survive, or no... or that it's equivalent to VAD in that a certain proportion survive. I don't know if... I don't want this to take away your question. Does that align with your question, or no?
- Kevin Walsh: Right. I'm trying to ask... Carson is saying for people who are not leaning towards supporting it for cardiac support, what's the argument for not supporting it. I'm saying, well that, here's the argument in my mind. I don't see the evidence that supports it.
- Elizabeth Russo: So, this is very important to parse carefully the difference between saying there's the demonstration of no benefit versus saying there's no demonstration of benefit, and recognizing that this slide is referring to one study of good quality. There were other studies of fair and poor quality that addressed bridging to bridging. So, sort of like the bridge to VAD, or VAD, but those had methodological flaws that precluded them from being included in this discussion. So, this summary is referring only to the Chamogeorgakis study, which showed no... oh, you have it open for me. Thank you. It showed no significant difference between the two treatment arms. So, the... those who survived in the hospital, there were 50% who survived given the mini-VAD treatment whereas similarly 50% survived who were given ECMO. So, there's no difference.
- Chris Standaert: With the assumption that if they were given neither, the survival rates would have been far lower.
- Elizabeth Russo: That would be my assumption.
- Seth Schwartz: And along those lines, I'm trying to understand that clinical scenario. I mean, it doesn't sound as if clinically ECMO is being proposed as an alternative to VAD. It's more a matter of access. Is that... Dr. Bulger, does that seem accurate?
- Eileen Bulger: That's exactly it. If you come to Harborview, I don't have VAD, but I have ECMO. I can stabilize you on ECMO, transfer you to the University of Washington where they can put a VAD in you. If you say no coverage for ECMO, I can't do that. You'll die at Harborview. That's the example.
- Seth Schwartz: So, then to be clear on these studies, when... if the comparison is directly ECMO to VAD and we're not seeing an inferiority of ECMO, it doesn't answer the question. The question is so what exactly are they comparing in this scenario... what exactly is the comparison? It's ECMO to what? So, I would ask our evidence vendor that question.

- Elizabeth Russo: This is comparing ECMO to VAD.
- Seth Schwartz: But I guess, how, how did the entry, how did the entry into that trial occur? In other words...
- Elizabeth Russo: Well, it's... it's the treatments that these patients received. It wasn't a trial. So, they looked retrospectively through their charts at patients who received both treatments who also had cardiogenic shock most often associated with, I think, myocardial ischemia, and they looked at the outcomes associated with patients who received two different types of treatment.
- Seth Schwartz: And in the trial looking at bridging, or in the studies looking at bridging, what was the comparison?
- Elizabeth Russo: You're talking about bridging for a transplant?
- Seth Schwartz: Bridging to VAD or bridging to, yeah.
- Elizabeth Russo: Well, those are of poor or fair quality and were not included in the evidence review.
- Seth Schwartz: So, we... so we saw basically no data on bridging.
- Elizabeth Russo: That's right.
- Michael Souter: Well, apart from the Chamogeorgakis... yeah, I can't pronounce it either, but you know the retrospective review. I mean, what the retrospective review tells you is when you take a mini-VAD, which is really a short-term tool and you compare that to ECMO, again a short term tool, and then you look at OK, what's the survival of patients who make it either to the placement of a long-term ventricular assist device or transplantation, which would be considered a long-term treatment, then there's no difference between those two arms. And again, it comes down to, you know, the logical question, which is one of access, and if you don't have access to the mini-VAD, you know, then or... or even to the longer-term VAD or even to transplantation in that acute circumstance, then, ECMO would appear to be a logical choice based on the retrospective review data presented by the Chamogeorgakis study.
- Seth Schwartz: That makes sense to me. I think... I guess what I'm getting at is, it seems like ECMO is always a bridging treatment in the cardiac patients is what, you know, as opposed to a definitive treatment. So, I'm just trying to

understand how the trials are actually... or the studies are... what conceptually is happening there if it's always a bridging treatment.

Elizabeth Russo: Unless it's a self-limited myocarditis.

Chris Standaert: Yeah, but in some way, it's always a bridging treatment to either recovery or definitive care in some other manner. It's not... this isn't clearly long-term ventilator support. It's not equivalent to that.

Seth Schwartz: Bridging to recovery, I don't really see it that way. I mean, if we're saying there's always going to be some definitive treatment other than mini-VAD or ECMO, then effectively it's always bridging, or in these trials were they simply looking at ECMO versus mini-VAD and that's the end of it? They either recover or they, or that's the end, or do some of those patients go on to get long-term VAD or transplant. That's why I'm just trying to sort out what we're actually looking at here.

Michelle Simon: On slide 15, they do talk about two studies and the bridging to transport, and they compared it to cardiopulmonary bypass. So, we do have some studies that are strictly about bridging, two.

Louise Kaplan: Can I ask for clarification again. In the study that we're looking in the results section, it does talk about bridging. So, it says a total of 18 were successfully weaned, and of those, 13 survived to hospital discharge; 31 patients were successfully bridged to either a ventricular assist device or a total heart, or heart transplant. So, they did address the bridging.

Elizabeth Russo: It goes on to say there is no difference between the groups with regard to in-hospital mortality, success to weaning, or bridge to long-term device or transplant.

Seth Schwartz: So, I guess along these lines, what I'm trying to determine is, are we... are we compelled to find evidence that ECMO is better, or are we simply interested in non-inferiority? In other words, if it's an access issue, if we're in a situation where there may be another alternative that is considered standard of care, but patients aren't going to have access to that, and we can show that in another environment that same patient who may not have access to cardiopulmonary bypass but may have access to ECMO, they're going to do just as well as the patient who has access to cardiopulmonary bypass, then that seems to be fairly compelling evidence that we should offer... or cover ECMO, whereas if it's, you know, if we're in the same setting where a patient has a choice of the two, or the treating team has a choice of the two therapies, and ECMO is more expensive, why would you offer ECMO if it's not superior.

So, I... that' why I'm just trying to understand the clinical scenario, and I'm hearing that it's more of the former is what is the actual clinical scenario that we're having to address. So, non-inferiority is actually then compelling.

Chris Standaert: Put up the transplant data for a second, a bridge... so, going on what you just said, ECMO is a... they view it as a bridge, and if... Louise just said that the heart issues and the mini-VAD study... if we were to view bridge to transplant as a different issue, does it fall along the same lines where the evidence indicates that this is equivalent to other options, or is it inferior to other options, or are there problems that access to all the options isn't equivalent and when ECMO is there it should be used if there is no other choice.

Elizabeth Russo: I do think it's important in considering this study that when you look at their discussion of limitations, the first one is lack of power, and their statement that a larger cohort of patients would be necessary to overcome this limitation, in this retrospective study, possible factors that may have biased the results were included refers to a single center database, selection for a specific type of short-term treatment may differ among heart failure units across the country, and they used two different types of devices. So, there are significant limitations that I think... sorry... significant limitations that need to be included in your consideration of the study.

Chris Standaert: Again, our fourth, sort of third arm, a bridge to transplant, do we have... my question is, do people feel we have the same issue, that there are circumstances where this is really the only choice. There... there isn't bypass or there isn't some other means to keep someone going for respiratory failure, and there's no other support mechanism, because they've failed everything else pending a lung transplant, and this becomes their bridge. The studies get tricky, because it's not a matter of superiority, because the other option is death. It's a matter of, is it a viable alternative in that setting? Is that how, how do we feel about that literature?

Michael Souter: That's a complex question that raises some considerable, I think, ethical issues in that the implementation of this would need to be very carefully thought out. For example, you'd have to be somewhat concerned at somebody using ECMO as an open ended support for a patient who is requiring cardiac transplant, but yet where there was no heart available, as it were, and so where do you go to in that circumstance with a possibility of indefinite request for support. So, I think that implementing that type of strategy would require, I think, some very... some very

detailed support beforehand. And again, we may be better just to consider that in those circumstances, you know, that ECMO should really be used to bridge somebody onto the VAD and just leave it at that, because if you get, you know, then there are well established methodologies and protocols for dealing with a patient who is on a VAD who needs to progress from there to cardiac transplant. I think that we may be making a world of trouble ourselves where we need to say that it's OK, use ECMO to go to a patient that is requiring cardiac transplant and have that as being kind of the only pathway, if you see what I mean. If we say that, OK, it's OK for our patient to get ECMO to get onto a VAD and leave it at that and then rely upon what's already established practice protocols for the progression from VAD to either cardiac transplant or in some circumstances from VAD to removal of support, because there's no other alternative.

Chris Standaert: The same issue there for pulmonary, for lung transplant. Do we have the same issue? I mean, is there another options? Is there another sort of, there's no VAD for, I suppose, in complete respiratory failure from the lung, and you're trying to get to a lung transplant. Do you have other choices, other ways to do that?

Michael Souter: I think we've got even less data to go on there. I think, you know, the data by using ECMO for support and for pulmonary support there is really for a badly acute...

Chris Standaert: ARDS.

Michael Souter: ...ARDS scare where you've got the potential for reverse... for reversibility.

Michelle Simon: And this would be a question for the evidence vendor. The only data we have on this bridge to transplant issue is these three observational studies, and it compares ECMO as a bridge and it says to heart and lung transplant. I wasn't... I don't remember exactly how many of them were lung, heart... which were lung, but in general, the ECMO folks didn't do as well, it seems, as those who were getting cardiopulmonary bypass. They had a higher mortality post-discharge. That's slide 20.

Elizabeth Russo: There were lung transplants in two and heart transplant in one. Two studies showed higher mortality rates.

Chris Standaert: Question for Dr. Bulger, then. Is this a similar issue where these are really equivalent choices where you could say, you know, the ECMO is more... people come out not as well. Their complications are higher,

morbidity is higher, or whatever you want to say. Therefore, they should be on bypass, and we shouldn't be transitioning the practice to ECMO, because bypass is superior and equally available. Are we running into a similar issue where you have acute respiratory failure in need of essentially transplantation and you, from an actual being able to treat them standpoint.

Eileen Bulger: So, cardiopulmonary bypass is not a long-term support system. It's used in the operating room, and it actually carries probably higher risks than ECMO. So, I would be careful about that as the comparator. I think you need to separate out heart and lung transplant, and lung transplant, the way it's being used is as a bridge to transplant for people already on a transplant list. So, they've been assessed, usually like people with bad cystic fibrosis is the program at the university hospital. They've been assessed. They're on a lung transplant list. They have an episode of respiratory failure. They can't rescue them. They put them on ECMO, and they get a lung transplant, and that is a bridge to a known endpoint that the patient's already been assessed for and while there may not be data, that's what it's being used for practically. Heart transplants are a little trickier, as you said, and I think most of those go to some other device, like a VAD or a tandem heart or something else, and then they have pathways to determine if they are transplant candidates or not. So, I think they are two very separate things, but cardiopulmonary bypass is not an alternative to people waiting for a lung transplant.

Chris Standaert: There is no other real comparable option.

Eileen Bulger: There is no other option for them.

Chris Standaert: So, absent ECMO, those patients with cystic fibrosis who come in, in acute respiratory failure, where they, again, the standard ventilation techniques don't work or are going to expire.

Eileen Bulger: They'll die before they get the lung transplant, yeah.

Chris Standaert: OK. Other thoughts or perspectives on that, or can we move on to ECPR? David, what do you think about ECPR?

David McCulloch: I'm thinking of... about... I don't have strong feelings about ECPR. I mean, I... when I look at Dr. Hammond's presentation and the agency recommendations, I know we're not there yet, you know, I find these fairly reasonable. I'm stuck on trying to rationalize that we come up with recommendations that seem as evidence-based as we can, evidence writ large, and thoughtful and ethical. It's easy to always take the stand that

we are evidence based, purest, if there isn't the perfect study, we have no evidence, we will not cover. I... that's a really easy and lazy way out, because we could actually say even the CESAR trial is not perfect. It should have been done in blah, blah, blah. So, we have no evidence. We're not going to cover under... I just think that's... we cannot, we should not do that ethically. I feel... and this is an ethical thing for the whole committee. I don't think there are hospitals out there saying, you know, dying to set up a new ECMO center in the Tri-Cities because we just can't wait to bring in patients and make a fortune in this. That's not what we're dealing with here. We face that with lots of other technologies where there's a huge population... we're going to talk about it this afternoon where you can make a lot of money by saying... under those circumstances, I think we should absolutely demand objective randomized control trial. In this situation, I think we have to take into account a lot of insight from ethical expert opinion in this... this is an emergent technology. Nobody's making a fortune in this. To me, provided we're really careful that we select the right people, this is an emergent technology that does look to me as if this can save lives and bridge to other things and I don't have the sense that unless we play hard ass and just say in the absence of the perfect study we're going to say we're not going to cover it, I just don't think we should be doing that here. So, I'm overall feeling... I mean, I'm, like a lot of what Dr. Souter said of... I get a sense talking to Dr. Bulger that, you know, this is for these small number of people who are really sick and who have the chance of long-term survival, this is an emergent technology that is really valuable, and as long as we're careful about selecting the right people, I'm leaning towards covering it with conditions, even though there is not perfect evidence presented.

Chris Standaert: I am hardly someone to accuse you of being intellectually lazy, first of all, but I think your statement is correct. Part of the point of this committee, expressly in our legislative mandate, is we are clinicians and applying our clinical perspectives is why we are the committee and why it's not evidence vendors.

David McCulloch: Right.

Chris Standaert: Yes. I just want to make a direct comment on ECPR, because we're going to have... we're going to have to talk about that in a few minutes. Do we distinguish it from these other things in some way? It looks like we certainly don't have RCTs on ECPR. I imagine that would be a tough trial design. Consent would be difficult.

Kevin Walsh: So, ES25, there was an inconsistent pattern of outcomes being relatively better in cardiac arrest patients treated with ECPR compared to conventional CPR with short-term CPR benefit diminishing over time, being reported in several studies, in contrast to one study reporting maintenance of benefit over the longer term. My interpretation of that is ECPR keeps people alive who were going to die anyway for a little bit longer. Maybe I'm not being intellectually rigorous in my interpretation of that.

Chris Standaert: (inaudible) either.

Michael Souter: For me, the ECPR question comes down, again, to what you think you can get out of it at the end of the day, and I think that... my easy way, just to be intellectually lazy perhaps is to split it up into cardiac arrest within hospital and without hospital, which actually have very divergent outcomes and I think that that's probably where I would come down to it. I don't see a lot wrong with the agency recommendations in that respect.

David McCulloch: I would agree with that and the... it's funny I... the whole idea of bringing advanced technology to out of hospital cardiac arrests has a long history in Seattle, right back to the 1970s where mobile coronary care units were being, you know, people died before they could get to the coronary care unit, so we need to have roving little ambulance out there waiting to... the history of that whole approach... most of those people have really bad disease and were going to die anyway, and I just what Mike said. Very definitely, if you get somebody who is in-hospital, perhaps waiting for a heart transplant or something else, and they have a cardiac arrest, I mean, I distinguish that, which is why I come back to I am... I think that the agency recommendation makes a fairly reasonable distinction and I would lean towards that.

Chris Standaert: Our expert had noted there is a... there are a lot of causes for in-hospital cardiac arrest, many which I assume would not necessarily be appropriate for ECMO. How to define... where... that data is... how we do that I have... things like a massive pulmonary embolism, is there a distinct reason, as opposed to advanced cardiac disease in someone who is of advanced age and medical illness.

Michael Souter: I don't see, honestly, any way to be able to make a distinction that would be of practical benefit in the acute situation. The idea of a code team being called to a cardiac arrest patient then running down, OK, what exclusion factors do they have for us to be able to run down the ECMO is just... it doesn't make any sense to me. I think that this is one of those situations where we have to relax our desire to be excessively

prescriptive and leave it to the judgment of the clinicians at that acute scenario and hopefully comforted by the idea that it's not going to happen a lot. Events may prove me wrong, I really hope not, but I don't really see this as something that's going to be offered on a day to day basis.

Chris Standaert: So, on this side? What do you think, Greg?

Gregory Brown: I would concur.

Chris Standaert: With Dr. Souter or with the recommendations?

Gregory Brown: With the recommendations.

Chris Standaert: With the recommendations from the agency director. OK. Yeah, go ahead, Joann. You're on this side.

Gregory Brown: Actually, I guess I would... the one way I would change it in its moving us to the next step, but for a number of these, the recommendation, or at least the... what I heard from our expert was is this was after all conventional efforts have failed, so.

Joann Elmore: I have three comments in thinking about the big picture. The first is that we all need to acknowledge that this is a terribly challenging clinical topic to study scientifically, as a clinical epidemiologist, it is really hard, and I think we all are acknowledging the limitations and the lack of data that was presented to us. With that in mind, this is a clinical scenario where its life or death, and we do care about patients. So, that's why I think we're all struggling and working as hard as we can on this topic. That's point number one. Point number two, I was pleased to see in the draft of the medical directors recommendations the condition of... they must... it must be at a center that is part of this national and international registry, and I had to smile, because for those of you that have been on the committee and that know me, when I first came on, I was very naive on the committee and every vote I wanted the condition that can't we sign them up for registry because there's terrible evidence, terrible scientific data, and we may vote to approve it, but can't we get something better. Can't we help move science? So, I was both pleased to see that there is a registry, pleased to see that something is existing so that if indeed our committee does vote we can add that in, but I was also displeased to see that this registry is housed at Ann Arbor. There are almost 20,000 patients, adult patients that have been registered in this registry. They may not have published the data. It may be biased. It may be terrible data, but I would have liked to have seen and heard about this data. So,

for my second point is that going forward when there are these large registries, my hope is that our evidence vendors will gather some of that data. I went online and I wasn't able to get beyond the sort of international statistics, but this could be a powerful and potentially useful piece of information, and then the final comment is that I also... if we as a committee move forward to conditions, I think a lot more specification is needed in the stem. So, I want to follow up on your point. It needs to be severe life-threatening. It needs to be potentially reversible. It needs to be acute respiratory or cardiac failure. And it needs to be unresponsive to conventional management, and with that, I don't even know if we need to get into many more of the specifications, but those were some of the things that I think were list... were lacking and not in the draft recommendations.

David McCulloch: Very well said, Joanne, and I'm... that makes a lot more sense to me hearing that there's three or four hundred patients in this registry does not make sense. There has to be...

Joann Elmore: 20,000.

David McCulloch: ...so I think...

Joann Elmore: That's international.

David McCulloch: ...and even with all the potential bias and this and that, there's just... there'll be a wealth of useful information in that. I just wish we could get some of it and just trends over time and... but, yeah.

Chris Standaert: Alright, moving on, you want to talk? Go ahead.

Louise Kaplan: I just want to say one thing about the ethical issues that people are raising. I think this is a very difficult issue to approach, because this is essentially a life and death type of issue, and that always makes it harder for people to make statements that might not be in support of this technology because the outcome would be death. On the other hand, when I looked up the American Thoracic Society to see if they had a more recent position, the only recent statement in which ECMO showed up was in their conscientious objector statement for people who are opposed to initiating treatment in futile situations, and that's where ECMO showed up. So there was one case that they gave a scenario for, but I think that's, to me some of the ethical issues that we really have to grapple with in this committee are around distributive justice, and it's one thing to say if it's life and death we should always pay for it, but if we're always paying for it, then what does the state also not have the

money to pay for, because the state does make choices, and I do think that the considerations go beyond these situations and it's... I just find it very challenging to say, and I'm not saying we need perfect evidence, but I find it very difficult to make a decision on one study. I find it very, very hard. That's very limited and of very low quality, from my perspective. So, I feel this extreme tension between the distributive justice side of the ethics that we have to grapple with and the life and death type of decisions that have to be made, which I think is really reflective of the larger societal issues that we fail to grapple with because we do think that we should be able to save everybody, and we should use every technology, and yet our outcomes really are not better than other countries that make much more difficult decisions about when to limit the technology. So, I think we need to really get beyond just is this going to be life and death, but what are the choices that we make by saying yes or no to a technology and what are the real outcomes that we're looking at, and what's the endpoints that we really want for the society, at large, rather than in one very small group of individuals, which is what I think we have to balance.

Michael Souter: I understand what you're saying, Louise, but I do have to take issue with the fact that, you know, we have to inject that element into the specifics of whether to support this study or not. I think we are charged because of the factors that you bring up that there is not an indefinite supply of money to support the assistance of the state. We do have to, you know, be mindful of that, and that's why we have to think about everything in terms of its efficacy, its safety, you know, the benefits that it will produce, the risks that it will produce. Those are the charges that we have that we must acknowledge and look very objectively at what we have, but as has been said already, we are a committee of clinicians. It is not our charge to balance the budget. We are not a, you know, we have to make the best independent decisions that we can facing the challenges that have been set before us by people who do have to balance the budget, but we can only look at things objectively at each time and say, OK. Is there enough evidence to support this in this context? Is this a safe practice? Is this an efficient one? I, you know, I acknowledge there may be deficits in other areas of care across the state, and I think that's important, and that's a motivation to do what we do, but it should not be a factor that influences our individual decisions upon each clinical scenario that we have to make a judgment on.

Kevin Walsh: I disagree, and I think that you invoked logic in asserting that there was benefit to supporting ECMO to bridge to VAD without... there's no evidence, but your logical argument was persuasive and made sense. I would advocate and support Louise in saying every day in terms of the

patients I take care of in the safety net health care clinic, I see people who are denied care by the state, and I have to deal with that logically with all of those patients day in and day out. So, I'm not willing to accept the argument that we should not... that we should divorce that issue as we weigh the evidence here, because the reality is that there's a finite pot of money, and it's going to be parsed out one way or the other.

Michael Souter: And I'm not denying that, but what I'm saying is that's a motivation for us to do what we do, but if we are going to go down that pathway, then I would want to know, OK, how much are we spending on treatment X? How much are we spending on treatment Y? Of the entire pinnacle of healthcare that's delivered across the state, it's not our charge, it's not something we are asked to do. There are other programs that have engaged in this, I'm thinking of Oregon, etc., which have made relative assignments of value in terms of what their citizenry wants the state to provide, you know? Should they be, you know, should they replace hips or should they do cardiac transplants? Those kind of things have been done. That's not our charge at this point in time. We are being asked to make a, you know, determinations of clinical utility and safety based, as best we can, upon the objective data and the reasons why we're being asked to do that is very much to address the fact that there is, you know, there are deficits of care. We want to be efficient. We don't want to kind of waste money, but the idea... but we can't intrude that element of knowing, OK. So, it's expensive so therefore we can't cover it. We can't do that in the absence of, you know, knowing, you know, how much the state spends across the entire array of healthcare, and we're just not qualified to do that. This is not the forum to do that.

Seth Schwartz: I think that's fair, but I think the challenge is that... I don't think you can divorce cost of care from what we do as clinicians. I think that it's... even though our charge is to take care of our patients and as clinicians, it's our job to represent what is in the best clinical interest of our patients, I think we absolutely can take financial considerations into account. When we deal with our individual patients, we do it every day when we're deciding on what studies we're going to do, and we're seeing it more and more now that patients are having these high deductible plans that we as clinicians dealing with individual patients also have to take into account the cost of care, and I think, you know, David said something earlier that, you know, there are certain technologies that we're worried about abuse of that technology, and I agree that we're not really worried that people jumping out and running to use ECMO, but at the same time, we know that it is sometimes compelling as a clinician when you're doing end-of-life care to offer anything that may potentially be life-saving even if you don't have evidence because you don't have any other alternative, and I

think that if we are too liberal in allowing this technology there is a risk that that could happen, OK? So, I think that, you know, as we've heard from Joanne and from others, we don't want to limit the opportunity to use this technology, which may be truly beneficial for people who have isolated events that are recoverable from, but I think that's a different scenario than end-of-life care, and I think we just need to be very clear that if... if we're... we're dealing with limited evidence here, but there may be some that you can kind of help get patients through an acute event that might allow them to live a long, healthy life otherwise. This is very different than an 80-year-old with heart failure. So, I just think we need to be careful, not that we don't want to leave room for clinical judgment here, but there need to be some constraints on that, so we're clear about the clinical scenario that we're talking about, as opposed to allowing it to broaden too much.

Michael Souter: I can agree with that, and I do. I think that comes down to our questions of efficiency, and, you know, what they, you know, the efficient utilization as far as our resources, but that's a different question from that of should we fund something not because it's expensive.

Chris Standaert: Let me bring this back around for one second. I mean, actually it is an interesting discussion, eloquent. You're actually all correct in multiple ways. The... Mike is correct. The charge of our committee is not comparing one technology to another in terms of cost or relevance or value to the... we're not a value assigning committee. That isn't our job, but again, as clinicians and the reason you are sitting here and you are sitting here is that your experience as a clinician working in the medical-ecosystem informs your interpretation of the evidence and the utility of the device and the cost... it's safety, efficacy, and cost-effectiveness. Those are all relative considerations for all of us, and you should use your perspective and your value and your perspective and that's why yours is different than mine and different than Mike's and mine, you know? That's the value, and you should use those in forming your decision. Recognizing, again, as I said, we are not strictly doing it that way. We can't say this costs X and gives this much value and that costs Y and gives us this much value, and we shouldn't cover this because we covered something. We can't do that. That's not our role, but certainly in using the things you were discussing and thinking about in the process of your own decision making and expressing to your colleagues is quite appropriate, because that's why we're here. So, question, then we're going to move onto our decision tool so we can...

