

*For copies of the official audio taped record of this meeting,
please make request at: SHTAP@hca.wa.gov.*

Health Technology Clinical Committee Public Meeting
May 20, 2016

- Chris Standaert: So, in the audience, I am Chris Standaert. I'm chair of the committee. This is the meeting of the Washington State Health Technology Clinical Committee. We have two primary topics on our agenda, bronchial thermoplasty for asthma, and autologous blood or platelet-rich plasma injections, which will be in the afternoon. Before we start, there are three committee members who are at their last meeting with us, yes?
- Josh Morse: Last public meeting.
- Chris Standaert: Last public meeting, physically present public meeting. Yes, we have a meeting in July. I believe they'll be there for that, but this is their last public meeting, and I want to thank them. So, Dr. Kaplan, Dr. Souter, and Dr. Simon. All three were founding members of this committee. Dr. Kaplan finished then came back and is leaving already. She can say why.
- Louise Kaplan: I am joining a program called Sea Global Health that partners with Peace Corps, and I'm going to be a Peace Corps response volunteer, and I'll be teaching at the University of Swaziland for a year in their nursing program there.
- Chris Standaert: That is totally cool. Yeah. That is totally cool. So, for the three of you, I, boy you were all here when I started, and that was a while ago, and I was a pup and this whole idea of applying evidence to policy, I didn't understand nearly as well as I do now, thanks in large part to the three of you. I think I learned an immense amount just from listening and talking to you. I think as a committee member, I'm grateful for your help and grateful to have been your colleague. I think as a citizen of this State, I am very thankful the three of you were here and were so thoughtful in your work. I think the State should be grateful, and we appreciate it. So, thank you. Alright. That being said, we'll move on. Josh, program updates?
- Josh Morse: Sure, very brief program updates and I thank you, too. Thank you, very much. So, today's topics, this morning after we do previous meeting business, the first topic will be the bronchial thermoplasty for asthma, and in the afternoon, or after the morning topic anyway, the next topic is autologous blood or platelet-rich plasma injections. Thanks, Christine.

Chris Standaert: Just a reminder, this is all recorded. So, when people speak, just introduce yourselves. That goes for the public, as well, when we get to public comments.

Josh Morse: So, the next meeting following today is the July 8th meeting. That is the phone conference meeting. It is a public meeting. Anybody can join that meeting on the phone. The agenda items for that day are limited to addressing the meeting minutes and decisions from today. The meeting after that is scheduled for November 18th, and the topics, the action anyway, action meeting, November 18th with the fecal microbiota transplantation or implantation topic and we have negative pressure wound therapy for home use currently scheduled for November, as well. We are beginning work on a topic for January 2017 on pharmacogenetics and likely will be adding a rereview of artificial disc replacement to that date, as well. We haven't initiated that, but we just finished the initial comment... the final comment period for topic selection, and that's probably the first one that will go would be the rereview of that topic.

So, these are the topics that were selected for the next series of reviews and again, that 30-day comment period ended I think yesterday. So, these are the selections at this point: Extracorporeal shockwave therapy for musculoskeletal conditions, interventions for treatment of migraines or other types of headaches, varicose vein treatments, skin substitutes, computer-aided detection as an adjunct to mammogram, and the rereview of artificial disc replacement.

So, for those not familiar with the program, there are multiple ways to participate in this process. We publish all of our information, as outlined in the statute that created this process on our Health Care Authority websites. Anybody can go to that website and join our email distribution list. That's the best way to stay informed about actions that are happening in the program and before the committee. Anybody may comment at a variety of points on the topics that are being considered for selection, selected, or in review, including publication of draft key questions, draft reports, and here at the meeting, as well, and of course, anybody is welcome to attend these meetings. These are all open public meetings and all of the meeting materials for today have been published a couple of weeks in advance of the meeting, and anybody is welcome, again, to present comments later on this morning on these topics. OK. Thank you.