Carson Odegard: OK. I'd just like to ask the agencies, what was the driving force, because all the categories that we deal with are... it was all high and a high

concern, and was there one category that was higher than the other? Was... were you looking at utilization trends that drove this, or was it the harm... the actual harm factor, or, I mean, if you can give us kind of an idea of how that... how it was chosen.

Steve Hammond: Bear in mind that there was a lot of unknown when we first considered this topic, but I think we just had high concern all the way around. On the cost, we knew it was costly but we also had a sense that utilization was rising. So, we wanted to know what is this good for? What are the safety risks? Should we place some conditions on the coverage? Does that answer your question? Right now, it's covered without conditions. So, we wanted to take a look at it and see, get some guidance from what the evidence shows.

Chris Standaert: Let's move on to our decision tool. We can bring this back to wherever we have to get to eventually. So, as always, our options are going to be cover unconditionally, cover with conditions, or not to cover. If the sense of the group as a large is take one of those two opposite ends, cover without conditions or cover... not cover, we don't need to go through a long discussion of conditions. If most people falling in that they would like to talk about conditions before we make that vote, then we should talk about conditions. So, I am... a quick straw vote, people want to talk about... my reading is that people would like to talk about conditions and sort of lay this out. So, is everybody in agreement with that? Anybody think otherwise? OK. So, as a... we don't usually do this, but people kept referring back to the agency recommendations and we have them on a Word document and can pop them up, and that gives us a place to start when we look at that. So, as we go through this...

Josh Morse: Can I interrupt for just a moment, this is Josh?

Chris Standaert: Yeah.

Josh Morse: I believe you often do your evidence vote before this discussion, but I could be wrong.

Chris Standaert: That's where I was going.

Josh Morse: In the initial voting on the...

Chris Standaert: We go through this first.

Josh Morse: Yep, I'm with you.

Chris Standaert: Right. I'm just popping them up so people have something to think about. We'll get to them as we go through this.

Josh Morse: Thank you.

Chris Standaert: Right. So, we go through them the order we go through, right? So, what we have to do is say that we considered safety, efficacy, and cost, in terms of our technology. So, on our document on page three, there is a discussion document and key factor health outcomes and what is the evidence there, and we need to go through this to make sure we actually have addressed all of this as we're supposed to do so it's clear we did this. So, if you go there, in terms of safety, we talked about several things, mortality, device where there are complications, which are fairly broad. That would be bleeding and all sorts of other things, um, disability as a safety outcome is a bit curious, but... so safety, personally my sense was that I found it difficult to sort out whether this was more or less unsafe than what the other option may be, because everything is wildly invasive or somebody dies. I don't know if other people had other thoughts on that. I had trouble sorting it out from the data. I wasn't con... I couldn't be convinced one way or the other. Other thoughts? No? OK. Yeah.

Louise Kaplan: Just a clarifying question. The key questions compare ECMO to conventional therapies, correct?

Elizabeth Russo: That's my read of the key questions, because what we're comparing to isn't VAD, its conventional therapy from my understanding of the key questions.

Gregory Brown: I think there's different conventional therapy for each of the four subcategories is the issue.

Louise Kaplan: And we need to be clear what the conventional therapy is in each of the categories.

Chris Standaert: It doesn't even say conventional... it says conventional treatment strategies.

Louise Kaplan: Yeah, so...

Chris Standaert: Right, that could be therapies. That could be cessation of therapy. That could be all sorts of things. So, what does, yeah... So, it's different than...

Louise Kaplan: ...what does it mean?

Chris Standaert: ...it mean all of that. So, conventional treatment strategies. So, what do you do with these patients with these conditions in the setting of absent ECMO or how does ECMO play into that role, into that, again, that ecosystem is how I would view that because treatment strategies isn't just... we're not comparing it to VAD. We're not comparing it to... we're saying, given your other treatment approaches for these patients, how does ECMO alter that roughly?

Louise Kaplan: I'm just trying to be clear, because ECMO is when everything else fails, you go to ECMO. So, is conventional treatment strategies everything that happens before ECMO or... because some of these studies looked at ECMO versus VAD?

Chris Standaert: If you don't have ECMO, yeah.

Louise Kaplan: Well, if you don't have ECMO then it isn't even an option, right? So, it just depends on where you have your event.

Carson Odegard: If you don't have VAD is what you meant.

Chris Standaert: Either way.

Louise Kaplan: Either way. If you're not in a... at Harborview or U.W., then where do you get ECMO in this state? How many hospitals in the state have ECMO?

Chris Standaert: How many hospitals in the state are in the ECMO registry? Six is the number I heard earlier, I thought?

Eileen Bulger: (inaudible) U.W. and Harborview are both in the ELSO registry. I don't know if Swedish or (inaudible) is in the ELSO registry or not. In the data they presented, there were six, but there are a couple centers that might have, you know, have it available for... if they do cardiopulmonary bypass for patients postoperative that they can't get off the pump, but they don't really use it for other purposes. They don't use it for respiratory failure and so forth. So, it's hard for me to know exactly how many hospitals would be using it on a widespread basis, but largely it's probably three.

Chris Standaert: Going back to our tool, we go to efficacy and effectiveness outcomes. The outcomes we looked at all-cause mortality, length of stay, survival, disability, functional status, health-related quality of life, and long-term health status are on our forms. Are there other things that were worth considering in our outcomes? Nothing else that struck anybody as an outcome point? OK. And in special populations, we had a couple that

looked at age and sex and dialysis or renal... end-stage renal disease essentially, and perhaps those patients did worse, but they are, perhaps, quite unhealthy patients to begin with I would imagine, but it didn't... actually, it didn't seem to make a difference in terms of age and sex... age and gender, as I recall, correct? And costs, we haven't talked much about. I'm curious what people think about the cost data. We actually have some. Sometimes, we have none. It's tricky. Cost is always tricky and you look at our studies and the quality then... the intermingling of populations and the lack of controls and the cost is really hard. Go ahead, David. You were going to say something?

David McCulloch: This is one where it is helpful to know the actual cost, you know, per day, per admission, and these are high. Where I think it gets totally into smoke and mirrors is when you then project and say... I mean, these were ludicrous, you know? \$7,000 per quality of life year... I... that is based on modeling data where you've just dialed the... I mean, an...

Gregory Brown: And I think that's 100% survival, or?

Chris Standaert: 100% survival.

David McCulloch: Right, but I mean, yeah.

Chris Standaert: Yeah, and frankly the state told us they don't actually know how much they pay for this. They don't actually know what...

David McCulloch: Well, because it, it's all, it...

Chris Standaert: It's jumbled in the ICU bill.

David McCulloch: Yeah, exactly. It's bundled with all the other high-tech things.

Chris Standaert: OK. That being said, we're going to go on to first our evidence vote and then we'll talk about this issue of conditions or no... what we do with that. So, on our evidence, go to page nine. You have your little cards, and the yellow cards are the ones we're after. So, we are supposed to vote on, is there sufficient evidence under some or all situations that the technology is effective, safe, and cost-effectiveness, and our choices are unproven, equivalent, less, or more, and our standard we have been using is, if you think there is a situation in which it is more effective or less safe or more cost-effective, that's the way you go. If you don't, you don't. If you think you're not convinced one way or the other, you're not convinced. So, in terms of effective, do we think that there is sufficient evidence under some or all circumstances the technology is effective?

Josh Morse: Seven more, one unproven, and two equivalent. Did I get them all or is it eight more?

Chris Standaert: I don't have an unproven card. Alright.

Josh Morse: Are you missing a card?

Chris Standaert: I'm missing the unproven card and I think I might need that. So, in terms of safety, do we think there is sufficient evidence under some or all circumstances that the technology is safe? And I will raise my hand for unproven. Oh, there we go.

Josh Morse: It's nine unproven and two equivalent.

Chris Standaert: And then cost-effective. Do we think under some or all situations?

Josh Morse: Eleven unproven.

Chris Standaert: so, people wanted to talk about conditions. Let's look at our conditions, and Joanne had some very articulate edits she would like to apply to those. This is where the agency directors started with us... started us, and people generally seemed to like the general concept of this but not all the specifics. Joanne, do you recall... do you have notes there saying exactly...

Joann Elmore: I do.

Chris Standaert: ...what you wanted to put in there?

Joann Elmore: I do, in patients with severe life-threatening, but potentially reversible, and here the group needs to decide, acute respiratory or cardiac failure unresponsive to conventional management... unresponsive to conventional management.

Chris Standaert: And then you wanted the registry.

Joann Elmore: And then I wanted the registry, and that was about it without a lot of the other... it was the bottom bullet... only at facility participating in the ELSO case registry. Right, but the question is, do we need all of the other ors and ands.

Chris Standaert: Let's go back up to the top.

Joann Elmore: Or does this allow the clinician?

- Michael Souter: I do think we need to put some limitations on the, you know, the bridging, because I... I think, you know, the open-ended commitment for a patient who has got pulmonary failure who is actually looking at, you know, whether it's a kind of terminal pulmonary failure. We could consider it as a bridge to transplant, but, you know, if they're not on the transplant list, then that's not going to work for pulmonary. So, you know, hearts they could go onto a VAD, but, you know, lungs they're going... they need to be on the pulmonary list already, and I'm not quite sure how... we need to kind of find some way to express that in this list.
- Chris Standaert: Like... or for whom there is a viable long-term definitive treatment awaiting or something like that.
- Michael Souter: But you could argue that those of...
- Chris Standaert: Imminent... imminently available.
- Michael Souter: ...well, again, you... that depends on your...
- Chris Standaert: Viable.
- Michael Souter: ...definition of imminent.
- Chris Standaert: But we can't say three days. We have no... I mean, we're...
- Michael Souter: Exactly, but I...
- Chris Standaert: ...we just can't do that.
- Michael Souter: ...but I think, you know, that the big thing about it is whether you're on the transplant list or not. If you're on the transplant list, a lot of your workup will be done. If you're not, then, you know, you're on a (inaudible) to nothing. So...
- Chris Standaert: So, that could be one condition. What you just said could be one condition.
- Michael Souter: ...yeah.
- Chris Standaert: And we have a separate one for transplants, for patients on a transplant list. Right? In the preoperative period for heart and lung transplants and then we can add on to that sentence, in the preoperative period for heart or lung transplants, patients who are on a transplant list and in need of...

Michael Souter: So, distinguish heart and lung there, because the heart you can go onto a VAD system and be sustained for perhaps long enough to be able to get onto, you know, a transplant list acutely. You're not going to be able to do that. You've got no interim tool...

Chris Standaert: OK.

Michael Souter: ...in the context of the lung situation.

Chris Standaert: So, the lung patients should be on a transplant list and the heart patients should... OK?

Michael Souter: Yes.

Chris Standaert: So, it's two sentences, both heart and lung is two sentences. So, get rid of lung or heart from that one, one or the other, in the preoperative period for lung transplant. Go back to your first sentence there, for lung transplant, patients who are on a transplant... who are on the transplant... on a transplant list... on a transplant list and require, what do you... how do you want to word that, bridging? A brief period of bridging pulmonary support to... I don't know. I don't have the words here.

Michael Souter: Well, I would, I guess I would probably say in patients who require bridging, in patients with pulmonary failure who are already on... who are already on a transplant list for... on a lung transplant list, then it may be used as a bridging therapy.

Chris Standaert: Patients on a transplant list and in pulmonary failure.

Michael Souter: Yes. It may be used as a bridging therapy.

Chris Standaert: And in pulmonary failure.

Michael Souter: Yeah.

Chris Standaert: ECMO may be used as a bridging device, as a bridging therapy.

Michael Souter: That's the sense of what we're trying to put across. It just needs wordsmithed into the sense of all the other paragraphs and clauses.

Chris Standaert: And the next sentence would be in cardiac... heart... which would be similar, except we would take out the transplant list. We'd say who have pending access to a more definitive treatment, or more definitive

treatment or support or form of cardiac support... support or transplant, I guess. Cardiac support is a new heart, yeah. OK. Get rid of transplant. So, it would be in patients with cardiac failure, essentially, is what you're saying, with cardiac failure not heart transplant, with cardiac failure.

Christine Masters: Get rid of heart transplant?

Chris Standaert: Get rid of heart transplant. In patients with cardiac failure who have pending access to a more definitive form of cardiac support, ECMO may be used as a bridging therapy, something like that?

David McCulloch: Covers VAD and heart transplant.

Chris Standaert: Yeah, exactly. (inaudible) about ECMO may be used as... so just parallel the other sentence.

Carson Odegard: I have a question about the transplant list. Now, are these... typically, are these patients already approved for a transplant, have a transplant, or are they on a long list? How long can the list potentially be?

Michael Souter: So, in order to get onto a list, you have to have usually an extent... to get accepted onto a list, you have to have been seen by a transplant clinician, gone through a program of evaluation. You get a workup done, and you get continuously scrutinized to see whether or not you're actually going to be able to survive on that list. Patients do get removed from transplant lists, because they're now so sick that they would not survive intervention with a transplant. So, it is something that is continuously evolving. The lists can be long. There is great variation across the country in terms of how long a transplant list for a particular organ may be, and it depends on whether you're waiting for a heart or a kidney or a lung or a pancreas for that matter, but there's a lot of state to state variability. At the end of the day, it comes down to where you are in terms of your listing, what your immune response is, serotyping, all those things. There's a lot of factors involved.

Carson Odegard: That's my question, because Dr. Bulger said that lung transplants are usually at that point in time, they've already... they're not just sitting on a list. Do I understand that, or they've already got the lung?

Eileen Bulger: So, the practice at the university is that they're on a list as Dr. Souter describes, which means they've been preevaluated. They're eligible for a transplant. Then they have some event that they can't recover from. So, they bridge them by putting them on ECMO while waiting for their lung to come... their lung to be available.

- Carson Odegard: Right, OK.
- Eileen Bulger: And it seems to work pretty well.
- Carson Odegard: Alright.
- Chris Standaert: Those lists get reshuffled depending on acuity.
- Carson Odegard: Yeah.
- Chris Standaert: So, you move up a number of slots if things are going downhill.
- Carson Odegard: Oh, yeah.
- Michael Souter: At the end of the day, it comes down to chance, but there will come a point where you... if you are so sick that you will get moved off the list because your care has... your outcome is going to be futile anyway.
- Carson Odegard: Yeah.
- Michelle Simon: Can I suggest a clean... a cleaning up of this a little bit. These are conditions for ECMO. So, we know that already. So, I would suggest for the second paragraph there, as a bridging therapy for patients in pulmonary failure who are on a lung transplant list – period, versus.
- Chris Standaert: So, what was that again? Can you say that again so she can... so you can get rid of, in the paragraph for the lung transplant, that all goes away, right?
- Michelle Simon: So, yeah...
- Chris Standaert: So, back out, just delete all that. All that. Keep going. Keep going. Get rid of in the... don't be shy. There you go. Go ahead Michelle.
- Michelle Simon: As a bridging therapy for patients in pulmonary failure who are on a lung transplant list, or already on, it doesn't matter to me.
- Chris Standaert: Should we have already? Yeah? Get rid of the word already.
- Michael Souter: Pulmonary transplant.
- Chris Standaert: Yeah, on a pulmonary transplant list. A renal transplant list. Then, get rid of the whole... from ECMO on goes away. Yes, gone. ECMO goes away – period.

- Michael Souter: Same thing for the heart.
- Chris Standaert: Now, the heart, as a bridging therapy for patients who have pending access to... get rid of... all the way to who. Oh, wait. Oh, no even, sorry. Patients in cardiac failure, so type cardiac failure... cardiac failure. And then you can get rid of the part from ECMO and get rid of ECMO and maybe use it as, yeah. That's nice. That looks cleaner. Can you go up to the top, and we'll go over it.
- Seth Schwartz: I'm just wondering with that cardiac failure one, is that, is that still a little broad, because I mean, there are a lot of people in cardiac failure who could get other forms of cardiac support, but they're 90 years old.
- Michael Souter: They probably wouldn't be considered for access to a more definitive form of cardiac support.
- Seth Schwartz: I, I guess my point is that that's a little bit vague. What does that mean? I mean, we're meaning... we may mean it as transplant or VAD, but...
- Chris Standaert: Say who are appropriate for and have pending access to.
- Louise Kaplan: Even the use of word... the term inappropriately selected case, I find in appropriately very vague.
- Chris Standaert: Very vague, that's why, yeah, that's why I'm... go back down to... wait, wait. Go back. Let's finish what Seth was addressing. So, the sentence of bridging therapy for cardiac patients in cardiac failure. How do we word that so that it is not... who are... who are...
- Seth Schwartz: In anticipation of transplant or something like that? I mean...
- Chris Standaert: Failure who... in whom a more definitive form of cardiac...
- Seth Schwartz: I mean, you want to say something about, like, with good long-term prognosis or something if they survive the acute event. I'm not sure exactly how you word it, but I mean, what we're talking about are people who if we get their heart working again, they're going to live a long time and be healthy, as opposed to somebody who just...
- Michael Souter: Or they get a transplant.
- Seth Schwartz: Right.

- Michael Souter: Why not just say as a bridging therapy for patients in cardiac failure awaiting ventricular assist... placement of a ventricular assist device or a cardiac transplantation.
- Seth Schwartz: I guess then I just have a clinical question. Is a ventricular assist device ever a final treatment? In other words, do people just come off of that?
- Michael Souter: Yes.
- Seth Schwartz: OK.
- Michael Souter: And I must say that's something where we shouldn't go down. I think they've got well evolved protocols for dealing with that and we want to stay away from that.
- Chris Standaert: Should we say awaiting a more definitive form of cardiac support? That's the same thing. Do you want to specify the ventricular assist device in case there's some other device somebody may want to use at some point, or you're tying yourself into that.
- Michael Souter: Well, ventricular assist device is pretty generic.
- Chris Standaert: I don't know the technical answer to that question.
- Michael Souter: More definitive form of cardiac support, that's kind of vague. I think that could... are we talking about pharmacologic support or whatever? I think that, you know, on the basis of the evidence that we have and we've seen, we're really talking about those scenarios where you're either getting a ventricular assist device or you are getting transplanted. End of story.
- Chris Standaert: So, waiting a ventricular assistive device.
- Michael Souter: Yeah.
- Chris Standaert: Or cardiac transplantation.
- Michael Souter: Yes.
- Seth Schwartz: Could we switch it a little bit and say something to the effect of, as a bridging therapy for patients in cardiac failure with a good long-term prognosis if they make it to more definitive cardiac support.

- Michael Souter: Again, they're not going to make it to those things unless they've got that. They go through that period of consideration... VAD's are a very finite resource, and you're not going to be given a VAD unless you've actually got a chance of making a good outcome. So, I think that we... I'm just trying to keep us out of making definitions, you know, that we don't need to get into.
- Chris Standaert: And it seems with a cardiac transplant...
- Michael Souter: It's already done.
- Chris Standaert: ...if your, if your prognosis is poor, you don't get the transplant. I mean, they, they...
- Seth Schwartz: But we're not... but this isn't specific to transplant. We've said nothing about transplant here. We're just talking about people in cardiac failure, and that's... and my point is that that's pretty generic. There's a huge... I guess that's what we're... as we have it defined right here, you can basically give this to anybody in cardiac failure.
- Gregory Brown: Well, in cardiac failure awaiting...
- Michael Souter: Well, get rid of the awaiting, and I would probably say, as a bridging therapy for patients in cardiac failure who have been either accepted or who are going to get... state it more elegantly, I'm sure. Have been accepted for placement of a ventricular assist device or cardiac transplantation.
- Seth Schwartz: That's too vague.
- Chris Standaert: Accepted for or awaiting. Is that the language do you think? Or accepted for or awaiting.
- Michael Souter: Eligible.
- Chris Standaert: Or eligible.
- Michael Souter: Eligible.
- Chris Standaert: Eligible for and get rid of or awaiting. OK. That works? Is that better, Seth, or do you think it's still too vague?
- Seth Schwartz: It's definitely better.

- Chris Standaert: OK. Let's go up to the top. The top two are almost the same. I think Joanne's is a cleaned up version of that second one. So, that second line, in appropriate selected cases, goes away yes? So, inappropriate selected cases goes away. Nope. The second one, that one, that whole sentence goes away. Yes, gone.
- Seth Schwartz: The comma after potentially in the first line.
- Chris Standaert: So, in patients with severe life-threatening, but potentially no, reversible, acute respiratory or cardiac failure unresponsive to conventional management. That would be the whole thing?
- Michelle Simon: The very first line they're talking about. We're requesting...
- Chris Standaert: And is that the whole...
- Michelle Simon: ...an edit.
- Chris Standaert: ...Joann, is that what, the language you intended?
- Joann Elmore: Yep, that was the language I intended, but I'm contemplating Seth's thoughts about, do we want to add in who are likely to recover. In other words, I get the sense that you don't want this to be put in as a bridge to nowhere.
- Seth Schwartz: Yes.
- Joann Elmore: As a bridge that's indefinite, and so...
- Chris Standaert: We could say but likely reversible.
- Joann Elmore: ...well, but, you know, you can reverse the respiratory stuff but everything else is haywire and gone down to... you know, down the drain. So, does the group want to add in anything else to this stem, you know? Who are likely to recover, because all I got was reversible respiratory stuff.
- Chris Standaert: In patients with severe life-threatening, acute respiratory or cardiac failure with potential for meaningful recovery unresponsive to conventional? You got to put something in there.
- Seth Schwartz: Well, the guidelines put in mortality.

- David McCulloch: Isn't that implicit in the bullets below it? It's the... the bolded (inaudible) and then followed by the...
- Chris Standaert: No. This is a separate condition. These are people who have, like, ARDS where you're expecting the pulmonary condition to resolve. So, they're not going to get transplanted. The other two are for bridging for transplants. These are the people where this is the treatment until they get better or they expire.
- Michael Souter: OK with that as it reads?
- Chris Standaert: Joann asked if we should put an and right there, but then... well, these are separate things. So, the other ones are talking about people on a transplant list or in need of a VAD or cardiac transplant, whereas this applies to the people who are independently in respiratory failure, but they're not going to a transplant. Those two sentences specifically refer to transplantation.
- Joann Elmore: I can see it being an and.
- Chris Standaert: But then, then you remove the use of this for anybody who isn't going to be transplanted.
- Joann Elmore: Oh, OK. Good point.
- Chris Standaert: It doesn't need an or. They just list it as three separate things, however you want to do it. These are the conditions. Get rid of the or's. I don't think we usually use or's. Just get rid of the or's.
- Seth Schwartz: Just for our evidence vendor, for the one study we were looking at. Sorry, I'm forgetting the name, the acronym for it. Was there an age criteria for admission into that trial, the randomized trial, the Cesar Trial? Was there an age criteria? Not minimum age. Was there a maximum age?
- Chris Standaert: We can get rid of... go back up. Go back up. Get rid of as bridge to VAD, because we just did that, and then stop. We have to talk about these. I'm sorry. Did you get your question answered?
- Seth Schwartz: No. I mean, I'm... I'm still struggling with, you know, this is a different decision in a 40-year-old than it is in a 90-year-old and so you can have, you know, you can be an otherwise healthy 90-year-old but do you put him on ECMO if they have isolated cardiac failure?

- Elizabeth Russo: They were only considering individuals over the age of 17 on this.
- Kevin Walsh: We're looking at a maximum. We're wondering a maximum age, not a minimum.
- Elizabeth Russo: The state doesn't cover people over 65 unless they're on... they're dual eligibles, right?
- Chris Standaert: Yeah. Some still are... some...
- Elizabeth Russo: They're... they're...
- Chris Standaert: ...some are still working in the state government.
- Elizabeth Russo: Well, you're right. You're right.
- Christine Masters: Then we pay secondary.
- Elizabeth Russo: Yeah. Well, and you've got dual eligibles but.
- Kevin Walsh: Can the vendors look and see what the entry into Peek was? Oh, it was 65? Thank you.
- Michael Souter: I think that's covered and if you've got somebody who you think has got the potentially reversible, if they're at an extreme of age, then they would not be potentially reversible. Now, you may say, well, OK. Well, that may be open to subjective interpretation, but what if you're 66, you know? That's a hard call.
- Louise Kaplan: There are some 66-year-olds who are healthier than 40-year-olds.
- David McCulloch: I think it's implicit in the sense of people who end up on transplant lists. I think that's as specific as we should get.
- Chris Standaert: ECPR? Do we think it is OK, ECPR and... for in-hospital cardiac arrest and can we put conditions on that beyond that? I mean, it's hard to believe every code team is going to start ECMO when somebody has a code. I just find it hard to believe that's going to happen.
- Gregory Brown: Well, theoretically it's going to (inaudible).
- Chris Standaert: Everybody from Harborview who codes is probably not going to get ECMO. I just can't imagine. It's not... that's obviously not going to

happen. Right. It's going to be part of a crash cart. So, we can get rid of, I guess you can leave four.

Joann Elmore: I mean, isn't it kind of covered under the first big bullet. I would get rid of that ECPR and then the hypothermia and, you know, if somebody is in acute cardiopulmonary shock, you know, then they're covered under the first bullet. So, I would consider getting rid of both of these, especially since we didn't have data on hypothermia.

Chris Standaert: Cardiac arrest is different than cardiac failure, and ECPR is... go up to the...

Joann Elmore: (inaudible) and see if you can get it covered in that.

Chris Standaert: ...go up to the first sentence. I'd say extreme cardiac failure. I suppose one could make the statement that that would cover ECPR, right?

Carson Odegard: Acute cardiac failure.

Michael Souter: Can we replace failure...

Joann Elmore: This is something we might consider...

Michael Souter: ...with...

Joann Elmore: ...failure, right?

Michael Souter: ...dysfunction?

Chris Standaert: OK, failure or dysfunction?

Michael Souter: I would actually just replace failure with dysfunction and that would actually cover both cardiac arrest and failure.

Chris Standaert: OK.

Michael Souter: We've got the severe life threatening and potentially reversible, which are the important descriptors.

Chris Standaert: OK. So, it's just to be clear in our documentation the intent of this is to cover the need for this if felt needed in cardiac arrest with in-hospital CPR. So go down, and you can delete both of those. Unfortunately, I don't think we have anything on hypothermia do we?

Joann Elmore: No.

Chris Standaert: So, take that out. All procedures only... after that, yeah.

Joann Elmore: But I don't think we need... even need the not covered. It's sort of everything else is not covered.

Chris Standaert: Right. Yes.

Joann Elmore: So, I would propose that we...

Michelle Simon: Well, it does cover the outside the hospital setting for cardiac arrest, not attest, I assume, but arrest.

Chris Standaert: Yeah. I would get rid of the cardiac support in lieu of that, I guess to Michelle's point. I mean, we assume this is in-hospital. Those people are doing this and not in a, like a... right.

Kevin Walsh: (inaudible) we're trying to parse those out (inaudible).

Chris Standaert: Right. It has, right.

Kevin Walsh: (inaudible)

Chris Standaert: So, we can leave that, yes.

Michelle Simon: its cardiac arrest, I think, not attest. There, under noncover.

Chris Standaert: Yes.

Joann Elmore: But then what about hypothermia?

Michael Souter: Well, it says other than.

Joann Elmore: We didn't have any...

Michael Souter: Yes.

Joann Elmore: ...just get rid of the accidental hypothermia.

Chris Standaert: I would put...

Michael Souter: I would put arrest.

Chris Standaert: ...I would put arrest and get rid of other than accidental.

Michael Souter: I would...

Joann Elmore: That's covered if they come in under the first bullet.

Michael Souter: ...it would be nice to make it clear.

Joann Elmore: Because we have no data. So, here we're putting in, clinically we all understand it, but.

Michael Souter: I'm just thinking about the patient who comes in pulseless who is, like, 20 degrees because they've fallen into, you know, the lake in the middle of winter and you want to start resuscitating him.

Chris Standaert: I think those are fine. Alright. Do we have other comments or edits?

Josh Morse: So, for my clarity, so the other than accidental hypothermia, you're trying to say that that's covered?

Chris Standaert: Deliberate hypothermia?

Josh Morse: It's not specifically not covered.

Chris Standaert: Yeah.

Josh Morse: Is there another way to say that?

Chris Standaert: Other than accidental deep hypothermia. Can we get rid of accidental, perhaps? Yeah. Did you mean to do this?

Michael Souter: Is it the other than that you're concerned about?

Seth Schwartz: So, you're saying...

Michael Souter: It's a double negative.

Seth Schwartz: ...we don't need it. It's a double negative.

Josh Morse? So, you mean for it to be covered?

Michael Souter: That may be better. It would be nice to have that very explicitly understood.

- Chris Standaert: The one on top covers this theoretically. What this says is that if somebody comes in with outside cardiac arrest, you're not putting them on ECMO because you had a cardiac arrest. You're putting them on ECMO because they have deep hypothermia, and that's why they... that's part of their cardiac arrest.
- Gregory Brown: How about we just say not covered outside the hospital setting? Again, the point is this... we bring a hypothermia patient to the hospital you can use it. If you bring a cardiac arrest patient to the hospital, you can use it. It's just (inaudible)...
- Seth Schwartz: But that's not accurate. The point is, if you had your cardiac arrest outside of the hospital, you shouldn't get it when you get to the hospital. That's what we're trying to avoid.
- Gregory Brown: You don't know. I mean. You're saying that you couldn't have some cardiac event in a 40-year-old and you'd never use ECMO in them?
- Chris Standaert: Standing outside the Harborview Emergency Room you collapse of a heart attack and they pull you in and you can't have ECMO?
- Gregory Brown: Yeah, because to me what I'm, what we're restricting is the evidence for its use outside the hospital setting that's not effective.
- Seth Schwartz: its CPR was outside the hospital. We're not talking about using ECMO in a mobile unit.
- Gregory Brown: Right. That's what I'm saying.
- Seth Schwartz: You're saying the opposite.
- Gregory Brown: No. If it's not covered outside the hospital setting. No. No. I just...
- Seth Schwartz: I think the point was, and maybe I can get our clinical expert to weigh in on this, but I think the point in the studies was that there's this unique situation where you have an in-hospital patient who has a cardiac arrest and you may use ECMO in that situation.
- Gregory Brown: Right.
- Seth Schwartz: And there may be some role for it, whereas they are not generalizing that to anybody who had a cardiac event outside in the community setting who then is brought into the hospital. There is no evidence for its use at all in that setting. Is that correct, Dr. Bulger?

- Eileen Bulger: Mostly. And the reason I say that is that there are young people who have major cardiac events with ventricular fibrillation who can be resuscitated in the field, come in, not have ongoing CPR, go to the catheterization lab and need some support. So, that's my... that's why it gets confusing. If you just talk about ECPR, yeah, I totally agree. Everybody that has cardiac arrest and failure should not come in and go on ECMO. That... studies have been done, and they look terrible, but if you exclude all ECPR, it gets confusing, because there are these sort of one-off things. In the hospital, they're one-off things. Not everybody arrests in the hospital. There are people who arrest from massive PE or, you know, something you would think is reversible.
- Chris Standaert: Can you just get rid of that and are we covered under our first sentence?
- Eileen Bulger: It's why it's tricky.
- Chris Standaert: So, if somebody, again, they come into the Emergency Room. They have a severe life-threatening, potentially-reversible, acute cardiac failure or they're going with fibrillation into the catheterization lab and they need... I mean, they would be covered under our first statement.
- Louise Kaplan: It seems to me it would...
- Chris Standaert: So, just get rid of the not covered thing.
- Louise Kaplan: ...yeah. It seems to me it would be easier if you just...
- Chris Standaert: Yeah.
- Louise Kaplan: ...said what is covered.
- Chris Standaert: Yeah. So, we basically got rid of everything he had and put up that. It's a good thing we started there. Alright. Do we like these?
- David McCulloch: Except that Joann's sentence needs to have at least as high a font size as the rest. I'm sorry.
- Chris Standaert: So, we're going to vote. In our vote, we're going to vote on coverage and you don't have to accept these conditions if you are voting. Your voting choices are going to be cover with conditions, which will be accepting these conditions, unless I hear otherwise and somebody wants some other edit, or you're going to vote no cover, or you're going to vote cover, which means cover under all circumstances and essentially

superseding these conditions. Those are your choices. Yes? No more questions or comments? So, we'll proceed to our formal vote. Please vote cover, no cover, or cover with conditions, as you see appropriate.

Josh Morse: I see eleven cover with conditions.

Chris Standaert: That being said, we need to make sure we are consistent with clinical guidelines. There is no Medicare decision on this, correct?

Josh Morse: That's correct.

Chris Standaert: And our clinical guidelines vary. They go by... they are somewhat vague. Some are almost 20 years old, and I think we are in alignment, as best we can, with the combination of the evidence and the clinical perspective we can bring to this. Alright. So, we are done?

Josh Morse: Yes. Thank you.

Chris Standaert: Thank you, guys. Well, we're going to try and get started close to 12:30 for the next one so we stay on time with that. So, we have about 20 minutes for lunch and catching up. We'll get going at 12:30.

Comments on our decision? In terms of transparency, we should respect the people who wrote it and read what they said. They did find a typo, which was corrected. So, the typo they're bringing up about stable versus stable in here, we already, it was already corrected in the document we voted on. It has already been corrected. Otherwise, there are some other questions that we actually did discuss during our meeting, as I recall, and we talked about them, and if there are comments from the committee or a comment they want to make on this they can. If they think this would change how we would think about anything. If I don't hear anything I will assume that's not the case, and we move on with our afternoon agenda. I'll give you all a chance to make sure you read it. OK. We're going to move on.

So, this afternoon, we were talking about spinal injections. I just want to make a few opening comments. This is obviously a very energetic topic. I don't know that we've had a crowd quite this large before. We may have, but I certainly recall one for quite some time. So, there's a lot of energy in the room and interest in the room and a lot of public comments to be directed at us and towards us so we can help make our decision. I want to point out several things. One, this is a re-review. So, we have an existing coverage decision decided five years ago, and in a re-review, our job is to look at the evidence, particularly the evidence that has emerged

since our decision and see how that informs how we think about the decision we made. Do we alter change, leave unaltered, what do we do with that? It's slightly different than a full review, because we're not... we're focusing on the newer evidence is what we're doing.

So, the literature report is complex. There's a lot of data. Personally, I think the folks from Spectrum... they went through a lot of data and tried to put it into a way that we could understand it and reference it and see it and work through it, and there are always issues with methodology and whether people agree or don't agree, but clearly their intent was to give us the data, and that's really what their job is. Our job is to interpret that data in the clinical setting and make a clinical coverage determination based upon our interpretation of that data and that is their job, and that is our job. We listen to the comments from the public, and we listen to them, and we listen to the agency recommendations, and we listen to each other, and that is how we do this.

To clarify some of my own role here, I'm the chair here. I'm a committee member like the rest of you in terms of voting, and my practice is as a rehab specialist and I'm largely a nonoperative spine provider. This is the bulk of what I do. I've certainly been doing epidural injections and other spinal procedures for 20 years. They are part of my practice, and I am interwoven with many parts of the community in terms of spine care in this area and I am one of the authors on the Friedley paper, which is one of the more prominent studies in our view, if I look at it myself, and I also was on the multisided pain workgroup with Dr. Baker and Dr. Dreyfuss as an administrator of that process early on. So, I'm familiar with all of that. I have no ties to any of that. I don't belong to... you know, that's all done. So, I have no ties to any of it and I just have perspective is what I have, just like all of us have clinical perspective.

Again, our charge is to look at the data, look at the evidence we have, use our clinical expertise and perspective, and make the right decision for the citizens of Washington on efficacy, safety, and cost. That's what we're supposed to do and I have immense respect for the people on this committee and that's what we're going to do.

So, the order of things typically is, we first hear from the state agency about utilization and outcomes. Then we have public comment. We have a large number of public commenters, the vast majority of which have donated their time to two individuals who will present a prepared talk that they have already arranged with the agency. The best we can tell from this list, we have 13 additional individuals in the audience who wanted to make a separate presentation signing up today who had not

prearranged with us to do that. So, our prearranged speakers have basically used up our normal comment time. So I will ask Josh to add on an extra 26 minutes to our public comment time. So, that means for those 13 you will all get two minutes a piece. There are about 50 people who donated their time to Dr. Messerli and Dr. Dreyfuss. So, they're getting far less than that per person, but we're trying our best to accommodate everybody and still make sure the committee has time to really make an appropriate decision. So, everybody who is on this list who is not prearranged... we'll go through the prearranged speakers initially. Then other people may get up to talk, and at the moment we'll go with two minutes a piece. I hope that works out. So, we want everybody to have their chance to say what they want to say to the committee. OK. So, we're going to start with the state agencies.

Shana Johnson: Good afternoon everyone. I'm Shana Johnson, and I'll be presenting the agency medical directors review and recommendations on spinal injections today.

So, as previously stated, this represents a re-review of the spinal injections topic. Since the initial review, there has been new data that has updated the evidence base on the impact of this intervention.

Chris Standaert: Can you step a little closer to the mic or move the mic towards you so people can hear you well.

Shana Johnson: On the impact of this intervention on patient oriented outcomes, pain, function, and risk of surgery. This data also includes new trials with comparisons to conservative care, not only therapy but also neuropathic pain agents.

I'm going to first start by giving a national review of the utilization. Then, we'll look at Western Washington, and then directly at the state agency data. On this map, the area of the United States with the highest utilization of spinal injections are noted in red. To give you an idea of the variability in the rate, Hawaii had 5 injections per 1000 whereas Alabama had 39 per 1000. Eight states, and they are noted in red, had injection rates greater than 25% the national average of 26 per 1000. By (inaudible) spinal injection rates were lowest in the Northeast and highest in the South. Higher injection rates were also associated with higher surgery rates.

Taking a look here in Western Washington, the circles in red note areas with injection rates that are higher than the regional rate, blue areas with rates lower than the regional rate, and the bigger the circle, the more

gender and age cohorts across. So, here you can see Olympia and Puyallup residents were more likely to have spine injections and Seattle residents were less likely. This could point to areas with higher regional burden of illness, or it could be the result of variation in practice.

Prior to looking at the state agency data, I just want to remind everyone of the decision in 2011. At that time, it was recommended to cover cervical, thoracic, lumbar, epidural steroid injections for radicular type pain that did not respond to conservative therapy and to noncover therapeutic medial nerve branch blocks, therapeutic facet injections, and intradiscal injections. This detail just goes into the more specific limitation of coverage for your review.

Looking at the utilization with the Public Employees Benefits Board, the rate of facet injections had a large drop starting in 2012 with a smaller decrease in the rate of epidural steroid injections. This drop was coincident with the HTC decision in 2011.

Here we have the Medicaid data. We see a decreased number of all injection types spanning from 2012 through 2014; however, there are multiple confounders in this data. There was the HTCC decision. During this same time period, many fee-for-service Medicaid patients transferred into managed care, and the Medicaid expansion population hit in 2014.

Looking at the numbers for Labor and Industries, there is a downward trend in all injection types from 2011 through 2014.

Next, I would like to briefly go over some of the medical policies and clinical guidelines that helped the agency come to their recommendations. Currently, all state agencies, Medicaid, PEBB, L&I, and Corrections, all follow the 2011 HTCC decision.

Medicare does not currently have a national coverage decision; however, there is a local coverage decision. The local coverage decision recommends epidural steroid injections for a variety of spinal disorders, radicular pain, neurogenic claudication, as well as moderate to severe back pain. Additionally, they also recommend facet injections or median branch blocks for patients with presumed facet joint pain. So, here you have a policy that's fairly broad. It covers most injection types.

When we move into the private payer realm, there is some variation in coverage noted. This is mostly related to therapeutic facet joint

injections. By therapeutic, I mean, use of the steroid. Aetna and Cigna do not cover therapeutic facet joint injections, whereas Humana does.

Clinical guidelines were also an important factor in our recommendation. The evidence report includes multiple clinical guidelines. Here I have the American Society of Anesthesiology Task Force on chronic pain guidelines for review. Across all guidelines, it is fairly consistent to recommend epidural steroid injection for radicular pain. The recommendations vary, in particular, in the areas of therapeutic facet injections, and these particular guidelines, they are recommended for presumed facet joint pain. Sacroiliac joint injections also see variation among guidelines, some recommending them and some saying that evidence is insufficient for their use... or correction, recommendation.

There have also been multiple systematic reviews on the efficacy of this, one in 2015 concluded that epidural steroid injections for radiculopathy do show immediate benefit in pain and function, but the benefits were small and not sustained. They found no long-term risk on surgery. In their review, they felt facet joint steroid injections were not effective for presumed facet joint pain, and they felt the evidence was insufficient for sacroiliac joint injections.

Another big question at hand is, so what's new since 2011. What has been added to our evidence base? This is just a snapshot of some of the bigger differences. A more comprehensive report is included in the evidence summary. For lumbar epidural steroid injection and radiculopathy due to disk and foraminal narrowing, the current report provides a meta-analysis supporting that the injections provide short-term improvement in pain but not function and no difference in risk of surgery. For epidural steroid injection versus discectomy and lumbar epidural steroid injection versus conservative care, there were new studies, but the data was shown to be insufficient to draw a conclusion. There is an interesting new study looking at lumbar epidural steroid injections versus gabapentin. In this study, they found no difference between epidural steroid injection versus oral gabapentin in pain or function. Additionally, there were two studies added to the data for epidural steroid injection in lumbar stenosis, reinforcing previous findings of no benefit, and there was long-term data added supporting that epidural steroid injection have not been shown to be effective for axial pain.

There is a new study with lumbar facet disease. In that study, it showed that intraarticular steroid injection versus intramuscular injection into the paravertebral muscles did show positive benefit over the short-term.

There is a new study looking at cervical epidural steroid injection and radiculopathy. In this study, combination of care including the epidural steroid injection and conservative care, which included both therapy and neuropathic agent, resulted in a better outcome. The report also noted worse outcomes in the epidural steroid injection versus the conservative care in regards to pain and functional measures over the immediate and longer terms. However, these longer terms were after the steroid injections' effect would have likely worn off. There is also a new study looking at sacroiliac joint point. In this study, the function was better in the conservative care group versus the injection group. Compared to the other study, which was positive, however, it had a relatively lower dose of steroid that they used in the injection compared to the other. In regards to cervical epidural steroid injections and axial pain and cervical stenosis, there were new studies and they showed no difference in groups.

So, taking the evidence that's new since 2011 and combining that with the old data, some of the following conclusions could be considered. Epidural steroid injections provide short-term improvement in pain but not function in radicular type pain. Epidural steroid injections do not seem to provide benefit in spinal stenosis pain or axial pain. The evidence taken, overall, although the data is certainly mixed, is that therapeutic injections are not effective, and the evidence is insufficient to draw conclusions on sacroiliac joint pain.

There were new studies in this evidence report that evaluated injections against conservative care that included both therapy and neuropathic agents that did suggest that conservative care may be equal to or better than the treatment of radiculopathy or SI joint pain in some patients, and this should be considered as part of the shared decision making process with the patients.

So, to that end, the agency makes the following recommendation. We recommend that cervical, thoracic, and lumbar epidural steroid injections continue to be covered for radicular type pain in those who have failed conservative care and sacroiliac joint injections for those with chronic pain. We recommend it continues to be a noncovered benefit for medial branch nerve blocks, intradiscal injections, therapeutic facet injections with a note that epidural injections for central spinal stenosis and axial pain are not a covered benefit. The limitations of coverage are fairly similar to the previous decision. That ends my presentation. Does the committee have any questions for me?

Chris Standaert: Thank you. So, give the committee a second. So, do people have questions? Yes, Louise.

Louise Kaplan: I was interested in the slide that showed the spinal injection use in Western Washington, and you took a very circumscribe geographical region. Was there some reason that you didn't extend it further north or south or across the entire state?

Shana Johnson: Well, that was data presented by the Washington State Health Alliance. And so, their reason for doing it in that manner, I'm not sure of.

Louise Kaplan: The state doesn't have data of its own that it could use to expand on that?

Shana Johnson: No. This data was taken from a source, a published source. Yes, that was not saved data. That was from a nonprofit.

David McCulloch: Can I just ask, so, Louise, that was originally the Puget Sound Health Alliance and they have, in the past couple of years, tried to expand to the state, but it's... they get the data depending on voluntary participation by healthcare organizations across the state. So I would think over time that will expand to the whole state, but I'm sure those were the data they had.

Chris Standaert: Any questions for Dr. Johnson? She will be available should we have more questions, I am sure.

Joann Elmore: The Medicaid data that we do have... well, actually all of the state data that we do have about procedures that are being covered. So, I just want to be clear that what the current coverage guidelines are, what is being covered is only what's under the current guidelines or is the state paying for anything that does not meet the current coverage guidelines?

Shana Johnson: If I understand your question correctly, no. We are only, we are all following the HTCC decision from 2011 on what we cover.

Chris Standaert: Any other questions or comments? If not, we'll move on to our public comments. Thank you, Dr. Johnson. I appreciate that. So, public comments. We have an order here. Again, we have several people who are prearranged to speak, and then I will go through the list in the order they were written. For people on the list, I will do my best to get your name right. I may or not. I know some of you but not all of you. I know some of your titles but not all of them. So, the people who signed up, Dr. Stanos, has donated time to help him. So, he has five minutes. Then, Dr.

Friedly has three, and then Dr. Dreyfuss and Dr. Messerli have a combined presentation up there. And for you and everybody else who steps up, what we need to know is your name, identify yourself. Identify your institution. Identify if you are representing some organization or group, and pertinent conflicts of interest for the committee. That would all be helpful, thank you. Yeah, go ahead.

Steven Stanos: Thank you, Chair, and members of the committee. For the record, my name is Dr. Steven Stanos. I am the medical director of Swedish Pain Services, and I will be providing comments to you today on behalf of Providence Health and Services, which includes the Swedish Health System. I am also president elect of American Academy of Pain Medicine, a member of the 15-member multisociety pain working group or MPW, a multisociety group that represents approximately 100,000 physicians.

Since 2013, Swedish and Providence have cared for more than 130,000 patients with back pain complaints alone, and we perform approximately 4000 spinal procedures per year in our outpatient facilities. We strongly support the use of appropriate interventional procedures for patients in the treatment of acute and chronic neck and low back pain. While outcome studies for interventional procedures can be challenging, we support the use of evidence based medicine, including appropriate use of systematic reviews in determining guidelines. We believe these guidelines can be practical tools for clinicians, as they care for a complex population of patients that present with spine pain. It is in the spirit that we provide the following comments, which we hope are going to be helpful, as you reconsider the re-review of the evidence to determine whether changes in policy are needed.

Our system is concerned for a variety of reasons that the 2015 scientific review board before you today did not represent an appropriate systematic review of efficacy studies, and I just wanted to concentrate briefly on three specific reasons.

First, the review was limited to randomized control trials, ignoring the best available evidence. Many high-quality prospective studies were inappropriately excluded, including but not limited to facet studies by Dolan, Ackerman, Namatacose [SP], and Fulman. The sacroiliac joint studies by Mahgers [SP] and Lililang [SP] and the epidural studies of Kennedy, Gharibo, and Rados.

Number two, the strength of evidence approach appears to not weigh high-quality randomized control trials fairly, as opposed to low-quality ones including high weigh-in of old studies that predated current best

practice standards and may have included antiquated studies that don't reflect contemporary techniques. For example, many of the studies they reviewed did not include modern diagnostic imaging, like MRI and/or there was contemporary use of image... or the use of contemporary image guidance for injections. Additionally, this was done at the expense of ignoring best available evidence, including some high-quality observational studies.

Number three, the formal review process lacked appropriate peer-to-peer review and ignored or underutilized content experts. They could have assisted Spectrum in a more accurate clinical understanding of the evidence.

Also, the Friedly, et al study, the trial that initiated the Health Technology Assessment re-review is a comparative effectiveness trial for lumbar spinal stenosis, a pragmatic RTC, which examined neurogenic claudication comparing glucocorticoids plus lidocaine to lidocaine along with no sham injection group. It is not an efficacy trial. That being stated, both arms of the trial reported significant improvements in pain and function, and this is contrary to the evidence review's interpretation. The Friedly trial did not evaluate the effects of epidural steroid injections in those with radicular pain and central stenosis. The Nam trial demonstrated efficacy within this context.

So, based on the fact that there is new affirmative literature for the efficacy of epidural injections for the treatment of radicular pain from all causes and new and uncited affirmative evidence for SI joint injections, we believe that there is no new evidence that suggests that the committee should reconsider its prior decision in 2011 to cover epidural steroid injections and sacroiliac joint injections. In other words, we assert that the current evidence support the committee's 2011 decision to cover these procedures.

We believe that a more appropriate review will support better patient care by limiting over-utilizations of services and preventing appropriate patients from being denied access to treatment they need and deserve, ultimately leading to better healthcare outcomes not only for the patients within the Providence system, but the entirety of those that your decision could impact in the state of Washington, which could include approximately 2 million patients, a growing number of Medicaid enrollees, public employees, and approximately 100,000 L&I claimants.

From an individual patient perspective, reducing or limiting access to spinal injections could cause unnecessary pain and emotional distress,

challenges with daily, family, and recreational activities, work loss, prolonged L&I claims, time loss payments, and also the increase in dependence on government welfare programs, but most importantly, as well, potentially complicate complication rates from other treatments, including misuse of medications and potentially inadequate or unnecessary surgery.

So, again, we thank you for the opportunity to provide our comments on this report, and we look forward to being a partner in the work ahead. Thank you.