Chris Standaert: Thank you, Josh. So, we will start with previous meeting business. So, we have minutes from our March meeting. The committee has had an advance chance to look, but people can look through them briefly. They look good to me. I did not see any corrections myself. We'll take a minute to look. If anybody has any questions or comments, please bring them up. If OK with everybody, a motion to approve.

Male: Approve.

Chris Standaert: Second?

Female: Second.

Chris Standaert: All in favor?

Josh Morse: All approve.

Chris Standaert: All approve. We move on. Now, we have to go through the decisions from our prior meeting and make a final vote. The first of these is extracorporeal membrane oxygenation, which again you'll find in your packet. We did not receive any public comments on our decision.

Josh Morse: That's correct.

Chris Standaert: And no comments from the agency directors either, or? The decision is in our document, and it was covered with conditions, as listed. So, one more read to make sure nobody has a language issue. It happens. You look at our words and then go, well maybe. Comments or questions? I'm open to them. Otherwise, a motion to approve.

Male: Approve.

Chris Standaert: Motion. Second?

Male: Second.

Chris Standaert: All in favor of approving the draft decision on ECMO?

Josh Morse: It looks like all approve.

Chris Standaert: Next, we move on to spinal injections to the next section. We did receive a public comment on spinal injection from Dr. Messerli, Dr. Vorenkamp, and Dr. Dreyfuss, and Dr. Vorenkamp was our clinical expert at the time, and we received a comment on language from the Health Care Agency. For the most part, the public comment from Dr. Messerli, Dr. Dreyfuss, and Dr. Vorenkamp relates to facet injections in the literature, and certainly we are open to discussion. I know we particularly did discuss the evidence of facet injections. I personally recall asking Dr. Detorri to discuss that a bit for us. So, I know the committee went through it and heard it, and that guided their decision, I would imagine. Some of the language refers to this limitation we put on, and we talked about the language a bit when we said it, and we basically kept the exact same conditions we had set five years or so ago when the decision was made, except we said limitations do not apply to injections for inflammatory arthropathy, and the question is, and I think it's a legitimate question, what exactly does that mean? I mean, we've pondered this at the meeting, as I recall, and what were we talking about, and my personal recollection and my personal belief is we were speaking about a known identified system inflammatory arthropathy diagnosed, established. Saying inflammatory arthropathy, does

that mean, that means inflamed joint process if you break down the Greek, right? So, I guess the question even the public comment and the agency directors were, well what does that mean? Does that mean... how do you say that a facet joint is inflamed? Does any inflamed facet joint apply? Frankly with some imaging, it's very hard to tell that. It's not quite like a red hot knee or something. You just can't see that, and I don't think our intent was anything that looked inflamed on an MRI should be... could be injected. I think... personally, I think our intent was in a setting with known systemic inflammatory disorder. So, what is the best language for that? It's probably not inflammatory arthropathy and known systemic inflammatory disorder. OK. The agency director gave us suggested language, but it's even, I think, yeah, maybe known systemic inflammatory disorder would fit better.

David McCulloch: Their language is pretty good.

Chris Standaert: You like their language?

David McCulloch: Yeah.

Chris Standaert: OK.

David McCulloch: Well, that's what I was wondering why... would it miss some other?

Michael Souter: I prefer Chris's.

Chris Standaert: Rheumatic disease. I'd take out the word rheumatic if I kept that. We could say a known systemic inflammatory disorder, such as...

David McCulloch: Yeah.

Chris Standaert: ...and use the... I'd take out reactive arthritis and ankylosing spondylitis, psoriatic arthritis and enteropathic arthritis.

David McCulloch: That still allows you to (inaudible) others. I mean, it's giving specific examples of the kind of thing we mean.

Chris Standaert: We're looking for. So, can we...

Gregory Brown: I like the (inaudible) systemic.

Chris Standaert: Yeah. Yeah. So, Christine, I don't know how to... so, it would be a known systemic inflammatory disorder, such as ankylosing spondylitis, psoriatic arthritis, or enteropathic arthritis. Yeah, it's kind of vague, I think.

Tony Yen: Can you say the three again?