Chris Standaert: Thank you, Dr. Stanos. Dr. Friedly, and for the speakers over here, you will see a little hand or a sign go up when you are getting close to your time. So, again, please identify yourself and conflicts and representing, and all that.

Janna Friedly: Right. Thank you. My name is Dr. Janna Friedly, and I am an associate professor at the University of Washington in the Department of Rehab Medicine. I am a researcher. Let's see if I can... and my funding for my research is provided by AHRQ, PCORI, and the NIH. I do not perform spinal injections as part of my clinical practice, and I have no financial conflict of interest in what I'm about to talk about.

What I would like to do is to present to the committee some important information about many of the studies that were included in this report that were published by Dr. Manchikanti. All of his studies are self-funded studies that are conducted in a sole private practice with procedures performed by a single provider with no external oversight by a funding agency or a data safety monitoring board. All of his manuscripts identify that there has been IRB approval with "The IRB" but there is no clearly identifiable accredited or registered IRB associated with these studies, and the only publically available information about his protocols is through clinicaltrials.gov, and there are multiple studies that are published under one entry with significant discrepancies in the methodology used and published in his papers.

This is an example of one of the clinicaltrials.gov entries that has six studies that are published underneath this one entry, and there are significant discrepancies in the study description, inclusion/exclusion criteria, primary and secondary outcomes.

He publishes the vast majority of his manuscripts in the Pain Physician Journal, which he founded. He is the CEO of the organization ASIPP, which owns the Pain Physician Journal, and despite being labeled a peer

reviewed journal, he has at least four randomized control trials that were accepted within eight days of submission, and another four randomized trials that were accepted within 14 days of submission, which is not consistent with a credible peer review process.

This is an example of one of his clinical trials and highlighted in yellow in the bottom left hand corner shows you that from time... from submission to acceptance was four days, and this is another example with a turnaround time of eight days.

He had at least twelve concurrent randomized control trials being conducted simultaneously, particularly in 2008 to 2009 that he published in his own private practice, which means that a single provider performed all procedures with over 1300 enrolled patients in his clinical trials. I wanted to present this information to you and it's up to the committee to decide how to apply this information to the evidence report. Thank you.

Chris Standaert: Thank you, Dr. Friedly. Dr. Dreyfuss and Dr. Messerli, combined you have 30 minutes. Dr. Messerli, you can stand. You need the mic.

Brandon Messerli: Can we get the slides up?

Chris Standaert: The slides are coming up. Again, identify yourself and the organization you may represent and conflicts of interest.

Brandon Messerli: Alright. My name is Dr. Messerli, and I'll be presenting with Dr. Dreyfuss today. We're both staff physicians at Evergreen Health. Our only financial conflict...

Chris Standaert: You have to get close to the mic, because this is all recorded and people all want to hear. Thank you.

Brandon Messerli: Our only financial conflict is that we perform these injections on our patients. Spine injections, when done for appropriate indications and with contemporary techniques, can provide significant benefit for pain relief, disability, quality of life, and they have a very low risk profile, as compared to alternative treatments. As part of a tiered multimodal treatment plan, this maximizes the effect of the injection, promotes natural recovery, and helps prevent recurrences. Alternative treatment options are not always indicated, effective, or desired by the patient and doctor due to risks.

Rather than eliminating spine injection access to 2.2 million Medicaid state and L&I enrollees, we recommend covering policies consistent with

the multisociety pain workgroup, or MPW, consensus guidelines, which were adopted by Medicare and Noridian and are appropriately restrictive while allowing physicians to care for our patients using an evidence based best practice approach.

I want to point out a state statute, 70.14.110, that relates to the Health Technology Assessment. "...the committee determinations shall be consistent with decisions made by Medicare and expert treatment guidelines, unless there is substantial evidence to the contrary." So, let's talk about those policies and guidelines.

In 2012, Dr. Jacques and Tavenner endorsed a plan with Medicare to move towards standardizing pain LCDs for national implementation. All CMS Contractor Medical Directors participated, and this was led by Dr. Hecker of Noridian. Consensus recommendations were sought from stakeholder societies via the MPW utilizing a scientific and democratic process with attention to best practice. You can find those in our appendix.

These are the 14 medical societies, representing over 100,000 physicians, including many that are non-interventionalists. Each had representatives at the MPW meeting and formulated and endorsed the practice guidelines.

These five met, including Noridian, and covering 45 of 50 states, have subsequently endorsed and implemented the MPW recommendations into their local coverage decisions for epidural and facet procedures. I'll state that all carriers in all 50 states cover epidural injections for radicular pain of any cause and also spinal stenosis with neurogenic claudication. All carriers in all 50 states also cover sacroiliac steroid injections; 47 of 50 states cover therapeutic facet steroid injections.

So, is there substantial evidence for a contrary determination? Unless there is high-quality evidence showing a lack of efficacy, there should not be coverage determinations that oppose Medicare and society guidelines.

Another statute in the state law states that evidence reviews shall give the greatest weight to the evidence determined to be the most valid and reliable.

Spectrum's definition of validity appears to only consider the presence of randomization and double blinding, and their key questions were formulated in order to exclude non-RCTs. The law does not state that

only RCTs can be included in these reviews, however. In our opinion, a well-designed prospective study is more valuable than an RCT with antiquated diagnostic and injection techniques.

What trials most represent contemporary best practice? It's the recommendation of the MPWE and Medicare carriers that advanced diagnostic imaging and imaging-guided injections should be utilized. Without the former, the etiology of the condition is unknown, and the best injection approach to optimally concentrate the injectate at the site of pathology is unknown. Without the latter, we know that upwards of 30 to 52% of epidural injections performed without fluoroscopic guidance are outside the epidural space and cannot be considered epidural steroid injections.

Unfortunately, a majority of the RCTs that Spectrum included for epidurals did not utilize imaging-confirmed diagnoses or image-guided injections and, at times, these trials were given higher relative weighting than trials with contemporary methods. In these trials, it is unknown if enrolled subjects actually had the indexed condition or if they actually received the indexed treatment. Are these the results a valid indicator of the efficacy of modern practice?

The Health Technology Assessment clinical experts also questioned Spectrum regarding the exclusion of non-RCTs. Spectrum's response was that observational studies can be helpful in certain situations where the outcome is hard and quantitative, such as evaluating mortality. However, they have been shown to overestimate the effectiveness of when it's based on subjective outcomes. In our opinion, although it may be more challenging to quantify and collect measures of pain, function, disability, and missed work, these endpoints remain of great value to the patient.

Well-respected authors of evidence-based medicine have studied and challenged the misconception that only RCTs should be evaluated. Cochrane review of 2014, Anglemeyer looked at nearly 1600 meta-analyses and over 200 medical conditions and found that on average there is little difference between the results obtained from RCTs and observational studies. Norris in the AHRQ report of 2011 stated that because it's unusual to find sufficient evidence from RCTs to answer all the key questions of benefit, that reviewers should routinely assess the appropriateness of inclusion of observational studies.

It is also worthwhile to note that in other Health Technology Assessment reviews by other evidence vendors, non-RCTs have not been excluded.

Validity of trial design also relates to outcome measures. The NIH taskforce recommended that in pain medicine, we utilize categorical data. It has been shown that group means are a crude assessment of effect and can conceal good responses in a subgroup of patients. Alternatively, categorical data allows the subgroup of responders to be revealed. A good example of this is the Ghahreman 2010 study when they looked at the mean data. There was no statistically significant benefit to epidural steroid injections, but when they looked at the categorical data, it was, and the NNT was only 3. Spectrum did not fully acknowledge all categorical data available in the cited trials, nor assign relatively higher weighting to these trials.

The validity of a meta-analysis also needs to be considered. Bias can occur with how trials are weighted and collated. If weighting does not account for quality of study design, then large RCTs with poor methodology can dilute the positive outcomes of smaller, well-designed trials. The methodology for weighting trials in Spectrum's meta-analysis is not clearly delineated.

Because there are multiple points of debate with how to conduct a systematic review, we must ask if Spectrum could introduce bias based on their choices. Well, Spectrum is a for-profit company that may have a bias to produce a work product that attracts further business by Health Technology Assessments and other organizations. I would like to point out, they have made over a million dollars for the 11 evidence reviews they've done for Washington State. I would also like to point out that it is unclear to us whether Spectrum has disclosed actual or potential conflicts of interest, as required by the state for all presenters.

Spectrum also may have a bias to produce results and conclusions that are consistent with prior publications by its authors, which also excluded non-RCTs and largely stated a lack of benefit for spinal injections. These four, as well as the current review, I'd like to point out, share three of the same authors.

Now, let's move on to discussing whether epidurals are safe. In April of 2014, the FDA released a warning stating the epidural steroid injections could be complicated by stroke, loss of vision, paralysis or death. Later that year at an advisory meeting, the MPW gave some points. When using non-particulate steroids, there have been no published cases of serious neurological injury. The cases of serious neurologic injury are rare, but when they occur, it's been when particulate steroid has been injected, particularly via a transforaminal route in the cervical spine or in the lumbar spine when imaging guidance was not used with standard

precautions. They also occasionally occur with interlaminar without imaging guidance.

Recent studies have looked at non-particulate steroids as an option as compared to particulate steroids. One animal study injected a non-particulate steroid directly into the vertebral artery and found that no animals had any complications. These two studies noted at the bottom compared particulate to non-particulate steroids in human efficacy trials and found that they were equivalent.

Thus, the MPW worked with the FDA to publish consensus considerations with how to reduce the risk for epidural steroid injections. These considerations were endorsed by the FDA. The publication is listed here and several of the main points are shown there.

Ultimately, the FDA decided that no new warnings needed to be published and that a contraindication label was not necessary, as the risk was very low.

Subsequent to that report, there has been one more safety trial that was published very recently. It involved over 16,000 procedures done at Mayo, Penn, and Northwestern, and I would like to point out that they used best practice techniques in their procedures. It is notable that there were no major adverse events that occurred in over 16,000 procedures.

When I'm sitting with my patient in the exam room talking about the indications, risks, and benefits of spine injections, it is also important to put it into context of what the risks and benefits are of their alternative treatment options. If access to spine injections is eliminated or reduced, then patients may turn to more aggressive medication use to treat their pain. Opioids have certainly been in the media on a nearly daily basis recently, and for appropriate reasons. There is an epidemic of opioid use and opioid related deaths. It also can lead to misuse, dependency, tolerance. It can have opioid-induced hyperalgesia, constipation. Also, there have been no RCTs looking at the use of efficacy for use of opioids in the treatment of low back pain beyond three months. Even for short-term relief, effect sizes are only moderate for treatment of pain and small for functional outcomes. With increased NSAID use, we may expect patients to have more GI ulcers, bleeds, and renal insufficiency. There is already over 100,000 hospitalizations a year due to this and over 16,000 deaths. NSAIDS also have a small effect size for treatment of short-term relief of low back pain and very limited data on chronic low back pain.

This graph shows the alarming trend of opioid-related deaths in the last 13 years. It's almost increased three and a half fold. There are over 28,000 deaths per year due to opioids.

So, let's talk about whether surgical risks... more patients will undergo spine surgery. So, for herniated disks there is a 3% complication rate with medical causes and infection and there is a 0.2% mortality rate. Looking at herniated disks and spinal stenosis, there is a 10 to 19% reoperation rate within four to five years of the initial surgery.

Looking at efficacy for herniated disk surgery, within five years of surgery there is almost a... sorry. There are only 28% of the patients that report complete resolution of their symptoms. For spinal stenosis within four years, only 60 to 70% rate their improvement in leg pain as major and that they are satisfied.

If spine injections are eliminated, other potential downstream impacts must be considered. Not only what I've mentioned, but also the unnecessary pain and emotional distress, disability, lost wages in labor, and related to Labor and Industries delayed return to work, employer hardship, prolonged claims and time loss payments and people seeking more permanent impairment. Thank you.

Paul Dreyfuss:

Paul Dreyfuss from Evergreen Health and also a clinical professor at the University of Washington. I'm going to present the evidence within the time that I have allotted to me. I'm going to highlight the pertinent RCTs using the best practice approach. I'm going to provide you the new trials, since the last report and provide you several trials that were not given to you by Spectrum.

The Friedly study was 400 subjects, randomized control trial. Those subjects had neurogenic claudication with spinal stenosis. The predominance of the injections were interlaminar. They randomized subjects to epidural steroid injection and anesthetic or anesthetic alone. At three weeks, there was a significant benefit in the epidural steroid injection group in regards to pain and disability. At six weeks, however, both groups actually showed significant improvement both in leg pain and in function. Additionally, 60% of subjects approximately had improvement such that they were satisfied with their care. Friedly did publically comment to the Health Care Authority that this study design does not address the question of which patients benefit from epidural injection of lidocaine plus corticosteroid versus placebo or another active treatment. This was a comparative effectiveness trial, not an efficacy trial.

It has not been established via randomized trials that epidural anesthetic administered via an interlaminar approach is only a valid placebo. Epidural anesthetic may have a therapeutic benefit for mechanisms different than how epidural steroids work.

There was a meta-analysis by Bicket in over 43 studies looking at epidural steroid injections to epidural nonsteroid injections to nonepidural injections. In their meta-analysis, they showed a statistically significant benefit to epidural steroid versus nonepidural injections. The predominance of trials in this meta-analysis utilized the interlaminar approach.

Furthermore, they did indirect comparisons looking at epidural and nonsteroid injections and found that they were two-fold more likely than nonepidural injections to achieve a positive outcome. They concluded that epidural nonsteroid injections may not constitute a true placebo.

Lumbar stenosis causing neurogenic claudication is a different condition than that causing lumbar radicular pain. The Friedly study cannot be used to judge the value of epidural steroid injections for radicular pain in light of central spinal stenosis.

Spectrum did conclude that a greater proportion of subjects receiving epidural steroid injections compared to epidural nonsteroid injections actually had successful short-term pain relief. They defined short-term as less than three months. If you have severe radicular pain, and you get relief for three months, you're going to be impressed. It is of great clinical benefit, and it facilitates natural recovery and allows other conservative care options to move along with ease.

Transforaminal studies reviewed by Spectrum that had the highest methodological rating were the trials of Ghahreman and Karppinen. These trials also used the best practice approach. The Ghahreman trial was 150 subjects, unprecedented in the fact that there was five randomized groups blinded, transforaminal epidural steroid injections, transforaminal anesthetic, or saline, and intramuscular steroid or saline. Primary success was defined as greater than 50% improvement in pain with functional improvement and reduced need for healthcare.

At one month, the group mean data showed significant benefit to the steroid group, as opposed to other arms, except for transforaminal saline, but the results were very bimodal. Patients responded great or

they did not, i.e. a nonparametric distribution. Owing to such, mean data is not as valuable as categorical data.

When you look at such, the transforaminal epidural steroid injection group obtained outcome that was successful in 54%, much less than all other groups, and this benefit was now deemed statistically significant.

As mentioned before, the NNT for transforaminal epidural steroid injections is 3; 3 is a very powerful number. Keep perspective on NNT. NNT for CABG to prevent MI is 10. For antidepressants to work, it is 6; 3 is impressive. It does, however, degrade with time. We are fully aware of that.

The Karppinen trial was 160 subjects with radicular pain from disc herniations. Randomized to transforaminal epidural steroid injections versus saline. At two and four weeks, there was significant benefit to the epidural steroid injection group versus saline, both for leg pain and for function, and there was cost-effectiveness, and twice as many patients had dramatic reduction in leg pain.

The Nam trial of 2011 looked at subjects with radicular pain secondary to central spinal stenosis. Randomized epidural injections, steroid versus anesthetic.

At two, four, and twelve weeks the steroid group showed significant benefit, both for pain and for function and those obtaining success defined as 50% improvement of pain was 76% in the steroid group, and this was significant.

Now, Spectrum did a meta-analysis utilizing their proprietary system, and they did not find benefit to epidural steroid injections for radicular pain in the short-term; however, a publication that came out very recently by Bhatia disagreed and found an alternate conclusion. They were a little more circumspect and included all transforaminal studies, including Vad and Ng, and they weighted studies much differently by a different system, and they actually found significant benefit to epidural steroid injections in less than three months' duration following this procedure, as compared to controls.

There was a very good comparative effectiveness trial using a best practice methodology by Kennedy comparing two different steroids, triamcinolone versus dexamethasone. Categorical success at three months and six months for 50% improvement of pain was 73% in each

group. This trial was excluded by Spectrum because it did not have a placebo arm despite being randomized.

Cohen did a comparative effectiveness trial utilizing best practice techniques in 84 patients with disc herniations and radicular pain randomized to three groups, including epidural steroid injections. Categorical success was 75% at one month for those receiving epidural steroid injections; however, the results did not reach significance, but they did conclude their interpretation of such was that these results can neither exclude nor prove a modest benefit for steroids.

In regards to intralaminar epidural steroid injections, the vast majority of trials, as you heard quoted by Spectrum, did not use contemporary best practice diagnostic or injection methods. Trials dated back to '74. It's now how we're doing things in 2016. There are no new interlaminar efficacy trials, since the last report. There are comparative effectiveness trials. There are three comparative effectiveness trials, Rados, Ghai, and Gharibo, that were not cited by Spectrum because they did not have a placebo arm, but they looked at fluoroscopically-guided interlaminar epidural steroid injections versus transforaminal epidural steroid injections and found equal effectiveness.

There was one comparative effectiveness trial by Ghai looking to do epidural steroid injections and minimize the number that were performed in patients that have radicular pain secondary to a disc protrusion. Double-blinded parasagittal interlaminar epidural steroid injections randomized steroid versus anesthetic. In this trial, categorical success at three months was 86% in the epidural steroid injection group, which was significant, and its benefit was maintained for up to a year. There was also benefit that was significant and maintained up to a year in regards to function.

Riew did the only RCT that actually evaluated surgery as the primary outcome to gauge the surgery sparing effect of epidural steroid injections; 55 patients with central spinal stenosis, foraminal disease, lateral recess stenosis, and disc herniations were randomized in a double blind fashion to transforaminal epidurals versus anesthetic; 71% of those receiving the active arm actually canceled their surgery at long-term follow up; 80% of those, even five years later, still did not have surgery.

Bicket did another meta-analysis of the surgery sparing effect of epidural steroid injections. Up to 50% of those considering surgery had epidurals combined with conservative care versus conservative care alone, actually avoided surgery, another trial not cited by Spectrum.

It was the pragmatic RCT in 50 patients that received epidural steroid injections combined with usual care versus usual care alone. The difference was small but significant stating adding epidural steroid injections to usual care alone was more effective, and this was largely due to increased work productivity from a point of view of saving cost. The theme is, epidurals combined with other care not performed in isolation.

In regards to cervical epidural steroid injections, there are no new efficacy trials. There is a comparative effectiveness trial by Cohen showing benefit of combining epidural steroid injections with conservative care, as we do in contemporary practice, which is the best method of how we treat our patients.

In regards to cervical facet injections, prior decisions by this committee were negative based upon the efficacy trial by Barnsley in whiplash patients. There is a new trial cited by Spectrum, by Park, in patients that have the facet pain diagnosed by contemporary methods and although this study had significant methodological flaws, it did suggest an added benefit to facet injections in addition to multimodal care at one year follow up.

There is a prospective trial in those with atraumatic facet pain not cited by Spectrum by Folman; 30 subjects had cervical facet arthritis, diagnosis by their criteria was relief from an intraarticular anesthetic injection. On a later date, patients obtained an intraarticular steroid injection. Up to 40% had a sizeable, i.e. 90%, reduction in pain in three months with the average time to 50% return of their pretreatment level of pain being 13 weeks.

Prior HTCC noncoverage determinations of lumbar facet injections were based upon the RCTs of Lilius and Carrette. Again, antiquated practice methods, not contemporary.

There are two new trials, both rated by Spectrum as having moderate quality of evidence and low risk of bias. Ribeiro showed significant improvement in pain and function following intraarticular facet injections, as opposed to IM injections, and in the intermediate term, Lakemeier showed no difference in pain or function in those receiving intraarticular facet injections versus RF, a currently covered procedure.

Additionally, there are three prospective trials, two of which were randomized that looked at intraarticular lumbar facet injections in those with physiologic evidence of joint inflammation. These trials were not

provided to you by Spectrum, because they did not have a placebo arm. Collectively, these trials showed benefit of this injection procedure in up to three months follow up.

With regard to SI joint injections, this is a covered procedure. There is only one new trial by Visser predominantly looking at the comparative effectiveness of different conservative care, but you need to be aware there is a trial by Lilian not cited by Spectrum because it's a prospective trial. It's not an RCT, but I implore to you that it was a well-done trial, because they selected patients with the condition based upon contemporary methods of dual-diagnostic intraarticular blocks with high-grade relief; 67% of patients experienced greater than 50% improvement of pain for a mean duration of 37 weeks.

Additionally, there are 10 prospective observational trials of intraarticular steroid injections in patients that have sacroiliitis that is true inflammatory sacroiliitis and those that have spondyloarthropathy. Success rating from 60% at a month to 90% at 10 months. All these trials were excluded because the key questions, according to Spectrum... or these trials were excluded by Spectrum because patients had spondyloarthropathy, yet this was not a key question to exclude that condition, and patients in this state do have spondyloarthropathy.

There was one small RCT by Maugers excluded by Spectrum that showed benefit of intraarticular steroid injections versus saline.

Final recommendations: We are not advocating for what doesn't work. That's listed. It's been cited.

Consider these facts in regards to epidural steroid injections for neurogenic claudication. All eight Medicare carriers cover epidurals for neurogenic claudication. You need to decide if there is substantial evidence to form a contrary determination to every Medicare LCD and every recommendation from 14 medical societies representing more than 100,000 physicians.

There is no reason to alter prior coverage determinations for the use of epidurals in the treatment of radicular pain from any etiology, inclusive of central spinal stenosis. Why? There is no new methodologically sound trials without a high risk of bias showing a lack of efficacy. All eight Medicare carriers continue to cover epidurals for radicular pain. We recommend following the MPW guidelines for safety, as well.

In regards to intraarticular facet injections, we endorse the MPW guidelines, realize there are new moderate quality trials showing benefit of this procedure. Spectrum excluded evidence in those that truly have inflammatory facet arthropathy that they can benefit from this procedure. We do not expect the cervical spine to behave differently than the lumbar spine.

With regards to SI joint injections, there is no reason to change your prior decision, because there's no new evidence showing lack of efficacy. In fact, there was evidence that was excluded by Spectrum showing both and effectiveness, especially in the subpopulation where you would expect to benefit from this procedure. Furthermore, all Medicare carriers cover this procedures. We do, however, recommend clearer restrictions to the performance of this and subsequent procedures in regards to SI joint injections.

So, I'm going to leave you with extra time and finish early and say thank you. I'm glad we could express our concerns and thoughts to you, the committee. I'm happy we can point out the limitations of Spectrum's report, but moreover, I wanted you to fully see all the evidence in the time I had provided so you can make a truly informed decision and not have a bias view of the literature. Thank you.

Chris Standaert: Thank you, Dr. Dreyfuss. So, we're going to our list of people who wrote in if they want to provide public comment, and we will have to check on the phones when we're done with that. People, I'm going to call you. Please, again, come up. Identify yourselves, your institution, who you represent, if anyone, and conflicts of interest, and you will have two minutes to address the committee. The first patient, Kathy Kroening. I hope I got that correct. Does the mic here work or do they have to go to the podium? Take your pick.

Kathy Kroening: My name is Kathy Kroening, and I am a healthcare consumer. This issue is not about statistics. It's about people. In reading through the final evidence report, I discovered that I did not have a lot in common with the populations that were studied. I am not Korean, Belgian, or Iranian. I am not a 40-year-old woman with chronic low back pain of unknown origin, nor am I an 85-year-old man with osteoarthritis. I am not a statistic. My name is Kathy Kroening. I am a nurse practitioner, and I am also a 54-year-old woman with an autoimmune disorder called peripheral spondyloarthropathy. This disorder causes inflammation in the sacroiliac joints and spine, as well as where ligaments and tendons attach to bone. I know exactly what is causing my pain. I have multiple scans documenting bone edema in at least three separate locations. I have had

an extremely positive response to steroid injections in both SI joints and facet joints in my lumbar spine and neck with pain relief of up to 12 months. There is no cure for this disorder, but it is very manageable if I am able to get the treatment I need when I need it. In August, I experienced a flareup of pain and inflammation in the right side of my neck. Over four months of communicating with my insurance company, a preauthorization request for steroid injection in my neck was denied, as was my doctor's request for a peer consultation. I was told this procedure was not covered under any circumstances and no exceptions would be made. During this time, my neck pain increased significantly interfering with sleep, driving, and exercise. This ultimately led to a systemic flare resulting in increased pain and inflammation in multiple joints, development of a severe upper respiratory infection, and the need for oral steroids. I paid \$1800 out of pocket to get the injection in December and have good pain relief since that time. I need injections in my SI joints and my neck once or twice a year. I cannot and should not have to pay upwards of \$8000 a year for treatment that is recommended by my rheumatologist, two spine specialists, and covered by my insurance... should be covered by my insurance. I'm almost done. You have the opportunity to make decisions that will improve treatment outcomes and quality of life. As a healthcare provider, I am asking you to untie our hands and let us do our jobs. Take the decision making out of the hands of bureaucrats and statisticians and put it back where it belongs, in the hands of healthcare clinicians with training and expertise to partner with their patients to provide individualized holistic patient centered care. And as a healthcare consumer, I am asking, please give me back my autonomy. Empower me and other healthcare consumers to work with our providers to be proactive in managing our health resulting in increased quality of life and productivity, decreased disability, and dramatically decreased healthcare costs in the long run. Thank you for your time.

Chris Standaert: Thank you, uh, Diana Kusulos.

Diana Kusulos: My name is Diana Kusulos. I am a patient at Evergreen Sport and Spine, and I'm an example of a patient directly affected by your decisions. Not only have I been helped by these spinal injections we're talking about, but I've also been effected by your decisions made a couple of years ago on radiofrequency neurotomy to cervical joints. I'm sure each of you has ever had a headache, and you know how uncomfortable that is. Well, think about having one every single day. It's very miserable. Injections, neurotomies, are the only way that I have had relief from these headaches. I would ask that you not only consider the patients who are helped and deserve to be covered, but I would also ask you to please

reconsider your decisions on the radiofrequency neurotomies. Dr. Messerli did a good job of covering the alternative of taking steroids, or taking opiates, and as you know, it's a big health... it's a big public health concern because not only are the patients taking opiates, but where do you think our young people begin getting opiates. It's in their mother and father's medicine cabinets. So, thank you for your time.

Chris Standaert: Thank you. Carol Glenn.

Carol Glenn: Hi. Can you hear me? I was a nurse for 40, almost 44 years. For the last 30 years, I was an HIV nurse from the early 80s until 2010. A very active lifestyle, hiking, camping. In 2006, I started developing really severe hip pain. I did all of the conservative things you're supposed to do, including physical therapy, chiropractor, acupuncture, everything. Anyway, they decided that my hip pain was related to ligaments, tissue in my hip area. I had two surgeries, one in 2007 repeated in 2008, almost 2009, no effect. Finally, I was referred to Dr. Ray Baker who I tell everyone he saved my life. I see him about every six months and I am walking as I am right now. I had injection two months ago. Gradually, it will decrease, I'll only be with a cane. By the time I see him at five and a half or six months, I am in tears and I can't walk. I have no quality of life. I love gardening. I have my four dogs. I am married. I am very active in my neighborhood, and as soon as I see Ray, and he injects me, I can, like, dance the ballet outside the hallway, and I cannot emphasize enough that this needs to continue. This is a really important quality of life issue, not just for me, but for many, many people in Washington State. Thank you.

Chris Standaert: Next, Carol O'Connell.

Carol O'Connell: Hi. I'm Carol O'Connell, and I'm a retired educator, and I am here to just speak to what I have benefited from and what several of my friends are and concerns I have regarding the action that could be taken today. I also want to say that this morning you talked about life and death situations and the quality of their life. This afternoon, I've heard you talk about ethical, safety, and cost, nothing to do with quality of life, and this, when you come to injections like you've heard from the other ladies, this is about quality of life, and cost, I'm just a, you know, someone who pays every month for 48 years for my insurance benefits. Ask my husband. I want to make sure that my dollars and the kind of rules that you're making today are in line with quality of life, not just for me, because I could access some, like Medicare, but I know a teacher. He's barely above poverty, and he has several children. He could not get a spinal injection. So, when you have so much pain, you have to turn to

something else. You can't access other things, so you end up going to drugs. I don't want to see him having to do that, and you may say, well, that's not going to happen. Well, I'll tell you, it does. You want that pain stopped so much that you can move that you can stand and do your dishes that you can pick up your child, you will do anything, and spinal injections are what we need. You've heard doctors talk today. I highly agree with the Evergreen doctors. There needs to be no change. Don't take that away from people. Give them the quality of life access that this injection will allow. I get very emotional. Sorry.

Chris Standaert: Thank you, uh, Ms. Kusulos, unless there is another of you in the room, I assume you signed up twice. So, we have two Diana Kusulos', but thank you for your comments. Katrina Lewis is next. Do you wish to address the committee? No. OK. Irene Young. Dr. Young, did you wish to address the committee. I assume that's you, unless there is a different Irene Young. Is she coming back? Nobody knows. If somebody sees her walk back before we're done with this, please let me know in case she wants to speak. Young Lee. You were signed up as well? You donated your time. OK. Henry Sherwood. Mr. Sherwood?

Henry Sherwood: Yes, sir.

Chris Standaert: Oh, OK.

Henry Sherwood: Thank you for hearing me. My name is Henry Sherwood. I'm a twice retired law enforcement officer with 38 years. I was forced out of the work due to severe osteoarthritis and COPD. I started with Cascade Orthopedic a number of years ago with Dr. Chin, approximately six years ago, as an experiment. The experiments resulted in approximately periods of time with the epidurals of four to four and a half months of substantial relief where I'm able to sleep at night and not have to be awakening four and five times a night due to severe pain. I have tried opioids and some other drugs, and the only purpose they seem to serve is to cause extreme constipation, which further aggravates the entire issue. So, I would highly recommend and would request that the committee continue with their previous and allow those of us that are suffering from this type of pain to be able to get at least some relief, even if it's relatively short term in the three and a half to four and a half month range at a time. Thank you.

Chris Standaert: Dr. Stacey.

Brett Stacey: Thank you. I'm Brett Stacey. I'm a professor of anesthesiology and pain medicine at the University of Washington and the medical director of the

Center for Pain Relief. My conflicts are A) I do perform these procedures, but my compensation is not directly tied in any way whatsoever to those procedures. And B) My insurance will be impacted by your decisions today. I want to speak briefly about the context in which these procedures are done and thinking about the subpopulations of patients who have received the procedures. I completely endorse, based upon my professional decisions I've made throughout my career, interdisciplinary care and taking care of the whole patient. Procedures, by themselves, rarely stand alone as treatments. Often in clinical trials, they are viewed as a single treatment and that isolated item is addressed in treatment. That is not modern medical approach to chronic spinal conditions. We believe, firmly, in using procedures in the context of comprehensive care. You should think about that when you're thinking about this decision. Secondly, there are subsets of patients who are not fully revealed in the data that benefit. If there are restrictions in place, think about whether you're going to make a blanket not covering versus covering under a limited basis, or only covering beyond the first procedure if there's a beneficial response. It makes sense to try to uncover those subpopulations, because the alternatives, as you have heard today, involved opioids, the downside to those are quite limited, the data is supporting them for greater than three months, which appears to be the duration we're looking for, is extremely limited and nonexistent, or surgical management or other more invasive treatments. So, I really strongly advocate you to think about the big picture and think about the fact that utilization of these procedures has gone down in the last few years and that there likely is more responsible use currently. Thank you, very much, for your time.

Chris Standaert: Thank you. Is there anybody else in the room who would like to address the committee? Yes, sir. Please come up. Again, please identify yourself and whom you may represent and any potential conflicts of interest. Thank you.

Richard Seroussi: My name is Richard Seroussi. I'm an attending physiatrist. I guess a conflict of interest is, I do a few of these injections every week on my patients. I don't have a very interventional practice, but I have a number of patients who really, this is, again as the lady earlier said, it's not really life saving, but it's quality of life saving, and I think the data by Dr. Dreyfuss was very compelling showing that there are subgroups that clearly respond to this kind of treatment, and we need to respect those patients and not get them lost in pools of data that might drown out an effect. Having said that, it looks like there is quite a bit of efficacy, according to his recent literature review. I want to just say a couple of other things. I've been an attending physiatrist for over 20 years. I have

probably evaluated 12,000 patients in my career. I understand randomized control trials are important, but as another patient had said earlier, we also have to allow physicians and patients to work on things together, and one more paradigm shift, potentially, for the committee is if I did a randomized control trial of dialysis, single dose, we might find in one week there was no difference between those who received dialysis and those who did not. I just want to plant that seed. I think that three months of efficacy for people who have severe radicular pain, I can promise you, they want whatever can be done to help their problem. Thank you.

Chris Standaert: Thank you. Anyone else in the room? Just as a reminder, once... this is the chance you'll have... the public... to communicate with us. So, once the... we start talking, that won't work so well. So, this is your opportunity. Yeah, essentially the final opportunity to address us on this. OK. Thank you. Now, we'll check on the phones. Is anybody on... are our phone lines open? So, we will unmute the phones. Hi, this is Washington State Health Technology Clinical Committee meeting on spinal injections. Is there someone on the phone who would like to make a public comment to the committee at this time? Can they hear us? Are we on? So, unless I hear anything in the next few seconds, I will assume there is nobody there. OK. Thank you. That concludes the public comment section of our meeting. OK. We're going to move on to our presentation from Spectrum with Dr. Dettori, and while he's walking up, I just want to introduce our clinical expert who has accepted what can be a challenging task. Dr. Vorenkamp is here with us today, and he is here to help the committee with technical aspects of the procedure and their applications, and we greatly appreciate his assistance. Thank you. Dr. Dettori.

Joseph Dettori: Thank you. Can you hear me OK? So, I want to begin by thanking my colleagues who helped me on this report, and they are listed there on the slide, and I want to also apologize for the length of the report to the committee, but it is what it is. So, I guess I have the controller here.

So, I think we've had enough background to this particular topic. I do want to say that this is a re-review, as was mentioned before. So, I will try to, at the end, put this in context with our previous report.

So, when we begin to evaluate the literature with respect to this topic, we found that there were a number of conditions where there were data present and so you can look at all of those conditions. We have radiculopathy that in the articles attribute the radiculopathy to disc pathology and/or foraminal narrowing, both in the lumbar and cervical

spine. We have lumbar and cervical central spinal stenosis. We have axial pain without radiculopathy. We have failed surgery. We have both lumbar and cervical facet joint pain, and we have SI pain.

With respect to epidural steroid injections, it is one of the most common injections. It has the most literature reported on it, and I think it's important for the committee to know that the FDA has approved several injectable corticosteroids for a variety of conditions, but they are not approved by the FDA for the epidural administration.

And for those who are not familiar with the different approaches, you've heard from the previous individuals some different approaches. This is a diagram of some different approaches that are used for the epidural steroid injections, the caudal approach going into the sacral hiatus, transforaminal approach, and the interlaminar approach, and of course, one of the advantages of you selecting a particular approach is that you try to get the medication as close as you can to the anatomical structure you believe is causing the problem.

So, with that shot background in mind, I just want to review the key questions. These are the key questions. What is the evidence of efficacy, the evidence of safety, differential efficacy and safety, and then the cost implications?

So, let's talk for a moment about the inclusion criteria that we used in selecting the articles. With respect to the patient population, we selected articles that did these injections on adults with subacute, which we defined as between 4 and 12 weeks, or chronic, greater than 12 weeks, of pain in the lumbar cervical spine with or without radiculopathy. With respect to the intervention, we had spinal injections, and that included epidural, facet, and sacroiliac. It also included intradiscal, as well, although there was nothing new on intradiscal, and there were only a couple in the old report.

So, we probably ought to take a second and talk about the comparators. We had a lot of comment thusfar about the control groups. Now, if you looked at the report carefully, you will notice that we did not use the word placebo with respect to the control injections. I know that that is one of the criticisms of some of the reports that came out prior, but we did call the control injections. We actually have five categories of comparators. One of them are control injections and we grouped the control injections as those injections that included an anesthetic with or without saline, or saline alone, or dry needle, and initially, we separated the results out, and if you look in the appendix, you'll see the results

separated out from those, each one being its own control, if you will, but when we looked at the data, we found that there really was no difference in comparing epidural steroid injection when the control was anesthetic or when it was saline or when it was dry needling. The comparison that was mentioned by an earlier lecturer, the Bicket study, his conclusion was based on indirect comparisons. His direct comparisons showed no difference when you directly compared the anesthetic group to the... or the nonepidural steroid group to the epidural nonsteroid group, and I'm going to talk about that in just a second. Nevertheless, these control injections can be put in the epidural space. They can be put outside the epidural space, and with respect to the facet joint, inside the joint, or just outside the joint. So, that's one category of control groups that we had. A second category of control groups are control injections plus other medications. So, for example, there were some studies that looked at adding clonidine and etanercept to the medication mix. So, we evaluated that separately. Then, the third category of controls were the controls that actually did a procedure on the intervertebral disc or a decompressive procedure around the disc. The fourth category is conservative care, and almost all of these included physical therapy as the primary portion of the conservative care. Then, the fifth category of comparators with respect to the facet joint was the medial branch radiofrequency denervation.

So, with respect to outcomes, we have essentially five primary outcomes and we have data reported on many more outcomes in the report, but with respect to the five primary outcomes, they are pain relief, physical function, a composite outcome, the risk of a subsequent surgery that is what percent of patients go on to have surgery, and then our safety concerns around adverse events. With respect to the pain and to the function, we looked at that in two ways. The first way we looked at it was the proportion of patients achieving success and success was defined in almost all of the papers as greater than or equal to 50% improvement. We also looked at the change from the baseline to follow up on a continuous scale and in doing so, we put that in the context of the minimum clinically important difference, the MCID, which we obtained from the literature for pain to be 1.5 on a 0 to 10 scale. With respect to function for the lumbar, the two main function outcome measures were the ODI, the Oswestry Disability Index, and the Roland Morris Disability Questionnaire. For the ODI, we used 10 points. For the Roland Morris 5 points, and then for the neck, the neck disability index, we used 8.5 points. With respect to the composite outcomes, several papers counted success only if the patient received greater than 50% pain relief and 50% functional improvement. You had to have both to be counted as a success, and that was the composite outcome.

So, study design. Our inclusion criteria were randomized trials. Now, it's gotten a lot of criticism in writing, and you heard a lot of criticism just a few minutes ago about us not including observational studies. I think the committee is aware that the randomized control trial is still the gold standard for efficacy. I want to say something about observational studies. There are two flavors of observational studies. One flavor of an observational study is a comparative study where there's no randomization, but there are two treatment arms, and you compare the effect based on the difference between the two arms, OK? There is another flavor of observational studies where you have one arm and you have a before and an after design. Essentially, a case series. There is a problem attributing a change in outcome to the intervention in those kind of studies, because you cannot be sure that it is actually the intervention that is causing the benefit. It ignores the fact of a placebo effect. It ignores the fact of measurement error, and it ignores the fact of the natural history of that particular condition. So, those are very difficult studies to include when you have randomized trials. So, we only included randomized trials, because it's the highest level of evidence.

With respect to safety, it's a little bit different story. Sometimes, safety concerns are very rare. Sometimes, events are very rare. Safety concerns aren't rare, but the events themselves are rare. So, you need large populations, maybe populations that are bigger than what randomized trials can afford to put in. Sometimes, the effect of an intervention, with respect to safety, doesn't occur until a long time afterwards, much longer than a randomized trial can run. So, we will often use observational studies in addition to randomized control trials for safety, and we included those in key question two, and we also included a report by the FDA and then for cost-effectiveness we looked at economic studies.

So, this slide, basically if you look down at the very bottom, it shows that we ended up with 72 randomized control trials to help inform our analyses. We also had three nonrandomized comparative studies, 22 case series. We had the FDA summary report, and we had three economic evaluations.

So, I think it's going to be... I think I need to take just a second to talk to the committee about how we evaluate our strength of evidence, because we use the grade evaluation methodology and I just... I want to make sure we're on the same sheet of music and that it helps you when you look at the report. So, GRADE has four categories when they try to discern what is the overall quality or strength of a body of literature. OK?

So, when you do a systematic review and you have several studies that try to inform the effect estimate, how do we judge whether or not that's good quality or not. So, GRADE has come up with this system, and they have four categories that you can end up in; high, moderate, low, and insufficient, and those four categories try to reflect our confidence in how the evidence reflects the true effect. You're going to see some effect measures when I show you the results, and as you look into the report, and this GRADE basically says how confident are we that that effect measure is close to the truth, OK? There is a system that goes into coming up with a GRADE. It's not just done arbitrarily, and this system has been organized in a way that it is reliable and transparent. So, I hope you could see in our report the transparency of how we got to grading the body of literature, but just briefly, the way that GRADE does this, it says, OK, first of all we're going to look at the study design, and if you use primarily randomized trials to come up with the effect estimate, you're going to start by placing that body of literature in the high category. So, you start off high, and then you evaluate that body of literature with respect to five other domains. The first domain is consistency. In other words, are the results consistent? If the results are not consistent or if they're inconsistent, then you can downgrade it from a high to a moderate. Another category is looking at the individual articles and... Erica, can you bring me a glass of water, please? Thank you. Looking at the individual articles and saying, OK. Just because they're randomized trials does not necessarily mean they're good studies. So, you look at them... you look at the individual studies that informed that particular estimate, and if the studies have some other problems associated with it, then you can downgrade again. So, you can go from high to moderate, to low. You also then look at another domain called precision. How precise is the estimate. If it's imprecise, you can downgrade it again. You look at the issues of publication bias. So, you go through this system, basically, to come up with a final GRADE. So, when you see that GRADE, it wasn't just us arbitrarily attaching that GRADE to the estimate. It's that we went through a system on every outcome that we put in our strength of evidence or quality of evidence table, and hopefully it's clear enough in that table where you could see where and why we downgraded.

OK. I show you this slide only to emphasize that there are several conditions, obviously. I just went over them. There are several different comparisons because of the different controls within each condition, and so it makes the report quite laborious. I also want to emphasize that most of the evidence is around radiculopathy that is attributed to disc pathology or foraminal narrowing and then also stenosis of the lumbar spine, and that is in distinction to the cervical data, which is not nearly as robust.

OK. We're going to talk about radiculopathy first. This is a slide that is going to show you short-term pain success, and we defined short-term as less than three months and then intermediate from three months to twelve, and then twelve and greater for long-term. Now, I want to take a second to tell you what's on this slide. We went to great lengths to try to provide you with as much information as possible. So, you'll see, if you look at the first column, of course, you'll have your... you have your study there. You also have the dates of the study. So, if you are concerned that an older study provides information that you don't want to look at, you can look at the results of that older study by looking at the dates. The red check mark to the left of the authors means that that study provides new data. Either it's a new study or it's a previous study that now has long-term follow up or provides additional data versus the previous report. The next column gives you some information about the control group, particularly if it was a nonepidural steroid injection that would be either saline or an anesthetic. Did I say that right? I didn't did I? Hold on just a second. Let me... it should have... it should say... it's epidural nonsteroid, which would be anesthetic or saline into the epidural space, as the control group, or it could be NEI, which stands for nonepidural injection. So, it's an injection outside. It may or may not have a steroid with it outside the epidural space. So, we gave you that information there, as well. We gave you the absolute follow up period, and then we gave you whether or not the study had fluoroscopic guidance. So, if you're concerned that a particular study did not have fluoroscopic guidance, you could look and see. Now, finally you can see that we provided the quality of evidence on this slide based on the process that I just discussed, the GRADE process, OK?

So, the results of the first slide, which is short-term pain success, and remember, we looked at pain two ways. The first has to do with success, the portion of people achieving 50% or greater success in terms of pain. We find that there was a benefit to epidural steroid injections and I cannot really see from here what that risk ratio is, but it looks like it's whatever it is. You'd have to look at it. I don't have it in front of me here, but it's statistically improved.

In terms of the intermediate term pain success, we find we have fewer studies that inform this estimate, and it is no longer statistically significant. And long-term pain, the same.

In addition to the proportion who achieved pain success, we also looked at the change in pain on a continuous scale and with respect to the mean pain improvement for short, intermediate, and long-term, we found no difference between groups.

Let's talk about function. Short-term function, we found no difference. Intermediate term, no difference. Long-term, no difference.

With respect to the continuous measurement of function, we found no difference between groups at any time period looking at those number of randomized trials and those number of patients. With respect to composite score success, we had data for intermediate and long-term, three trials, no difference between groups, but you'll see that the GRADE was insufficient for intermediate term and low for long-term.

Cumulative risk of surgery is a new outcome to this report versus the prior report. That is why the checkmark is next to the outcome. Looking at the cumulative risk of surgery, there was no difference between groups.

So, that was radiculopathy, comparing ESI with control injections. We have other control groups, as I had mentioned earlier. So, now we're looking at epidural steroid injection versus discectomy. We had one report in our prior report, which showed that epidural steroid injection had poorer outcomes versus discectomy. We have a new report that is half the size but they found no difference in groups in the short-term with respect to epidural steroid injection versus discectomy. Radiofrequency nucleoplasty we have two new added RCTs, and you can see the results there. We had... they reported epidural steroid injection as poor outcomes compared to nucleoplasty with respect to pain and ODI improvement in the short-term and the intermediate and the long-term. No difference in risk of undergoing surgery. With respect to conservative care, the prior report had one old RCT, a small one. We had a larger, new RCT that was added, and in that particular one, epidural steroid injection had better outcomes than the intermediate term than conservative care. That body of literature was graded insufficient.

So, we're moving from radiculopathy as a result of the intervertebral disc to lumbar or central stenosis now. Here, we have three studies with respect to short-term pain success, and we found no difference, and then long-term pain success, no difference, fewer trials, though. In term of mean pain improvement, no difference.

With respect to function, short-term, no difference. Mean function improvement, no difference in the short-term. Composite score of success no difference in three randomized control trials.

Cumulative risk of surgery, no difference. Epidural steroid injection versus other controls, that was against control injections, the data I just showed you. Now, we have other controls. Versus decompression, we have a newly added RCT that looked at the MILD procedure, the minimally invasive lumbar decompression procedure, and in that particular trial, epidural steroid injection was associated with a lower likelihood of success versus that procedure, and there was no difference in pain scores or ODI improvement, and versus conservative care, no difference in pain or function in one RCT in the prior report.

So, moving on to axial pain now, without radiculopathy. With respect to pain, function, and composite success and also the continuous outcomes, we had no difference in two randomized control trials. With respect to failed lumbar surgery, we had no difference between groups at any time period and one newly added randomized control trial.

With respect to lumbar facet pain, in our prior report, we had a comparison of intraarticular steroid versus intraarticular control, which was a nonsteroid. We found short and intermediate term pain function no difference. We added a new study that compared intraarticular steroid versus intramuscular steroid injection, and on this one we found in the short term a greater improvement in the intraarticular group for both pain and function. For pain, it reached the MCID threshold. For function, it did not, and then the intermediate term we found no difference.

We have a study that looked at extraarticular steroid versus extraarticular nonsteroid control injection. There were two trials and we had no difference between groups at any of the timeframes.

SI pain, we looked at intraarticular versus conservative care. We added a new study and we had no difference between groups in the short term with respect to pain or composite score success or mean improvement in pain. With respect to function, we had less improvement in the steroid group compared to physical or manual therapy, although this didn't reach an MCID. Then the extraarticular steroid versus extraarticular control injection, we had one prior report study where we had greater improvement in pain in the extraarticular steroid group versus the control.

So, moving onto the cervical area, we had less studies there, first of all, radiculopathy. So, we have one newly added RCT of 105 patients and in the short term, there was no difference between groups with respect to pain. In the intermediate term, we had less improvement in pain with

the epidural steroid injection group compared to the conservative care group, but this did not reach MCID level. With respect to function, we had worse function in the short term and in the intermediate term for the steroid injection group versus the conservative care group, but neither of these reached MCID levels, and there was no difference in the risk of surgery.

Then, we had another study that was new that compared epidural steroid injection plus conservative care versus conservative care alone, and in the short term we found that the epidural steroid injection plus conservative care did better than the conservative care alone; however, it did not reach the MCID. Intermediate term, there was no difference. Then, this sort of had sort of counterintuitive, because when you looked at the function, they reported... this study reported that the group that received the steroid actually had worse function in the short term; however it did not reach MCID, but it had worse function in the intermediate term, and that did reach the MCID. I'm not sure how to explain those results. Then the risk of surgery, there was no difference between groups.

Then, we get to the nonradicular neck pain, the axial pain. We had one newly added study of 120 patients. We found no difference, or they reported no difference in pain and function, success or improvement.

Cervical spinal stenosis, one newly added study, no difference between groups pain and function. Failed cervical surgery, one newly added study, no difference between groups.

Move on to the cervical facet joint. This is intraarticular steroid versus intraarticular control, which is a nonsteroid. We had short term no difference with respect to pain and function. In our prior report RCT and a newly added report no difference as well.

So, I want to move on to safety, if I can. We categorized our safety outcomes into three categories, catastrophic adverse events, serious adverse events, and nonserious adverse events, and you can see examples of what those were in each of those categories.

With respect to catastrophic adverse events, we found no reports of any catastrophic events across 60 RCTs reported on adverse events. That was over 6000 patients and no such events on any of the 25 observational studies, as well. The FDA has a review, a safety review, where they looked at their adverse events reporting database and they identified 131 major neurological adverse events that included death, arachnoiditis,

brain stem stroke, motor incomplete tetraplegia, paraplegia, spinal cord infarction, cardiac arrest, blindness, and meningitis, and they concluded that these catastrophic events are very rare, but they do occur. They also made a statement that they were unable to make a causal connection between these catastrophic events and injection location, cervical and lumbar spine, injection approach, use of imaging, or type of steroid.