- Chris Standaert: So, the three, so a known systemic inflammatory disorder, such as ankylosing spondylitis, psoriatic arthritis, or enteropathic arthritis. So, it gives them some examples and guidance as to what that means.
- Tony Yen: And you said, you used the terms disorder, is that right?
- Chris Standaert: Yes.
- Tony Yen: Known systemic inflammatory disorder, such as.
- Chris Standaert: Yes.
- Tony Yen: Ankylosing spondylitis. Psoriatic. OK.
- Chris Standaert: What do you like, disorder, disease?
- Gregory Brown: I like this.
- Chris Standaert: OK. Disease? Known systemic inflammatory disease? It still has to have some significance to make that word, right. If they... the name has to appear. So, if we make that a, you know, correction to our decision, the decision would basically be what it was before. We didn't change anything, except that we're allowing inclusion for these known systemic inflammatory diseases. There was one public, well one comment made by the directors that we should put the word therapeutic but for facet in terms of noncovered indications. Say therapeutic needle branch block injection, intradiscal injections, and we said facet. They want the word therapeutic in front of that, which I don't feel strong about one way or the other. So, add the word therapeutic or six of one half dozen of the other in my perspective. Yes, no's? I see a lot of...
- Gregory Brown: Actually, I think that's important, because...
- Chris Standaert: OK.
- Gregory Brown: ...sometimes you will do these diagnostic injections with just a local anesthetic.
- Chris Standaert: See, that's the, yeah.
- Gregory Brown: And that's one option, I mean, but, but the point is, is, you know, we don't want them to start doing selective injections at every level, because they (inaudible).
- Chris Standaert: So, if you put in therapeutic, you're going to open up the door to the diagnostic. One problem we have with this, is that they... from a clinician standpoint is they didn't consider facet interventions as a whole. We consider them in two separate decisions, which is really just sort of confusing. It's the same disorder, right, and we have two separate aspects of treatment, like, diagnostic, anyway. So, this gives us a bit of a dilemma, but facet injections (inaudible) means no intraarticular injection is covered be it for lidocaine or bupivacaine be it for

- steroid. You can say it's diagnostic, but do you then say, you know, I'll do a diagnostic injection and add some steroid. I mean are you?
- Josh Morse: I think the issue here was the semicolon really in that this policy really applied only to therapeutic injections and did not apply... the review did not apply to diagnostics, and it's just a grammatical exclusion of therapeutic by having a semicolon instead of a comma.
- Chris Standaert: Well, there shouldn't be a semicolon there anyway. It's not, yeah.
- Josh Morse: And that is a carryover from the original policy.
- Chris Standaert: So, I mean, if, if they, if we put therapeutic, we're definitely opening the door to people to just put do diagnostic facet injections and say they should be covered, which...
- Josh Morse: They are currently covered actually.
- Chris Standaert: They are?
- Josh Morse: Yes, because this review did not include diagnostics.
- Chris Standaert: Oh, boy.
- Josh Morse: So, they are covered for the pathway for facet neurotomy. You have to have it covered to get to it.
- Chris Standaert: What you call it... I'm going to be... procedure label said diagnostic injection of the facet, yeah, interesting. I know there's a gap. Our neurotomy talk didn't talk about diagnostic intraarticular facet injections. They're just not talked about anywhere.
- Josh Morse: And the implementation was... reflected that was challenging because of that because of common coding. Being the same code. The review did not address diagnostic aspects of these injections.
- Gregory Brown: Well, I mean, I guess my question then is... for the medical directors is, does therapeutic help you in any way?
- Charissa Fotinos: It doesn't exclude the opportunity to... no, not necessarily. If it doesn't change what we already cover, probably not unless it creates more specificity. Can you read the difference for me again, please?
- Josh Morse: My understanding is if you simply change this semicolon to a comma, therapeutic would apply to all of the interventions in the sentence, whereas if you read it now, it appears that it only reflects therapeutic for medial branch nerve block injections. It was, I believe, really just a typo or a, yeah.

- Charissa Fotinos: Sounds reasonable.
- Josh Morse: From the initial...
- Chris Standaert: So, take out the comma, or take out the semicolon and make it a comma.
- Josh Morse: ...that's another way to fix...
- Chris Standaert: OK. Let's do that then. They can sort out what they want. OK. With those corrections, are there comments on these... this decision or a motion to approve? Second? All in favor of approving our decision with the correction.
- Josh Morse: All approve.
- Chris Standaert: Alright. With that being said, we are going to move onto bronchial thermoplasty for asthma. I'll start with the agency representative speaking, and then we'll have time for public comments, and then our evidence vendor. Before we start, I'll introduce our clinical expert, Dr. Amy Markezich, a pulmonary and critical care medicine specialist at Overlake who has been kind enough to agree to help us with our process today, and we appreciate it.
- Charissa Fotinos: Good morning. My name is Charissa Fotinos. I'm the deputy chief medical officer for the Health Care Authority, and I will be reviewing bronchial thermoplasty for asthma. A little bit of background. In Washington, more than 600,000 people have asthma. This is up to 2013. Nearly a quarter of those are children. The Washington prevalence of asthma is a little shy of 10%, and the national range is from Tennessee, a low of 7 to 12 in Rhode Island. About 1 in 8 women and 1 in 14 men currently have asthma, and between 8 and 11% of children in middle and high school have asthma. More than 5000 people in the State of Washington with asthma are hospitalized each year, and not quite 100 people die each year of asthma in Washington, and that was from 2014, about 90 people.
- Things I think that are important to consider, as we review this topic, is that managing any chronic condition is difficult and that particularly with asthma, baseline compliance with asthma controller medications is marginal. There was a large retrospective look at not quite 70,000 patients from five health plans, and granted it wasn't whether or not the medications were used, but they look at primary fill rates within 30 days of having a prescription written and only about 15 to 20%... about 20% of people did not fill their initial script within the first month. Then, looking at folks covered days in terms of prescription fills over the following twelve months, about 20% continued to fill their inhaled corticosteroids for the year, about 30% of leukotriene antagonists, and about a quarter of folks who had the combined therapy. So, management of chronic asthma is a challenge, particularly in terms of compliance.
- This shows the... the top picture shows on the left a patent airway and on the right demonstrates the muscular increase with asthma and the bronchospasm.

The lower left shows the catheter used for the thermoplasty and then the right lower picture depicts the catheter in one of the bronchials.

This shows the different areas of the lungs treated, generally three different sessions are used and you can see all but the right middle lobe are treated. So, much more extensive than I would have appreciated initially in just reading the description.

We are discussing this because our concerns for safety are high. Our concerns for efficacy are high, and cost concerns are medium.

Key Questions: What's the clinical effectiveness of bronchial thermoplasty for the treatment of asthma? Is there clinically meaningful improvement for patients with severe asthma? What are the harms associated with bronchial thermoplasty? Does the effectiveness of bronchial thermoplasty or incidence of inverse events vary by clinical history or patient characteristics, and what are the cost implications and cost-effectiveness of bronchial thermoplasty?

Outcomes of interest, in terms of effectiveness, quality of life, asthma control, number of exacerbations, lung function, whether or not a change in hospitalization or Emergency Room visits are notable. In terms of safety, both procedure related events and mortality.

Current state agency policy: Medicaid requires prior authorization, Public Employee Benefits, it is not covered. Labor and Industries and Department of Corrections both require prior authorization.

This shows graphically the type of diagnoses for which it was used on the left is 2013, on the right is 2014, I think, but I can't... I don't have the screen in front of me, but basically, the majority of diagnoses with one exception or for various types of asthma, which is consistent with its FDA approval.

The numbers are not large, in terms of utilization from the Health Care Authority perspective. This includes Public Employee Benefit Plan, both fee for service and managed Medicaid plans. You can see stable use in terms of numbers of patients from 2013 and 2014. Interestingly, not any of the patients required or received three treatments, as is recommended, as treatment.