Serious adverse events, again, rare or infrequent anyway, depending on the particular study reporting some of the serious ones from 0 to 4%, over 6000 patients. Then, nonserious adverse events, again, relatively infrequent. I have to ask you now, the committee if you have a copy of the report, I assume, in front of you, right, a hard copy? I'm going to have to ask you if you wouldn't mind turning to, I think it's page 196, which is the bibliography and I want you to just take a peek at reference #182. Is that the right page number for bibliography? Anybody find it? 182? OK. Yeah, 196 and reference 182.

Chris Standaert: Page 196.

Joseph Dettori: Yeah, OK. So, OK, Mandell. OK, so this is a study that we identified early on in our search, but we made a mistake in abstracting the data from this study. So, if you look at the end of the report where we have all of the abstraction tables in the appendices, you'll find that study, but what you won't find is the outcome, which is the vertebral body fractures. You'll basically find the proportion of people with the various conditions that make up this study. We erred in that, and this sort of fell through our quality assurance check, and I was reviewing the report in preparation for this presentation and came across this study and could not find where we reported this outcome, vertebral body fracture. I went back and looked at the article and that's how we discovered it, and that just occurred about three days ago, but it's worth, at least, I think, mentioning it to you, and I made a copy... I made lots of copies of the article. So, we can hand it out to our colleagues in the audience if they want a copy, and if you... if you would like, we could also give a copy to the committee. Chris, is that? OK. So, could you pass that around, Erica? And then while she is doing that, let me just give you a brief overview of this particular study.

This was a retrospective cohort study that identified... it's a study of an administrative database from the Henry Ford Health System, which is an HMO type of system, and they have access to ICD-9 codes. So, this particular study identified 50,000 patients in their health system who had an ICD-9 code that was consistent with some kind of lumbar neuropathic compression. From among that 50,000 group, they identified 3400

patients who also had a code for an epidural steroid injection, and what they did was they randomly selected 3000 out of the 3400 to be the epidural steroid injection group and then they matched... they did propensity score matching to a control group and selected 3000 of those people. Then they had a five-year follow up period and during that five years, they looked to see what the incidence of vertebral fracture was. Now, they only included patients who were 50 years old and older, and using survival analysis, they report a hazard ratio of 1.21, which they concluded was an important find, and basically their conclusion is for every injection... because they were able to identify patients with multiple injections, and their conclusion was that for every injection that a patient got, they increased their risk of vertebral fracture by 21%. So, there are problems with an administrative database. We all know that. There is misclassification. There are exposures that you wish you had, that you could hopefully adjust for an analysis, like smoking and things like that that you don't have access to. So, there are problems with that kind of database, but it's a mistake on our part. It fell through the cracks, and I think it's a piece that you need to consider, or at least I want you to have access to it for completeness.

With respect to differential efficacy, we had two basically we had two comparisons, epidural steroid injection versus control injections. All of these studies were in our last report. We have epidural steroid injection versus disc decompression. Our last report that looked at these characteristics, and none of these characteristics were identified as being subgroups that had differential effectiveness with respect to epidural steroid injection control injections, epidural steroid injection versus disc decompression. We had one new study, which came out of Dr. Friedly's study. They did a hypothesis generating study that looked at several potential risk factors or subgroups, I should say, that may have differential effectiveness and I think out of all the ones they looked at they found one, a baseline score, but in general their conclusion was, at this point, they didn't really find anything with respect to differential efficacy. She left so she can't really give me a nod if that was true or not, but I think it is.

Cost-effectiveness, we have three studies. The first two with respect to epidural steroid injection and lumbar radiculopathy versus controls and those were reported last time and they concluded that there was, there was... epidural steroid injection is not cost-effective versus surgery or , let's see, the second was versus... was it conservative care? I don't remember that second one Robin, do you?

Robin Hashimoto: Yeah, it's over nonepidural saline injection.

Joseph Dettori: OK, versus control injection of nonepidural saline. Thank you. That was in the old report. The new report, we have one new one with lumbar spinal stenosis, and that was a comparison of epidural steroid injection versus two other controls. One was minimally invasive decompression, and one was an open decompression, surgical decompression, and they found that the minimally invasive was more cost-effective than spinal injections, and spinal injections was more cost-effective than surgical decompression, but all of those costs exceed the \$40,000 sort of threshold that some people think per quality life year is an important one. Epidural steroid injection was higher, as well, so.

So, let's see if I can summarize this in a way that puts it in the context of our last report. So, with respect to radiculopathy due to disc or foraminal narrowing, we found that there was an association of a mild short-term improvement in pain in the lumbar spine but not function. The benefits are small, and they're not sustained after the three-month period. It's similar to our previous report. We added a meta-analysis and we added long-term follow up. With respect to cervical pain and function, we did not find any evidence that it was beneficial with respect to conservative care. This is a new comparison to this report. There is no effect on the risk of subsequent surgery, and that's a new comparison to this report, and we did not find any subgroup or characteristic that would make one think that there is a subgroup out there that at least we can identify that is differential effectiveness, and that is similar to our previous report. With respect to spinal stenosis, we found no benefit to the different control groups, similar to our previous report.

Axial pain, we didn't find any efficacy, similar to our previous report, and we added long term follow up. Not effective in terms of failed prior surgery, similar to our previous report, and we added cervical and longer term follow up. We have this new comparison with respect to SI pain, and the SI pain compared to physical or manual therapy didn't show that it was more effective. Same conclusion as our previous report with respect to facet joint injections, and with respect to safety, we added the catastrophic category, which is new to this report, which is very rare, but it does occur. Then, what you don't see on that slide, of course, is any summary of this article that I just pointed out to you, as well. So, committee, I am open to questions.

Chris Standaert: Thank you, Dr. Dettori. The committee can digest for a second. There is a lot of information that we'll be sorting through.

Joseph Dettori: I can, uh, well I'll just go sit down with our group.

- Chris Standaert: Would you prefer to sit?
- Joseph Dettori: Yeah, just because we'll probably need, depending on your questions, it was sort of a group effort.
- Chris Standaert: OK. Well, committee members, do you have questions on the evidence report, and this is not your only time to ask questions, but certainly a very good time if they're in your head from the presentation. Yes, Tony.
- Tony Yen: I have a question for the evidence vendor. I thought the presentation by Dr. Friedly was actually fairly compelling in terms of discussing the literature behind I think the studies that were authored by Dr. Manchikanti. Could the evidence vendor, can you make any comments about Dr. Friedly's criticisms behind this type of evidence, because it seems like this updated report bases itself on a lot of this from this one author.
- Joseph Dettori: Let's see. So, I think that, let's see. So, what do I say about Dr. Manchikanti. Dr. Manchikanti was one of the reviewers from our previous report, and we asked him if he would be a reviewer, because he was publicly criticizing the process and when Leah was involved, she suggested that maybe we ask him to be a reviewer, which we did. Of course, he was critical. His study designs have... his early study designs were... as they were reported, were not very good, and he got criticized a lot from it, and it seems to me, my opinion is that he has at least learned to report his results in a way that is better, OK? So, now behind the scenes, I don't know. I think that we were very critical of his... particularly of his earlier reports. Like I said, the reporting has gotten better and, you know, we can only do so much investigation to this process, but he has been known to not have a good handle on methodology, from my perspective.
- Chris Standaert: So, I didn't know that. That was a very good question. I didn't know it was coming up quite so quickly in this review. I'll ask you if my understanding is correct, too. So, one of the concerns I have looking at the data and Dr. Manchikanti's work is that it... he has many studies. They tend to be 120 people and then multiple studies. So, they sort of overwhelm the other studies, because the numbers are so big. His reports all tend to say... they tend... they're almost all epidural steroid plus anesthetic or anesthetic alone. He says anesthetic is not a placebo. He is quite clear about that in his papers, and he finds 70+ success rates for everything, for every group saying they are no different, and if you were putting those into a meta-analysis where you're weighting things. If there is a difference seen in smaller studies, the size and frequency of his

studies with those overwhelmingly positive responses would essentially washout any smaller benefit you might see without them, but that goes... but they are, in the literature, as peer-reviewed studies, and they have to go into the report, but that would be my understanding of one of the statistical concerns with that work.

Joseph Dettori: Well, let's see. I think, is this on still? OK. So, with respect to... that's true with respect to the frequency. It's less true with respect to the size when you use a random... as opposed to fixed effect model... use a random effect model, the size gets washed down a little bit. So, the smaller studies have a little bit stronger say than they would otherwise. So, yeah. I mean, he... it was a real problem to try to sort out his data. We spent a lot of time trying to do that, and I... so, I mean, I don't know what to say about it other than what we've already said.

Michael Souter: So, and I'm just going to follow up on that then. I mean, but you do make, as you said, you were able to give us the weighting applied to the studies when looking at the composites of outcomes here. So, for example, just looking at true lumbar radiculopathy, I'm referring to your slide, #17, where you attribute to the Dr. Manchikanti study there, you know, a weight of 26.7%, and it's really the, you know, presumably that's its weighting effect upon the overall composite outcome, and I think the implication is, and the suspicion from all that were you to take out Dr. Manchikanti's studies, what would be the resultant effect on those outcomes at the end of the day, especially where they're dragging, perhaps, an evidence of effect right across the central line.

Joseph Dettori: Yeah, so, I mean, we, of course, we didn't do that. We didn't do a sensitivity analysis excluding one author. So, I can't answer that definitively, but you can look at... so, you're looking right now, for example, at slide 17. Well, Dr. Manchikanti contributes three out of the five studies. So, you can look at the other two that's left, if you prefer to do that and, you know, you'll see that Cohen is on the left hand side and Ghai is on the right hand side. One is transforaminal. One is intralaminar. I mean, I don't know how you're going to interpret that, but you have the ability with... I think with these figures you have the ability, if you want to block out Dr. Manchikanti, you won't get a quantitative estimate, but you can get a qualitative estimate.

Kevin Walsh: If you block his out, I was doing that while you were finishing. I don't see a huge difference in any of the results.

Joseph Dettori: Yeah.

- Chris Standaert: Do we have other questions? We must have other questions.
- Gregory Brown: Gregory Brown, so I understand for the grading of the evidence, once you've reviewed the studies, that they're, you have the GRADE grading system that you used. At least in orthopedics, which is what I'm familiar with, we also look in various areas. We don't just look in therapeutic. We look in therapeutic, prognostic, diagnostic, and economic. So, in the prognostic category, actually level one evidence is a well-designed observational study with 80% follow up. So, did you look for any observational studies that would qualify for that?
- Joseph Dettori: Well, we just looked at therapeutic studies, not prognostic studies. In other words, we didn't have a key question that tried to evaluate prognosis, which is fundamentally different than differential efficacy. So, we didn't have a prognostic question.
- Gregory Brown: I'm sorry. Maybe I'm confused, but I thought if we're trying to look for subgroups where things are more effective or not, that's a prognostic factor.
- Joseph Dettori: Yeah, so, let's see if I can explain this. I don't know if I can, but I'll try. So, if we think about... if we think about... let's just first think about therapeutic for just a second, and then we'll get to prognostic, but if we think about therapeutic, I already told you the problem with looking at a single arm study compared to a double arm study, OK? There is no comparison group, right? When we look at prognosis, you have the same potential pitfall, and that pitfall is that if you... when you look at prognosis, you're looking at an exposure, OK? You're looking at gender. You're looking at age. You're looking at some kind of characteristic that we call an exposure, right? And you can have two groups of exposure. Let's say we have male and female and you're looking at specific population, and let's say you're a... you're an orthopedic surgeon? So, let's say you're looking at... let's say you're looking at spine surgery. So, you might say, OK, in patients who receive spine surgery, the females do better than males, OK? That kind of comparison is like a single arm therapeutic study, because it gives you information about men and women, their success, relative to people who have surgery, but the higher question to ask... the question that we asked in our key question is, is there differential efficacy, which means in a scenario where, let's say, women do better than men with spine surgery, OK? Well, do women do better than men without spine surgery? Let's say that they do at the same rate. Then, it's not the spine surgery interacting with gender that's important. It's only the gender factor. So, when we talk about differential efficacy, we're talking about this interaction between the

treatment, so you have to have two levels of treatment, and the exposure. You have to have at least two levels of exposure, and it's a... it's an interactive thing.

Gregory Brown: I understand the differential efficacy.

Joseph Dettori: OK.

Gregory Brown: What I'm trying to understand is, did you make the A priority assumption that no observational study would meet level one evidence, so you didn't even look for observational studies, or did you actually look at them and see that they were only this design you're concerned about.

Joseph Dettori: Well, again, therapeutic studies... there is, we don't...

Gregory Brown: I'm sorry. You're not answering my question. Did you look for any level one prognostic evidence so that we could look at subgroups that were better... did better or not?

Joseph Dettori: The answer to your question is couched in the fact that we don't use the terminology level one studies first of all, OK? That's not current vocabulary in evidence based medicine. With respect to prognostic studies, studies that look at, at least two characteristics and try to find the effect of the characteristic on the outcome, OK, is only done with respect to questions about prognosis, not about subgroups and how they react to a treatment. So, I think I fulfilled my prophecy, which was I didn't think I could explain it clearly enough, because those concepts are intertwined. So, I'll give you a bottom line. We did not look for observational studies in this particular systematic review other than for safety.

Chris Standaert: Other questions?

Gregory Brown: Yeah. I still had another question.

Chris Standaert: OK.

Gregory Brown: If I understand correctly, the meta-analyses by Bicket and Bhatia that were included in, was it Dr. Dreyfuss' presentation, are peer-reviewed meta-analyses and have a number of more studies than you cited and shown effect, and I guess I'm trying to understand the cognitive dissidence of two published meta-analysis that show an effect and yours... that were peer reviewed, and yours that's not peer reviewed.

- Joseph Dettori: I'm sorry, which meta-analyses?
- Gregory Brown: Uh, Bicket and Bhatia I think were the two that were cited.
- Joseph Dettori: Well, the Bhatia one, I'm not familiar with because it was published here, since we've written the report. So, I can't comment on that. The Bicket review is that the, is that the review that looked at whether or not it was nonepidural injections and is that the one that you were trying... they were trying to sort out the control groups, I think?
- Gregory Brown: Apparently, epidural versus nonepidural injections.
- Joseph Dettori: Yeah. So, they were trying to... I think the purpose of that study was to try to sort out whether or not control groups differ in the way that they react, and they included some... they did an indirect comparison of studies to come up with their conclusion, basically.
- Gregory Brown: OK. So, have you ever done a network meta-analysis?
- Joseph Dettori: I have.
- Gregory Brown: OK. Could you have done it in this kind of situation?
- Joseph Dettori: There was really no need to, because we had direct comparisons.
- Gregory Brown: Well, but the point of a network meta-analysis to include those indirect comparisons also to see if they're consistent across the reporting, correct?
- Joseph Dettori: Yeah. We, typically, because you... so, in the GRADE system, for example, one of the domains is directness. So, if you... if you... an indirect comparison gets downgraded. It's not as strong as a direct comparison. So, you know, we didn't do indirect comparisons to see if it validated the direct comparisons.
- Gregory Brown: But what you can show is that a... two active interventions and the difference that they find is consistent with other studies that had a placebo control, say, and that those are all consistent findings?
- Joseph Dettori: Well, yeah, I suppose you can. You know, here's the problems with respect to the criticism that the pain community has levied against the AHRQ report and also levied against our report and that is, is that, the control injections, whether they be saline alone or whether they be an anesthetic, is 'therapeutic' and not a placebo. Well, you know, I mean I

don't know how, you probably can't... you probably can't have a true placebo with an injection, and what they do is, they take randomized trials and they separate the strength of the randomized trial and they treat the two control arms as case series, and they say, oh. Well, this control arm they got better. Oh, and this therapeutic arm, it got better. Therefore, both of them are therapeutic, and, you know, if that's true then maybe we should... maybe we should not do steroid injections. We should just do saline injections. That's probably going to be safer if it's just as therapeutic. So, I think there's some fallacy in that line of thinking. The control groups may not be a true placebo. That's why we didn't use the word placebo, but I think that, you know, the... I don't believe from the literature that I've read and the people I've heard talk that pain specialists are willing to give up the steroid and just use saline, even though they claim that there's some therapeutic benefit.

Gregory Brown: My last question is there any denominator on... or estimate of a denominator for the FDA adverse event reporting?

Joseph Dettori: No. They... and that's part... that's the problem with that particular... they don't have a denominator. So, they just give counts.

Gregory Brown: OK. Thank you.

Chris Standaert: So, a question about the spondyloarthritis issue in SI joint injections. It seems that would be the classic example of a true inflammatory arthropathy, for which one would think steroids would work, and there are studies on that, and that wasn't decided to be a sub... I could see you calling it out as a subgroup, a subpopulation. The decision to just exclude that? I mean, I'm curious.

Joseph Dettori: That was a limitation in the scope that actually came from the state.

Chris Standaert: That's interesting.

Joseph Dettori: So, that was part of the exclusion criteria from the state, not our decision. Any more questions?

Joann Elmore: Can we follow up on the SI joint then, because our prior voting with conditions approved SI joints based upon a little bit of data that was reviewed many years ago that included one low quality RCT with about 40 patients or so, but that looked promising, and in this follow up review that you have done for us, there... we have been shown just one additional RCT with 51 patients that was low quality that was negative. So, we, as a committee, are supposed to see what has changed in the last

couple of years and all we see is the addition of a negative study, but yet, I think there are some clinical issues that we, as a committee, like to consider. So, would this be a chance for us to ask our clinical expert for input on the topic?

Chris Standaert: Sure. Feel free.

Joann Elmore: For SI joints.

Chris Standaert: What's the question?

Joann Elmore: Well, can you expand upon clinical relevance of injections?

Chris Standaert: Mic.

Joann Elmore: Can you expand upon clinical relevance of injections in the SI joint?

Kevin Vorenkamp: Yes, so one key component is that, like the other therapies, the injections are never done in isolation. So, the one study they did show was comparing it to manual therapy or comparing it to physical therapy, whereas that is a combined therapy. It's often used to facilitate therapy. There are a number of studies, I can provide PDFs or a single copy to circulate, for the SI joints and Dr. Dreyfuss presented several of those showing that there is significant benefit to that.

Chris Standaert: Other questions? I'll keep pressing. I will ask you about the fact intraarticular. I thought you... in the lumbar, I thought you gave us two studies, one that was, it was three joints bilaterally, intraarticular versus six sort of superficial injections. Another one was an injection comparing to neurotomy. Wasn't that in your report, intraarticular to neurotomy showing equivalency? Was that not in your report and I just saw that elsewhere?

Joseph Dettori: Let me just... let me just peek at the report just to make sure, because I've got it in front of me here. Specifically, the question you're asking is, what were the comparisons that were in the report with respect to facet?

Chris Standaert: No. I was thinking those two studies were in, and I'm thinking along the same lines Joann was just after that we're... what's changed since we decided this, and if those are the two new studies, then they're the two new studies, but your conclusions was there is nothing... there is no benefit, but that one... it's a small study, the intraarticular versus superficial injection showed the intraarticular worked better to a degree.

Joseph Dettori: Let's see if I... if I'm remembering correctly, the lumbar... the new studies were the cervical. Is that... is that what you mean?

Chris Standaert: The Ribeiro study.

Joseph Dettori: Oh, he... oh, intraarticular versus intramuscular?

Chris Standaert: Yeah.

Joseph Dettori: Yeah. OK. So, he's... yes, he's in there. Is that the question?

Chris Standaert: Yeah. That's the question, but is that... I'll go back to what you concluded about facets. I'll go to your conclusion page. Not effective for presumed facet joint pain, but is this our new data saying that maybe they are if that's the only study we have.

Joseph Dettori: Oh, I see what you're saying.

Chris Standaert: Yeah.

Joseph Dettori: You're... I think, let me rephrase it if I can. Just to make...

Chris Standaert: OK.

Joseph Dettori: ...sure I'm understanding. You're asking why we concluded that if we have a new study that shows some...

Chris Standaert: Yes.

Joseph Dettori: ...facet, yeah, OK. So, yes. That comparison is new and the comparison is intraarticular epidural steroid with anesthetic versus a nonarticular... an extraarticular intramuscular. So, I think the thinking on that is that, I mean, you'll have to interpret what that means, I think, because, you know, it's one thing to have an anesthetic in your joint initially and, you know, can the patient be blinded if you're not, you know, sticking it in something else in the joint.

Chris Standaert: The quality of the study is what...

Joseph Dettori: Yeah. I think...

Chris Standaert: ...drove it down.

Joseph Dettori: ...the size and the quality...

- Chris Standaert: OK.
- Joseph Dettori: ...and the comparison, the comparison group, but it is a new study and it does make that comparison.
- Chris Standaert: OK.
- Kevin Vorenkamp: Dr. Standaert, could I just make one correction. He just misspoke and said epidural steroid injection, but it was an intraarticular facet compared to intramuscular. Then, there was also the Lakemeier study, as well, looking at facet.
- Chris Standaert: So, that's what I was asking. So, that was in... was the Lakemeier study in your report? That's what I'm... I'm not sure that was in the report.
- Joseph Dettori: Lakemeier doesn't sound familiar. Is that a... it is, Lakemeier?
- Chris Standaert: There's intraarticular facet to neurotomy or radiofrequency denervation.
- Joseph Dettori: Right. That's a different comparison.
- Chris Standaert: Yeah. It's showing equivalency in those two.
- Joseph Dettori: Yeah.
- Chris Standaert: OK. Are there questions?
- Michelle Simon: I have a question for you. This is Michelle Simon. This seems to be our strongest slide with regard to outcomes. This is lumbar radiculopathy epidural steroid injection versus control injections. It seems to be one of the few statistically significant results that we have to look at, and I'm curious, if I look at the new studies, there are six new studies here. It seems all of them have a pretty positive risk ratio, and if I drop out the two Dr. Manchikanti, which seem to be there is some discussion about whether or not that's valid, then the risk ratios are even better. It's, like, 1.58, 1.7, 1.73, and 1.15. They're all pretty good. So, I'm curious, do you think that this represents an evolution in the practice using guidance? Is that what's different between the new studies and the old studies, or do you have any comment on that?
- Joseph Dettori: Let's see. I guess the answer to your question is, no. I don't have any new insights. I can do what you can do now, which is sort of look across and see that... so, let's just, let's just do this. It might be kind of helpful for us to do it together. If we look at fluoroscopy, you know, well let's

look at transforaminal, for example, and all of those have fluoroscopy. You have four studies. You can drop off Dr. Manchikanti. I don't think that really changes much. Only one was strongly positive. I don't know if I heard correctly from one of the clinicians that they don't do intralaminar anymore. Did I mishear that? I misheard that. OK. OK. So, if we look at the intralaminar, we have two that had fluoroscopy. One of those is Dr. Manchikanti. We can take him out, I guess. So, it looks like, you know, those are more in favor. Then, yeah. I wouldn't say that ... in my opinion, it doesn't look like fluoroscopy makes the difference in terms of whether or not the epidural steroid injection is favored. So, I think the results are fairly... well, I wanted to say they're fairly consistent, but actually we knocked them down for inconsistency because the I-square on the heterogeneity was higher than we'd like to see. So, that's why they got a low evaluation.

Chris Standaert: Do we have other questions while people are pondering? So, the normal order of things, we would finish our questions. We would give you all a few minutes, and then we come back and do our discussion, for which the Spectrum folks will still be here, and we can keep asking them questions if we'd like. It seems people are thinking. We'll take a ten-minute break here and what time do we have? OK. We'll take a break. We will come back at 3:20, so about 12 or 15 minutes, just so we can get through our work today.

OK. We're going to get going again, if the committee could take their seats. If the audience could take their seats, and if you want to please have conversations, you're welcome to, just take them out in the other... in the hallway. Thank you. So, we're going to get going, but first I was informed that I didn't give Dr. Vorenkamp enough chance to really introduce himself and just tell us his background so we understand that. So, if you could do that for us, that'd be great.

Kevin Vorenkamp: OK. I'm Kevin Vorenkamp. I'm director of the pain medicine fellowship at Virginia Mason in Seattle, and I work with a number of organizations, the ASA, AASRA, and SIS. My field of practice is predominantly interventional pain medicine.

Chris Standaert: Conflicts of interest?

Kevin Vorenkamp: No conflicts.

Chris Standaert: OK. Thank you. So, if you guys could pull up the... so, we have a... this is our time for discussion to sort through what we have, and unlike this morning where we basically had a blank slate to start with, we have a

starting point. Our charge, really, is to look at our prior decision and look at the interim data and evidence and see what we, then, think or do with that. For people over 20, we need it a little bigger, I think. Thank you.