Again, this is a different way to show the diagnoses, large number of folks were treated for asthma. There were a few people treated for bronchiectasis in 2013, which is not one of the FDA indications.

Overview of findings. You'll hear a lot more detail from Hayes when they do the thorough evidence review, but there were seven studies that total about 480 patients. Three of these studies were randomized controlled trials. One, the largest, Castro compared thermoplasty with sham treatment. Cox and Pavord were medical management. I make the point about the Pavord Study that its primary objective was to look at safety and the feasibility of the procedure

rather than really efficacy, and the patient numbers were small. There were three case series with very small numbers and one retrospective cohort.

This just shows the different stages of treatment based on the degree of control for children and adults, children over the age of 12 and adults and what sort of medications are indicated based on the need for management of symptoms and, as you can see, the three randomized control trials, and I'm really only reviewing those. It did show that the patients receiving treatment in those studies did have a high dose corticosteroids, as well as long acting beta-agonists and were at step five therapy, so pretty equal in terms of their severity and need for high dose medications. Looking at baseline FEV-1 scores, the Pavord Study, folks in that study have very poorly controlled asthma based on the FEV-1 of less than 60% and in the other studies, Cox and Castro, FEV-1's were closer to 80%, so slightly different, and it may or may not make any difference clinically, but it's worth noting.

This is from the systematic review that was done in Cochran. It was referenced in the evidence study, but I felt it was a useful visual tool to think about the randomized control studies, look that up in total. The arrow just points to the study that's primary object was to look at safety and feasibility, and it was as small number and, as you can see, it's got a wide confidence interval, but basically when you look at, this is looking at asthma quality of life questionnaire, and whether or not there was a clinically-meaningful improvement. You see that it favors bronchial thermoplasty but the minimal clinically important difference is 0.5. So, it didn't quite meet the threshold of clinical importance, and this is consistent with the study, at least the larger study of Castro, which used Bayesian methods but also did not meet the probability of superiority posterior probability or superiority.

This looks at the asthma control questionnaire, slightly different, but again pointing to that study with small numbers, but really overall showed no difference in terms of asthma control questionnaire in terms of symptom relief when the studies were combined.

I represented this study because this shows the harms associated with thermoplasty. Again, this is for hospitalization related to the treatment, and you can see that the risk ratio is three and a half times higher in folks who received bronchial thermoplasty than those who did not.

This shows 12-month follow-up in terms of the need for short-acting bronchodilators per week, and again, at 12 months really there was no sustained difference in terms of the need for short-acting bronchodilators.

Safety concerns, certainly in the short-term there is an increase in adverse effects noted in patients receiving thermoplasty. Of particular concern in the near term were the increase in hospitalizations. In the thermoplasty group, there were 8% versus 2% in the control group, and so for every 17 patients treated, about one required hospitalization. I think this is whether or not it's

spurious or perhaps noteworthy that in the Castro follow-up, there was an increased incidence of bronchiectasis, 2% and usually bronchiectasis incidents were reported per 100,000 years. So, that just seemed to be... and whether that was present before I don't know, but that just seemed worth noting. There are guidelines by number of agencies that exist. They are equivocal at best in their recommendation of support. There is not a national coverage decision, and a number of commercial plans still consider the therapy investigational. Concerns cited include approval was based on a small body of evidence, again, just shy of 490 people, three studies only which were randomized, one sham, and the long-term safety questions remain. Many guidelines do recommend that if thermoplasty is used that it should occur in a specialist center or in the context of a clinical trial or a systematic registry.

Based on these points, the body of evidence supporting the widespread adoption of bronchial thermoplasty is limited. The concerns regarding the potential for industry bias, which was in the trials that were used for approval, unequal comparators and the issues of patient compliance at baseline, suggests caution in interpreting these findings and the concerns regarding the potential for harm are significant.

The agency medical directors' recommendation is that this therapy is not covered and that the agency will cover in the context of appropriately designed clinical trials and/or systematic registries, and that is all of our presentation.