So, as a committee, we have a starting point. We have the prior decision, and we can let our conversation go wherever we want, and people can... we can redirect this however we want. We basically have six categories that could be compressed to five. We have lumbar epidural, and cervicothoracic epidural. We have sacroiliac joint. We have intraarticular... therapeutic medial branch blocks, intradiscal injections, and intraarticular facet injections. Again diagnostic medial branch blocks and radiofrequency neurotomy by whatever term you want to call that are a separate thing for this... from this particular topic. We looked at them separately. And again, I could see combining the epidurals, potentially, if people want to do that, but we really have five separate technologies about which we are speaking. So, we can start a discussion. We can go any way people want and somebody can talk about gestalt of what they think. Somebody can talk about any particular starting point, and we can go where we go. I'm open to anybody that wants to offer an opening perspective.

David McCulloch: I'll give you an opening perspective.

Chris Standaert: Thank you.

David McCulloch: This is David McCulloch, and I, in contrast with a lot of the things that we're asked to make decisions about, in this area, we have a fair amount of data. There are a fair amount of studies. That's the first thing I want to say. Clearly, the misery caused by back pain, acute and chronic, is real and you can see why there is such an incredible amount of energy in the room about it. It's also true that, you know, there's huge placebo effect, which I don't say in a pejorative way of if somebody is in extreme and somebody sticks a big needle in their back that has a beneficial... that can appear to have a great effect. For all those reasons, this is an area where you absolutely need to be really careful in the studies you select and try and have control arms and all the stuff that we've done. So, I'm... my initial gestalt is just I... I actually think that the way that Spectrum, our external vendor, went through and really sort of broke it down and parsed it down is a very appropriate way to go about that, and it's very helpful having the previous decision, having where the forest plots were and where the new studies are. That does give us all a chance to kind of look and see whether that makes any difference. Despite the fact you can get incredible testimony from impassioned of people who get better, we need to not be immune to the potential harm of keeping injecting

concentrated corticosteroids right in active vertebral bodies, etc., etc., and you know, in well-designed trials, you need to look at whether... how far from the midline the therapeutic effect is, whether it crosses the midline and the thing about meta-analyses is, a meta-analysis of ten badly done studies will give you crappy results, but if you pick enough careful and do that, meta-analysis allow you to, you know, narrow the confidence central and get some idea of the size of the effect and reliability of getting this. I am... my overall picture is, I feel as if we got... we got a lot of useful information on which to make a thoughtful recommendation.

Chris Standaert: Thank you. Other perspectives that may help us? I might have to start calling names. Carson, what do you think? See, it comes to this.

Carson Odegard: Well, the... I'm just wondering the way we should look at this and maybe concentrate our efforts on effectiveness. I'm just wondering if we can... if we can come to a conclusion on safety and cost-effectiveness and kind of get that out of the way.

Chris Standaert: Let's start with safety and cost-effectiveness.

Carson Odegard: Yeah. Start with that.

Chris Standaert: OK.

Carson Odegard: Get that out of the way and then... I mean, this does bring up a question. It's a new safety question that we might want to talk about. Other than that, I don't think we see any, you know, new evidence of safety issues or cost-effectiveness.

Chris Standaert: Alright. Let's start by talking about safety. So, we have, you know, very rare reports of catastrophic complications and looked at 6000 patients in the studies, but the catastrophic things are way less frequent than that, and you'd need 20, 30, 50 times that size population to find them, I would suspect, at least, but we don't know the number. We don't know the end, and part of your question, Greg, about the (inaudible) reporting base. It's just sort of who reports. It's a voluntary system, so you have no idea in the end... I mean, there are millions of these things done.

Gregory Brown: A percentage of those were from that infected, you know?

Chris Standaert: Mm, yeah, Tennessee. Yeah, and bad things do happen. They are clearly well recognized in this field. They are rare, but they do happen. More minor things are more common, and there is the corticosteroid and the

cortisol suppression, and bone density issues, which are a concern, too, in terms of overall health. Do people find safety to be a major deterrent in the short term or a major deterrent in terms of repeated in the absence of something clearly beneficial happening, or just in general.

David McCulloch: I was struck by this paper and potential harm from repeated injections simply because I, in one of my roles at Group Health, had to review unusual... patient safety thing of an elderly, relatively-thin lady who had been getting epidural steroid injections into her lumbar spine about every two to three months for the past three or four years and then had a collapsed vertebral fracture, which of course, gave her more back pain, for which she got another epidural steroid injection, but an antidote, but it's nice to see some studies looking to see whether is that under certain circumstances, potentially a negative worth looking at.

Chris Standaert: In our system, they may well be getting the injections from their orthopedist or their primary care doctor. They may well be getting trochanteric injections from their rheumatologist. They may well be getting... this happens all the time, people get... unfortunately, it's not well aligned.

Joann Elmore: Can I ask a question about the safety, since that was... we did have some new data, and that's what we're supposed to look at in this review is, what has changed, and in the prior decision that was cover under certain conditions, for the epidural injections, we... on the last vote, the committee voted a maximum of three and six months, and I do not know if there was any scientific evidence that really guided that. It was probably based upon clinical judgment, but I would ask my colleagues and perhaps our clinical expert what guidance should we consider now in light of a little bit more data on potential safety concerns.

Chris Standaert: Somebody that was here recall the discussion on numbers? Mike, do you recall that?

Michael Souter: Part of our discussion before was driven by what was perceived as an overly enthusiastic repetition of injections, which clearly were in appropriate, and it was felt that we needed to put some kind of brake on that. I don't think it was specifically targeted at reducing the risk of bone collapse in such circumstances as have been revealed here, but nonetheless, you can imagine that being, you know, an attributable consequence to an inappropriate frequency of injections. I think it was driven as much by, it's just not the right thing to do with doing them every week, which, in fact, were some of the cases that were alluded to

on our previous review. So, I think that we put a brake on that. I can't remember what drove that particular number.

Chris Standaert: Six versus four versus three.

Michael Souter: I think it was just... a number was chosen and it seemed to be relevant. It seemed to, you know, fit what would be a responsible prescribing pattern, as described by our clinical expert at the time. Yeah, that's about all I can really say on the subject. Michelle, have you got anything?

Michelle Simon: I remember we looked at some state agency utilization data, and there was some outliers with regard to frequency of utilization and that kind of freaked us out a little bit. So, that was part of it, yeah.

Chris Standaert: Dr. Vorenkamp, do you have... so if there are concerns about bone density and fracture and you... so if you did these six times a year, an epidural injection or a facet, whatever injection you want, that means you're doing it every two months, or roughly, give or take, and your clinical benefit, clearly, is fairly short-term by the time you're redoing this, and in your experience, is that routine clinical practice? Are you going to do this every two months to people or is that more frequent than the clinical realm.

Kevin Vorenkamp: Generally not, although some of the evidence suggests that to get six months or more of relief, often it does take two of somewhere between 1.8 and 2.6 injections to get six months of relief after that. So, I think three within six months is reasonable. I have, within a 12-month period, I have... personally, I have a lot of hesitancy doing more than four. The Medicare guidelines are six per year, which I think is an appropriate top level, but personally, in my own clinical practice, above four I would have to have a strong reason to do it.

Chris Standaert: Yes, Louise.

Louise Kaplan: Just in follow up to that, are there any professional association national guidelines?

Kevin Vorenkamp: Certainly, the strongest was the multisociety pain workgroup, so that's 14 societies, spine relevant societies, that have made the guidelines toward Noridian and the other carriers, and I believe six was the amount that was adopted by Noridian, and I believe that was the recommendation from the MPW.

Michael Souter: Another thing I would say on the safety side is, you know, looking at it from a slightly different perspective from the effects, the inadvertent effects of the delivering the drugs epidurally, or steroids epidurally. I think we still do have to be aware, as was mentioned earlier by some of the audience, of the consequences of, you know, what are the alternate sources, because we do have people who are in some pretty... I think they perceive themselves as being in pretty desperate straights, and there are, you know, avenues that are available to them to get opiates out there in the community, and I think that is something that I think we have to bear in mind there that there is a downside to this element. It's something you shouldn't logically happen. We should be... our care delivery should be protected against those kind of things, but I think that will have to be thought about as a kind of attributable consequence of whatever decisions we might make and so I think that is something that does not form our balance of safety effects.

Chris Standaert: Kevin, did you have a thought on that, or are you?

Kevin Walsh: I have a problem with that. I mean, it sounds like a veiled threat to me, you know? Either let us do this, kind of, this thing that might not be all that good but might not be all that bad, or, you're going to turn all these patients into narcotic addicts, and that doesn't wash.

Chris Standaert: Well, was there data you found on sort of minimization of use of narcotics, or alteration in narcotics with the use of epidural injections or other spinal injections. Did you look for that, or did you happen to find that? So, does the data support that argument one way or the other? Do people take more if they don't get injected or take less if they do get injected?

Joseph Dettori: There are a few studies that looked at medication use as an outcome, but that wasn't uniformly presented. So, we, you know, we do have... we can give you some information. Let us go to the tables and... if you're interested, but it's not a... it's not that frequent.

Chris Standaert: OK. Thank you. Yeah, Carson.

Carson Odegard: Beyond just some minor complications, has anything changed in the world of radiology over the last five years, as far as exposure. I could ask the expert this question. I would imagine that it's probably less exposure now with fluoroscopy than... to not only the patient but the physician, as well.

Kevin Vorenkamp: In terms of how much exposure. I'm not clear on the question. Radiation exposure. Certainly, the shift in guidelines is that all these procedures should be done with fluoroscopy. So, certainly, that's a lot more exposure than doing them blind, but it's from a safety standpoint that's far superior, as well as from an efficacy standpoint, but in terms of the actual radiation exposure, I am not aware of any data looking at that. Overall, to the patient it is a very low exposure. To the provider, it's significantly more.

Carson Odegard: I would imagine.

Chris Standaert: Yeah, I don't know the data. I think it's low. I mean, if you go back 20 years ago, they used these plain arm fluoroscopy machines, which were essentially like an x-ray. I don't know for a fact, but just looking at them and hearing them hum, I suspect they had more, but I don't know that for a fact, compared to a C-arm, a mobile fluoroscopy arm. Are there issues on safety, or do we want to go to cost-effectiveness, which could be a short discussion? I don't know. Let's talk about cost for a second, because that's our third arm. Like Carson said, we'll get them... we'll get through the two of them. Anybody see any compelling evidence on cost one way or the other? I'm seeing some heads shake. No. It's a common problem for us, unfortunately. Cost-effectiveness is tricky. It always depends on comparators and it depends on alternatives. It depends on what else happens. It depends on natural history. It depends on all sorts of things, and what you count and what you don't count and... but I'm not sensing anybody feels there is compelling evidence one way or the other on cost. So, why don't we move to our efficacy and effectiveness component? I think we can go by procedure. If we start with epidurals. We will start there because it's on the screen. That was our prior condition, radicular pain with fluoro or CT to follow what Dr. Vorenkamp said, to make sure you're in the right place. Some of these procedures cannot be done without imaging reliably at all. After failure of conservative therapy, which we left deliberately somewhat vague. Couldn't do more than two without meaningful and clinical improvement in pain and function, which is left to the agency directors to define, and no more than three in six months is what we said, which has the corollary of six in twelve months. We didn't say no more than three in six months and four in twelve months. We just stopped there, and we didn't specify disc versus stenosis versus anything else. What do we have in terms of new evidence for epidural injections for lumbar? We have some studies. What do you think, Seth?

Seth Schwartz: Well, I mean, as far as for lumbar radiculopathy, that's the only area where we see the meta-analysis of the newer studies does report a

benefit, which is consistent with what we saw in our previous assessment. So, I'd probably have to... I'd probably accept that as real. Certainly, in the other outcome... that was in terms of pain control. In terms of the other outcome measures, we didn't really see a whole lot of benefit, but, I mean, there wasn't a whole lot there, and that was breaking out just the radiculopathy. I think when you look at spinal stenosis, the new data was even less compelling, but... for what it was. The same is true for cervical. There wasn't... there wasn't a whole lot of compelling evidence for benefit from what we've been shown in these meta-analysis.

Chris Standaert: Thoughts? So, is it worth it then for radiculopathy pain in different origins or are we thinking cervical versus lumbar? Or, do we think our emerging evidence is really not enough to parse that?

David McCulloch: I didn't see anything... I mean, really, I'm echoing what Seth said. I mean, the new studies showed, yeah. There may be slight modest benefit. I'm stuck in my head with the three and six months, six and twelve months, twelve and two years, and I wonder how much vertebral body will be left by that point. I mean, I just wonder whether we should be looking at a maximum total number.

Chris Standaert: Adjusting the numbers a bit? Yeah, to that degree, my experience is similar to what Dr. Vorenkamp said. Most people I know are hesitant when you get to more than four in a year. You're thinking, but that's my own experience.

David McCulloch: Twelve in three years.

Chris Standaert: You're hesitant.

David McCulloch: Sixteen in four years.

Chris Standaert: You get hesitant, yeah. Yeah. So, no other reason to call out other particular things in there for anyone? These were the conditions. There's no other conditions, yes?

Josh Morse: You have the complete document in your... yeah... right there.

Chris Standaert: So, the sense that there isn't a benefit in terms of acute pain that in certain clinical circumstances is translatable. Although not typically thought of as curative or really evidence to tell us this curative of a problem. Alright. Let's move down one. SI joints. It didn't exactly get a lot of new data that we have. We were more restrictive. We said you

can do one. I mean, clinically, SI joint, it's hard to figure out if it's really the SI joint or not, clinically. Hence, we said you can do it once to see if it really works. If somebody has more problems, you can keep doing it. At the moment, I don't... again, I don't totally understand why we excluded spondyloarthropathy. That would concern me personally if we changed that without making that a specific issue, but we didn't get... we had that one new study, which wasn't very big and was sort of multimodal. It's just... it's a little fuzzy because of the multimodal nature of it. What do you think, Tony? You impressed by anything in the SI world?

Tony Yen: I was actually still thinking about the thoracic and epidural injections a little bit. I'm not seeing a comparison right now between what Noridian covers and I wasn't here during the last time this topic was reviewed. So, I'm trying to understand, you know, how Noridian came up to its decisions in the context of the literature that was available. I don't know if that decision was made between the time that this committee made its first decisions versus now.

Chris Standaert: The Noridian decision was made after this committee's decision.

Tony Yen: Right.

Chris Standaert: And that was... that was a multisided work group. It was a consensus group working on a consensus document.

Tony Yen: Right.

Chris Standaert: And the issues of... process issue of different outcomes issue of what we're answerable to, you know, and different processes lead to different outcomes and different evidentiary standards lead to different outcomes and different information, and we have a very distinct evidentiary standard and a very distinct procedure, and from my own experience... it's not the same. It's not that one's better or worse, but it was different. Different outcomes lead to different conclusions. So, that wasn't directly this... it wasn't a Health Technology Assessment type process necessarily, but it was a consensus of 14 or so specialty societies.

Tony Yen: I did notice from the Noridian standard, is that... with the cervical and thoracic epidurals, it didn't state any specific coverage, as far as I'm... or am I missing something from the Noridian coverage policy?

Chris Standaert: Cervical... Noridian policy, with which you're familiar?

Kevin Vorenkamp: Yeah, they're all...

- Chris Standaert: Separate from lumbar.
- Kevin Vorenkamp: ...they're all together.
- Chris Standaert: They're all together.
- Tony Yen: Alright.
- Kevin Vorenkamp: I've got a copy of you want to see it.
- Chris Standaert: We have a copy in our report somewhere. The agency directors gave us a copy. Yeah.
- Josh Morse: Page 11.
- Chris Standaert: Of the agency report.
- Joann Elmore: Slide 21 and 22.
- Tony Yen: I'm looking at slide 11 of the agency.
- Chris Standaert: Yes, you are.
- Tony Yen: So, I'm missing something?
- Chris Standaert: Yeah. I'm just wondering if they just worded it differently, that's all. I don't know. Do you think there's reason to call them out separately based on what you know, from what you've seen, or if we have new evidence to separate them out. We lumped them together five years ago assuming similar parallel processes. I mean, from a frequency standpoint, data is a little harder in the neck... in the cervical. They're roughly 10% of the lumbar... 10% of the whole body of epidural injections are cervical versus lumbar is 90%. So, everything, data, everything is lower.
- Tony Yen: It seems like, as Seth has stated before, I think the evidence is most compelling for the lumbar epidural steroid injections for radiculopathy for short-term relief of pain. And the evidence does not seem to be as strong for cervical or thoracic.
- Chris Standaert: That one cervical study. We don't have any actual thoracic studies, I don't think.

- Joann Elmore: That's a good point. I just looked on page 95 in the large evidence review that shows us the different sort of policy decisions, and Noridian... it is just lumbar epidural steroid injection and then facet joint injection, or median nerve branch blocks.
- Chris Standaert: I don't usually do this. I'm going to ask you, as the person who knows this is sitting right there. Is there a... does Noridian have a separate policy for a cervical and thoracic and there are several different ones here, cervical, thoracic, and lumbar epidural injections, or are they all under the same context.
- Paul Dreyfuss: Cervical is not under the lumbar epidural LCD. There is a separate LCD that looks at peripheral and neuroaxial blocks that are sort of lumped together and cervical is within a separate LCD but the essential terms are similar.
- Chris Standaert: OK.
- Joann Elmore: So, it's covered?
- Paul Dreyfuss: It's covered.
- Chris Standaert: The same sort of conceptual...
- Paul Dreyfuss: Because the concepts are the same, and it just hasn't been updated yet, because of process issues with Noridian.
- Chris Standaert: Thank you, Dr. Dreyfuss. So, SI, we'll go back to that still. There's not a lot more evidence to be thinking about. Why don't you go down one? Go down to medial branch for us. So, for these three, the top two, compelling evidence anywhere for medial branch nerve blocks or intradiscal injections that people saw to be thinking this. Facet injections, there was some data. They downgraded it due to quality. There was some data. Again, this is... do we have what we think merits reconsideration of that? And this is, again, for intraarticular steroids.
- Carson Odegard: (inaudible) change their policy, because they explicitly do include it.
- Chris Standaert: They do, yes. Medicare does on the whole. Noridian does, yes. There are conditions, obviously, but they do. Again, we're supposed to look for evidence. Ideally, that's what different about us, right. It's not just sort of what we think is OK. It's evidence.

- Carson Odegard: The other difference I found, again, not necessarily evidence based is that they require a period of nonoperative or noninjection management prior to allowing it, though.
- Joann Elmore: That's a good question, because I was looking at the stem of our... what we were supposed to look at. In other words, in patients, I believe it's with subacute or chronic pain. So, they defined subacute as four weeks. So, I want to just verify is that the patient population and is... are we requiring a minimum of four weeks of pain for this.
- Chris Standaert: Well, we're not covering facet injections at all. Do you want to go back up to things we allow?
- Joann Elmore: Things we allow, yes.
- Chris Standaert: We said the cervical, the epidural... failure of conservative care, and there are times maybe... there are times people are incapacitated and cannot have... I mean, they... they can't get off your exam table, much less make it to PT. So, you wouldn't necessarily want to...
- Joann Elmore: The agency...
- Chris Standaert: ...wait for four weeks.
- Joann Elmore: ...medical directors' discussion, he had the stem, which is in patients with subacute or chronic pain. So, I think that's what prefacing. So, I think whatever conditions we vote on, it is a priority in patients with subacute or chronic pain. With subacute, he defined as four weeks, four to twelve weeks, and chronic is greater than twelve.
- Chris Standaert: For all conditions, Jo? So, the question was...
- Joann Elmore: It, it's not... this is the agency medical director, because we are voting, hopefully soon, on what we want to cover or not cover, you know, with conditions, whatever, and it's my assumption that they asked us to look at a coverage decision in adult patients with subacute or chronic pain. So, I just want to... even though it's not listed here, I want the members to know that someone cannot show up with one week or one day of pain and get an injection, according to what has been asked of our committee. At least that's my understanding. So, they have to have a minimum of at least four weeks of pain.
- Chris Standaert: Let's go back to the key question.

Joann Elmore: It's in the key question. I had to go there, too.

Chris Standaert: So, the issue we run into, though, is that if you say subacute that doesn't necessarily mean you can't inject somebody. That means our decision cannot apply to people with less than four weeks of pain. So, that's where it gets a little tricky. So, if you took that logic, you'd go the other way. You say our decision doesn't apply to acute pain and then all bets are off, but I'm not sure what... our decision previously wasn't... I don't know if it was decided that way.

Josh Morse: Includes failure of conservative therapy.

Chris Standaert: Yeah. Typically, that period of time. I don't think we have many. I mean, there aren't studies deliberately on people with three days of pain getting epidurals. I can't say that never happens, and frankly I couldn't say that would never be clinically appropriate in my own decision, but rarely, but I don't think you're going to find a study on that. It's not impossible, but that would be uncommon, I think. Alright, does anybody see any new evidence on facet injections they think might do anything? I see a shaking head. So, overall, I personally haven't heard a lot of people talking about things that would change what was said, other than perhaps the frequency or the total number being a concern... being given evidence on complications and concern on complications upon reviewing our prior decision. Why don't we go to our decision tool, then, and we'll get to the vote.

Gregory Brown: Did we resolve the spondyloarthropathy question. We said there's no evidence. Certainly, from a clinical perspective.

Chris Standaert: So, if somebody has a spondyloarthropathy, but you cover a sacroiliac joint injection if it works, then yeah. We cover them at the moment. So, if we choose to change that, then there's an issue with do we say it does not apply to spondyloarthropathy because we didn't look at literature on spondyloarthropathy and they... from a clinical standpoint they are a very rational group to be thinking that might help them. I'm just one person. So, other people may or may not share that view.

Joann Elmore: In our last review, it's my understanding that the committee voted to approve SI joint injections due to a review of, you know, one low quality RCT, but also a lot of observational and cohort studies in a richer patient population that showed a suggestion that it was beneficial. If we were to just look at the last five years, we only... we were only shown one RCT that was negative and low quality, but in my mind, that doesn't change my thoughts in regards to the prior committee decision.

Chris Standaert: Let's go to our coverage tool. So, page three of that tool, way in the back of your thing.

Joseph Dettori: Dr. Standaert, I couldn't tell... did you want me to comment on the facet... the studies presented?

Chris Standaert: I don't think we need, no. I don't think we need that.

Joseph Dettori: OK.

Chris Standaert: I was trying to... I was asking them what they... what the committee... what they thought. If they have a question, they can certainly ask you. Alright. So, we have several things under here. Under safety, we talked about safety. There are injection related adverse events, which is a big category. It is all under one column, and I think we also all called out the... or a number of people called out the bone density issues and the fracture risk issues as an area of concern, and perhaps moreso than it was previously, than it was five years ago. Other safety outcomes we haven't put in there? Efficacy, effectiveness? So, this does comprise a number of things, so pain, function, quality of life certainly falls into this category. It is sort of encompassed by what we have in here. Issues of reducing risk of surgery and reducing opiate use would probably also fall in here, I would think. Did you find any data on the opiate question for us?

Female: So, that is an outcome that we did abstract, and we found no difference for lumbar epidural steroid injection, for radiculopathy, stenosis, axial pain, failed back surgery, and facet, and the majority of those studies were actually done by Dr. Manchikanti. Cervical, as well. We only actually found one difference for epidural steroid injection versus intramuscular. At twelve months, there was a decrease in analgesic use in the epidural steroid injection group.

Chris Standaert: Analgesic broadly defined, including Tylenol and ibuprofen and all that sort of thing?

Female: Yes, I believe so. Let's see if they have any, yes. I believe so, and it was 64% versus 9%, a big difference.

Chris Standaert: Which study was that?

Female: Stav, S-T-A-V-, 1993.

Chris Standaert: 1993.

Female: Correct.

Chris Standaert: OK. Yeah, we have issues of modern versus older techniques and all that to consider with that. So, not a lot... no affirmative data either way really. It's a concern, but we're a bit of... we're not showing a lot of evidence that limits opiate use, nor do we have the opposite.

Louise Kaplan: Even if you give consideration to that, given... even within this state the agency medical directors guidelines for opioid use and the pain management rule, if you did a study in this state, it would be really hard to tease out some of the impact of the environment, within which we prescribe as to what might have reduced opioid use among patients with chronic noncancer pain.

Chris Standaert: And I would think in this population, it is very hard, because of the older population, in particular, has a lot of other things that hurt, knees and hips and shoulders and elbows. So, in these studies what the opiate is for matters, too, right? Are people actually taking it for their spine pain or not, but again, I don't think we have a... our data is not helping us a lot. Special populations? No.

Gregory Brown: That brings us back to the spondyloarthropathy. There's no evidence on it, but it is certainly a special population that we've been discussing.

Chris Standaert: We should call that out. So, we could call out spondyloarthropathy as a special population in case it becomes relevant as we go further. Cost? We certainly talked about cost and cost-effectiveness. We talked about a bit of a dearth of data and then complications of trying to assess data in this area and the unsatisfactory nature of what we have at the moment. No other thoughts. OK. So, we will move on.

So, we're going to go to our vote on effectiveness, safety, and cost-effectiveness. These are your yellow cards. Josh and I had a conversation about, are we voting on the last five years or are we voting on totality, thinking the last five years might inform the next decision we make, do we change anything or not, whereas totality gives us some idea of are we in the right direction anyway, and he was leaning towards totality. If that's comfortable with everybody, we'll vote on a totality of data we have, as opposed to just the last five years.

Joann Elmore: Sounds good to me.

- Chris Standaert: Yeah? OK. So, this is everything ... all comers in there then. So, is there sufficient evidence under some or all situations that this technology is effective, unproven, equivalent, less, or more? Again, if you think it is more in some circumstances, that's what you vote.
- Joann Elmore: Any circumstances at all?
- Chris Standaert: Yes.
- Josh Morse: I see 9 more, 1 unproven, 1 equivalent.
- Chris Standaert: And safe? So, safety, under some or all circumstances this technology is safe.
- Josh Morse: 6 less, 4 unproven, and 1 equivalent.
- Chris Standaert: And cost-effective, the same questions.
- Josh Morse: 11 unproven.
- Chris Standaert: Unless somebody speaks up now, I assume our straw vote will automatically move towards we are going towards conditions and want to discuss them, because that's where we start. And do people want to go technology by technology or do we want to just... what's better? Do we go through each technology or is better just to do them all at once if nobody wants to change anything?
- Josh Morse: It's up to you.
- Chris Standaert: So, I'll ask for... if we start with this as our background, this is what we said five years ago. Does anybody want to change any part of this, more restrictive, less restrictive? David, you had mentioned the number. We don't have a lot of great data, but you have concerns about number, obviously.
- David McCulloch: I have concerns. I mean, I noticed when safety come up, at least half the committee said unproven feeling that the data aren't sufficient to change it, but I do have a... I worry about people getting repeated, repeated, repeated.
- Chris Standaert: But the majority of the committee voted for less, so six out of eleven.
- David McCulloch: Yeah.

- Chris Standaert: The majority voted for less safe. Yes.
- David McCulloch: OK.
- Chris Standaert: So, go... finish what you're saying. I'm just...
- David McCulloch: Well, I just... again, I feel that we would be picking a pragmatic random number, but I'm... this seems too many.
- Chris Standaert: In six months, four in twelve months; three in six months, five in twelve months, three in...
- David McCulloch: I'm a simple mathematician, three in six months means six in twelve months.
- Chris Standaert: Yeah.
- David McCulloch: It means 12 in 24 months, so.
- Chris Standaert: And you can, again, you can put a, you know... make that three in 12 months or you could say, if you thought perhaps more than that in one year might be appropriate, you could word it the other way at a 12-month maximum also to what our clinical expert said earlier saying that occasionally you will cluster them occasionally. So, you might wind up with people who have two or three within a relative short period of time, meaning several months. Then, perhaps somewhere within that year, you might be thinking they're in trouble again.
- Kevin Walsh: Correct, and I think you might be challenged if you limit that short-term, although we don't do a series of three like we did in the non-fluoro-guided days. The other question is, if you're bridging, although it's very rare to do more than three or four in a year, if you're not, are you then going to systemic steroids, which have the full systemic effect, as opposed to the epidural effect.
- Michelle Simon: A couple of the guidelines talk about a total of four therapeutic injections per region, given a per rolling calendar year.
- Chris Standaert: What page are you on, Michelle? Sorry. What page are you on? OK. Louise, go ahead.
- Louise Kaplan: The other thing that is interesting in some of the other local policies and Noridian is that you have to... you can repeat if there's documented more than 50% benefit. So, rather than just continuing to repeat, having actual

benefit before you decide to repeat. Some of them are very specific. It's interesting to look at how prescribed some of them are with the types of medications and the dosage and frequency.

Michelle Simon: Local coverage decision for Noridian says a maximum of five. Oh, that's the facet joint, sorry. Never mind.

Kevin Walsh: Noridian is six.

Seth Schwartz: If you look at our existing conditions, I mean, I think they were trying to capture two things. One is, there's no reason to keep doing it if it's not working. Two is, we want to stop outliers. We didn't want people to be getting twelve in a year or fifteen in a year, which we had seen in the utilization data.

Chris Standaert: We did see, yeah.

Seth Schwartz: And I think beyond that, we felt it was reasonable to leave the decision to the clinicians to determine how many exactly they need, just as long as it's not going crazy. I haven't heard compelling data that we need to reduce the number more. I think, I mean, there are some safety concerns, but I think we don't have a great concept to know exactly how they're used and to limit it much more than this, I think, is nitpicking a little bit. Yet, at the same time, the data of the effectiveness is not absolutely dominant. So, you know, I... if you feel strongly we need to limit it a little bit more, I don't think that would be unreasonable, but I'm not seeing anything that compelling that would encourage us to change this.

Chris Standaert: If you go to our data in our evidence review, they have a procedures per patient average. This is on, what page am I on, 62? In 2008 and 2009, it was 4.1 and 4.3. In 2010, 1.8 and 1.9, 1.6 and 1.7, 1.8 procedures per patient. So, in the last five years, they have been relatively stable, and certainly much less than we were the four or five years before that in the state. So, there's no range, no. There's no range. There's no scatter. We don't know if we still have outliers doing 12 in 2 years. Clearly, it seems... we can't tell for sure, but it seems to have some of the desired effect. This decision seemed to have some of the desired effect, or at least that along with informing the community of different utilization standards had some effect towards what we did versus that, obviously. Does anybody want to change that or add something or say four in twelve months or five in twelve months, or just leave it there. I certainly understand the concerns, and we have new data to make us have concerns.

- Joann Elmore: I recommend leaving it this... the way it is, and I know I'm the one that raised the question to ask of the committee members, but I, I don't see any way to prescribe... it's based on medicine and evidence.
- Chris Standaert: OK. So, SI joint injections. Are we going to change... we can vote on these in totality if they don't change a whole lot. So, SI joint injections?
- Carson Odegard: So, my question comes back to our spondyloarthropathy. If I've got somebody with rheumatoid arthritis and an inflamed knee, I'm going to do conservative therapy for three months before I've given them injection. So, again, is that requirement causing problem for that group or are we going to say sacroiliitis is different than chronic pain and so therefore, it doesn't come under this, but then we need to be clear that this is not discussing sacroiliitis.
- Chris Standaert: Maybe the agency can help us. Maybe Dr. Vorenkamp can help us with his experience with this. So, the vague... where it says after failure of conservative therapy is deliberately vague. When you have somebody with a flare of their spondyloarthropathy with acute, raging sacroiliitis, there... I mean, OK, so this is just what you do, because this is the treatment of choice, and essentially they have failed... they are usually on something else. They have taken, you know, it's not like they never took an Advil. So, there's something to that, and I don't, unless the agency has some other opinion, I would think that would still fall under this.
- Male: (Not Speaking In Mic)
- Chris Standaert: That was a facet injection is what she was denied for the spondyloarthropathy.
- Seth Schwartz: I think if you're talking about acute sacroiliitis.
- Chris Standaert: I don't recall. I don't know if the speaker is there and can correct me, but I believe it was the facet that was denied. I'm sorry. Go ahead.
- Seth Schwartz: I mean, I think our charge has been for chronic pain and that was the criteria for our search was pain for more than, what was it, four to twelve weeks or something like that. So, that situation of an acute flare of something probably doesn't even fall under what we looked at.
- Chris Standaert: OK. So, you could call out an exclusion saying this decision not apply to known systemic inflammatory disease.

- Female: If we could provide some clarification. The decision today is meant for... to not consider inflammatory arthropathies or spondyloarthropathies of those conditions, because those are kind of a distinct etiology from degenerative disease and other chronic pain that we're talking about today.
- Chris Standaert: Do we call that out in our decision at the end and say this does not apply... so is it when people go through and review and somebody says I have a known diagnosed spondyloarthropathy with pain that this does not apply?
- Male: I mean, technically you probably wouldn't have to, but I have to say from an implementation standpoint, I think that would be helpful.
- Chris Standaert: Add that at the bottom. Tell me what people think. So, any other changes in SI? We're going to allow one. If it works, you can do it again. If it doesn't work, you're moving on. OK. And the other ones. I did not hear any strong advocates for therapeutic medial branch blocks or intradiscal injections anywhere here or in the room frankly, and facet injections. Do people feel compelled or interested in changing that other than the fact that we might actually call out spondyloarthropathy from all of this. Same?
- Group: Same.
- Chris Standaert: OK. Do we want to add a line... so, when this comes in, do we want to add a line, not there, or somewhere at the beginning of the document or the end of the document saying these decisions do not apply to patients with diagnosed inflammatory arthropathy. These limitations do not apply to patients with diagnosed inflammatory arthropathy for joint pain, essentially, I would think, or any general, yeah, Tony?
- Tony Yen: Can I ask just one more question for our clinical expert over here? For facet joint injections, are there any other applications beyond spondyloarthropathy that are actually effective that is literature based?
- Kevin Vorenkamp: Yes, and I think there were three studies that were presented earlier, particularly when it's SPECT imaging positive. There are some correlative studies that do show benefit. I can pull those up here beginning with their slide 110, I believe.
- Tony Yen: When you say SPECT imaging positive, you're talking about systemic inflammatory disease, am I right?

- Chris Standaert: No.
- Kevin Vorenkamp: No, with a bone scan.
- Tony Yen: OK. Sorry.
- Chris Standaert: He's going back to older studies before this review, yes.
- Kevin Vorenkamp: Sorry. I'm almost there. Yeah, so that Ackerman study, overall these three prospective studies with physiologic evidence of facet joint inflammation, these were all excluded in the report. A total of 151 patients with benefit maintained at three months. So, that's the Ackerman, the Dolan, and the Pneumatics studies. Typically, in clinical practice, often the facet joint, the main pathway for facet joint pain now is medial branch blocks and facet neurotomy, which we're not talking about today. So, there's usually an indication either of patient variable that would have you go down the facet steroid option.
- Chris Standaert: Tricky. We have one study showing equivalency between a neurotomy and an injection, one small study, and could you... the question is, could you obviate a neurotomy if somebody had a prolonged enough response of a facet injection, but you're trolling into shallow waters, unfortunately.
- Kevin Vorenkamp: That's one of the two, the Ribeiro that was mentioned earlier, as well as the Lakemeier, that both showed supportive evidence for the facet intraarticular.
- Chris Standaert: So, are you proposing we change facet to intraarticular or just saying that we can leave that under the spondyloarthropathy if that's what we're worried about, the non sort of axial spinal pain disorder.
- Tony Yen: So, at least with the evidence that we've been presented over here, it seems like there is not any evidence for the efficacy of facet joint injections, at least with the evidence that we're presented. On the other hand, is that sufficient to override what Noridian has said? And that's what I am thinking about right now.
- Chris Standaert: OK. And so our charge is to look at the evidence and, you know, the issue of what we do with society injections and Medicare guidelines, we don't have any obligation to follow exactly what they say, if we feel the evidence takes us elsewhere, right? We're supposed to look at them and be informed by them and make sure our... we're in alignment with them when the evidence does not suggest otherwise. If we feel the evidence is compelling in some way or the other, either there's strong evidence to

compel us to think it should be different or there's a... we're compelled by a lack of evidence. Then we go where we think the evidence best fits, is really our charge. OK. So, we didn't change... did we change... we didn't change anything. Alrighty then. So, if there are no other comments, we can move to a vote, and basically we are reaffirming the same thing. We didn't change anything.

Carson Odegard: Did we just want to say inflammatory disease as opposed to systemic, so we're not arguing over whether?

Chris Standaert: Does not apply to patients with systemic inflammatory arthropathy, I would think.

Carson Odegard: Systemic or just inflammatory arthropathy?

Chris Standaert: It's a... you don't want just an inflamed... that's what... an inflamed.

Carson Odegard: Well, there's mono-arthropathies is my point, so.

Chris Standaert: Yes, but do you consider it part of a sys-... part of an autoimmune disorder of some sort or... yeah, you can give them mono-arthropathy, but you're giving them something other than a degenerative joint, right?

Carson Odegard: Alright. I'm just asking. I don't feel strongly, but, I mean if all you present with is sacroiliitis, someone can argue that's not systemic. That's my question.

Chris Standaert: I guess I think of it in part of a systemic... it's a broader reaction, but I guess non...

Carson Odegard: I'm just saying...

Chris Standaert: Inflammatory...

Carson Odegard: ...inflammatory arthropathies.

Chris Standaert: Agency, what do you guys... what works for you there?

Female: I like inflammatory arthropathy.

Chris Standaert: OK. Inflammatory arthropathy. So, take out systemic inflammatory disease and change to inflammatory arthropathy. You're frozen. I'll have to get you a sweater. Or a steroid injection, yeah. That'll warm you up. ECMO, we got to warm you up. Inflammatory arthropathy.

Michael Souter: (inaudible) spell check.

Chris Standaert: Leave it. Or individuals with inflammatory arthropathy. We can get to spell check later. Yeah. We're good on time. OK, that being said, so we are basically reaffirming everything except saying this does not apply to... talking about limitations, the scope of our review. So, we're going to vote on this unless there are further comments, questions? Speak now.

Male: I think the language around the... applying to patients, I think you're trying to limit to the condition that's being considered for the injection and not the patient who may have a separate inflammatory arthropathy.

Chris Standaert: Explain for me.

Female: (Inaudible)

Male: Yes. That would be more specific than...

Joann Elmore: Do not apply to injections for inflammatory arthropathy.

Chris Standaert: Procedures for, yeah. I guess inject... procedures for or injections for. I guess they're all injections aren't they? I'm not talking (inaudible). I mean, they're all injections. So, injections for...

Gregory Brown: In other words, if you have rheumatoid arthritis, you can get an injection for anything?

Chris Standaert: Take away patients with. It does not apply to injections for inflammatory arthropathy. Take away, no, not the whole thing. Just take away patients with. There you go. Respell inflammatory. Alright. So, we're going to vote, unless I have other thoughts. So, we have three choices, as always. You can cover unconditionally, and we're going to vote on all of them at once, yes? No, go back up. He wants to see lumbar epidural is what he wants to see. So, there. Thank you. And the agency directors had recommended for radiculopathy, but radiculopathy is a different definition than radicular pain. They are different phrases. They mean different things. So, we're treating pain. That's what we're treating. So, I like radicular pain better, personally. OK. Other questions? OK. We're going to vote. You have three choices, cover, and we're going to do all procedures at once essentially. So, cover meaning forget the conditions, they're all covered, no cover meaning you don't like this at all and they all go away, or we're going to cover these with the stated conditions above for all the specified procedures, right? So, people please vote.

- Josh Morse: Eleven cover with conditions.
- Chris Standaert: So, again, are we aligned with guidelines and other things. It seems we are relatively well aligned. We're consistent with what we said before. We differ in some regards, but we view the evidence somewhat different or prioritize it differently and feel we have an evidentiary basis for our differences. I think that is it.
- Josh Morse: I may have missed it, but did you cover... there is no national coverage determination on this.
- Chris Standaert: There is no national coverage determination on this, no. We have a variety of society guidelines. OK. And committee members, so for the public, unless you want to hear what we're doing... you're welcome to stay and hear what we're doing. We're done with that particular topic. There's no other vote that's going to happen. So, we're going to talk about reviews in progress now for committee members. We got a few more minutes of work to do here. So, do we have things in our packet on this?
- Josh Morse: In the back here.
- Chris Standaert: Do people want to take a break or just go? We got 20 minutes, just go. Yeah, that's what I thought. In case somebody's got to hit the bathroom, I thought I'd ask.
- Josh Morse: They're in your binder in the back.
- Chris Standaert: Alright. OK, committee. So, people in the audience, I appreciate your attendance. We have a few more things to do. So, either just keep it really quiet so we can get our work done or just step out in the hallway would be fine, but you're welcome to stay and listen to what we're discussing. That's fine, too. So, we have a document in the back of HTCC assessments... what we have coming up. Josh, what do you want to talk about?
- Josh Morse: I'll just jump to the end of this and tell you what we put on here, since the last time you met, and that's the... if you look at page three. You've seen the other presentations, or the other topics that are happening for May. So, for... it seems like way in the future, in November, we have the fecal microbiota transplantation or FMT. That review has just begun here in the past few weeks and is underway. I don't... we have not yet released the key questions for that. We have not published those, but the...

- Carson Odegard: Before or after lunch?
- Josh Morse: ...good question, probably after lunch.
- Chris Standaert: And can we hold on the actual pictures. That would be... no video please.
- Josh Morse: So, you can see the policy context is on here. You may be familiar with it. It's just... the primary known treatment is for C. difficile... people who are not responding to other therapies. On the next slide you'll see the proposed schedule starting from the bottom. So, this is proposed to be done next November and back to the top, we anticipating releasing the draft key questions, unfortunately not in sync with your meeting, but in April, which is, I guess, just a week away, two weeks away, and you can see the schedule in there. So, we have also kicked off the negative pressure wound therapy topic, and that is also scheduled for November. This is used in treatment of slow or nonhealing wounds, and it is on the same targeted schedule here, November, ultimately before you... and then the key questions here in a couple weeks. The kind of... in the next one out, which would really be 2017, noninvasive screening for colon cancer. This is a topic that was selected awhile back, but we are getting it in the queue now for then and don't have a full schedule for that, but it would be next January.
- David McCulloch: So, Josh, can I go back to the... so we recently looked at the fecal microbiota transplantation at Group Health. I don't want to say that to bias you, but I know that there won't be a lot of good RCTs, but there are a number of prospective case series of people with recurrent life-threatening C. difficile who have either been treated with antibiotic after antibiotic and then they tried this and showed outcome. So, I think this is an area where... I just would like... whoever is doing the thing, I would hope they wouldn't just exclude all those studies and come to us and say there were no valid... because we've got to look at something.
- Josh Morse: OK. Let me just give you two other updates that we don't have presentations on. So, can you switch the... so you're probably... you've all seen... Christine is going to show you... this is basically the prospective topics document that was released a few weeks ago. The comment period closed about a week ago, but we can just show you what's on here if you have any questions about these proposed topics. They're still... we are... we have yet to digest all the comments that have come in, but we will be then taking these to the director. So, I sent you an email message about this, but the first one there is the extracorporeal shockwave treatment for musculoskeletal conditions. This is an older

technology, but there has apparently been (inaudible) brought this back up, and it was prioritized or recommended for prioritization. So...

Male: Let's do it before (inaudible).

Josh Morse: ...OK. The second one, we're probably going to be changing the title on this, but... based on some feedback. These are basically non... or these are interventional treatments... that might not be the right phrasing, but the nondrug kind of conflicted with the inclusion of botulinum in there. So... but we're considering this topic, a number of modalities for treating migraines and other headache types. The third one is the left atrial appendage closure device. There was recently a formal coverage with evidence development. I mean, this happened two days after we released this document, I believe Medicare released an NCD on this for the over 65 population, which has their formal coverage with evidence development. So, I'm not sure what that means here in the next couple of weeks, as this goes forward for the final selection piece. Is anybody familiar?

The next one is treatment for varicose veins and a few different... I think there's at least three different potential interventions in there, stab phlebectomy, chemical ablation, and laser ablation. The other two, so skin substitutes, I think we may have talked about this before here. Briefly, this is a variety of different products for treating severe wounds or nonhealing wounds, and this has been reviewed by a few other... it is an issue. That's why it's on this list.

Michael Souter: Are you going to include burns?

Josh Morse: I am not sure about that.

Michael Souter: That would be... I know that's certainly going to be a complicated area if it does include burns, so.

Josh Morse: And the final one, if you can scroll down, Christine, it is the computer-aided detection... which is an adjunct, I believe, with mammography. Right. So...

Joann Elmore: No. This is a little add-on that the radiologists charge an extra \$20, \$30, sometimes \$50 to have a computer help read, and there's actually growing evidence that it is not effective. In fact, it shows that it makes it worse. It over reads them.

Josh Morse: Yeah. So, this is on the list. We've received at least I think one comment on this and we're still deciphering whether there is federal law that addresses this. It's controversial, now, I think. If you scroll a little further, there's one re-review topic that has been proposed, and that's the artificial disc replacement, new indications for the artificial disc.

Chris Standaert: Heaven forbid we go through a list without talking about the spine, yeah.

Josh Morse: There is new evidence... there is a formal signal search attached to this document that describes what was in there and then, we are intending to do a formal... we're in the process of doing a formal signal search for bone growth stimulators.

Chris Standaert: That's different than what we did before, the ultrasound where they used... we did stimulators before, or did we just do ultrasound?

Josh Morse: No, we did... you did all the bone growth stimulators and the question is, is there any new evidence that could impact... could alter that. So, quickly, the two or three other things I need to say about what to anticipate here in the next... we're going to have a very... we already have a lot of things going on, but we will be doing a recruitment again in May for at least two, perhaps three, committee members. Dr. Souter, Dr. Simon... actually for at least three committee members we will in May. So, we will be... I will be reaching out to you at that time, which is only six weeks away. We would also likely be doing an RFP here very soon for new evidence vendors and you'll see the information about that coming up. We're down to two evidence vendors at this point. It's Spectrum and Hayes until we go through the RFP process. Our other vendor has decided not to continue for the next cycle. Well, ICER actually is committed to other things, and they are not re-upping after the presentation you saw today. That was their last, the ECMO, yes, for now, so. They have been awarded a pretty significant grant, I guess is how to describe it, to study individual high-cost medications and their organization is working full force on that now. They were given a foundation grant, pretty significant. So, they're looking at... what's the first... so the PCKS-9... the new... I think these are all publicly available. You can see the reports. They are trying to get these out for use. They're doing their value assessment modeling on these drugs to determine, you know, what is the appropriate value for things like that, so.

David McCulloch: Who puts the value in the U.S.A. versus anywhere else in the world?

Josh Morse: Yeah. So, that's... I think I covered it all, RFP, clinical committee recruitment, it seems like there was a third one, but I'm forgetting that,

so. We are completing the rule making process that you may have... I sent a couple emails about the rule making. So, we went through an informal comment period on that. It's known that rules were released to stakeholders with questions about that. The next phase would be a formal submission from the agency indicating moving towards the final step that... if that's on target, I anticipate that would happen in the next month, which means the rules may be changed here in the next 90 days. I don't know. So, that may lead to the necessity to reconsider the bylaws, which is another thing that will be on your radar screen once that process is concluded, just to make sure everything is aligned, so.

Louise Kaplan: (inaudible)

Josh Morse: So, I did not send you a follow up. Dr. Kaplan is referring to the Senate Bill 5145 that I sent you some information about a couple of weeks ago just to let you know that that had passed out of both houses.

Chris Standaert: What was that, the...

Josh Morse: So, that bill does... makes two... proposes to make two changes to the Health Technology Assessment law, one is to require that at least one member of the committee is somebody who has been nominated by... and I don't want to misstate this, but I think it's a statewide medical... I forget how they phrased it, but basically an entity like the WSMA or an entity like the WOMA. So, that's a requirement that... it turns out there is already a member on the committee who was nominated or suggested by one of those. So, it's not a big change. The other piece that is proposed in that legislation is to take the clinical expert and make them a nonvoting member of the committee and that functionally would mean there's a slightly higher bar to be... I mean, there is a... there is... I shouldn't say slightly. There are requirements in the law that would mean a different level of scrutiny for the clinical experts who might be proposed for that position. So, the way it reads is, if you're going to have a clinical expert, they need to be a nonvoting member of the committee. So, that would be an additional... the intent is, that would be a 12th member of the committee, and therefore, that person would sit at the table. They would not be voting.

Chris Standaert: Could the committee choose not to have a clinical expert?

Josh Morse: So, I... we could... I don't want to get into the theoreticals on record at all.

Chris Standaert: OK.

Josh Morse: Right now, because it's... the change hasn't been... so that bill, as Dr. Kaplan started saying, was vetoed by the governor last week because other... a whole host of things were caught because there's some budget issues going on that they haven't completed... some other work. So, but it could be... it could still be passed by the legislature. It doesn't require... there is still another way. So, it's not certain what will happen with that legislation at this point.

Female: (inaudible)

Josh Morse: Right. So, you know, this is the legislative process, and it is... I think it's uncertain at best what will happen with that. Somebody sent me an email notifying me that that had occurred, but, you know, there are things happening at that level that are getting in the way.

David McCulloch: Other proposed rule changes or they were going to eliminate chop blocks and late hits on the chairman of the committee?

Josh Morse: The rule changes are a long time coming, and they're in response to some...

Carson Odegard: You know about chop blocks.

Josh Morse: ...some other issues.

Chris Standaert: What country are you from?

Josh Morse: Legal issues that you've been briefed on in the past and it's a long... it's taken us quite a while to, you know, carefully get those rules right. They've been through one... they're in their second public feedback process now, and there will be another formal public feedback process once this one is done. There will be the formal one, and those rules, I believe you saw a copy of those. I think a copy of those proposed rules was sent out in that public... in this informal public comment period to you. Or maybe I just... I outlined the key changes to you, so. So, those are all the updates I have.

Chris Standaert: OK.

Josh Morse: Alright. Thanks a lot. Thanks for your time.