- Chris Standaert: Do we have questions for the medical director?
- Joann Elmore: I have a simple one. Could you go back to slide ten and just read the fine print for us? It's the pretty colored one.
- Chris Standaert: Yeah, what, yeah, explain that...
- Joann Elmore: 2014...
- Chris Standaert: ...slide.
- Joann Elmore: ...2013. I just couldn't read the small print.
- Charissa Fotinos: I'm sorry. Oh, yeah.
- Joann Elmore: Back one more.
- Chris Standaert: The one with the big red (inaudible). It looked like it...
- Joann Elmore: So, that one, yes.
- Chris Standaert: ...yeah.
- Joann Elmore: Could you just read the small print for us, please?

- Charissa Fotinos: Yeah. I need to actually see the small print, 'cuz I can't see it from here, um, this is just a, a graphic.
- Chris Standaert: Can you get to a mic?
- Charissa Fotinos: Yeah.
- Chris Standaert: Thank you.
- Charissa Fotinos: This is, uh, just a graphical representation that shows by space the number of procedures done for that particular diagnosis. So, on the left 2014, the top left corner is the diagnosis of asthma not otherwise specified, just basically gives you a sort of pie chart in a square view of numbers of procedures done for different diagnoses. So, you can see, again, asthma not otherwise specified. One was with exacerbation, the upper left corner, bottom is chronic asthma on the lower left, and then on the right is acute and chronic respiratory failure. So, basically just shows the diagnoses that were used and the size of the square shows the proportion for that end. On the right, the diagnoses were chronic obstructive asthma, bronchiectasis, and asthma not otherwise specified. So, this is just a different way to represent the breakdown of diagnoses by year.
- Chris Standaert: Other questions? Yeah, go ahead, Louise.
- Louise Kaplan: I just wanted to ask, how do I get this on?
- Joann Elmore: It's on.
- Louise Kaplan: Oh, it's on? OK. Oh, I'm sorry. I didn't see that. On table 11, the one that follows this, you had previously told us that PEBB does not cover and L&I, let's see, L&I, Corrections, and Medicaid require prior authorization. I was wondering if you could tell us two things. One, what is the prior authorization criteria for approval, and then is there any follow-up data on this select group of people who have had the procedure?
- Charissa Fotinos: As far as the Department of Corrections, I do not believe there has ever been a request for it, and I wish Dr. Hammond were here, but I think that's how he responded. L&I really wouldn't ever be in a condition in a position to cover it. So, they were not aware of it ever being requested either. So, that leaves the Medicaid plans. I know that in terms of fee-for-service, we did approve it in the instance of a patient who was on absolutely maximal medical therapy of everything, was really limited in their ability to even get around their house, had frequent hospitalizations in emergency departments, and there was really nothing left to try. As far as the outcome related to that, I don't know, but it was sort of, there was absolutely nothing left to be offered.
- Chris Standaert: Yeah, go ahead, Dr. Odegard.

- Carson Odegard: Yeah, I was wondering when this came before the agencies, when you look at these numbers, was your concern primarily safety at the time, because the utilization is so low?
- Charissa Fotinos: Both safety and efficacy largely, and even though the numbers are low, there was none, and now there are a few, and it seems to be popping up more in terms of mention.
- Seth Schwartz: I guess I have one other question. I'm not sure what slide it was, but there was a slide about the refills in terms of sort of medication adherence, and it sounds like the, again it's surprisingly poor in the state of Washington, and I'm curious if that's a phenomenon that's been described previously as something we know as a problem in asthma in general, or is that just unique to this data set.
- Charissa Fotinos: I don't think it's unique to asthma. I think it's fairly common in any chronic condition that requires daily medication therapy. Those numbers weren't necessarily from Washington. I can pull the original study and see. It might have been a Kaiser database or something, but really, all it looked at was prescription fills. So, that doesn't mean that folks used it or didn't have... borrow their friends or something. So, it's really sort of a, I think, a high level view that compliance is a challenge. So, I think in terms of thinking about these studies, really, if you're going to add something that has the potential for significant harm, you really want to make sure that you've maximized every other type of therapy and that compliance is assured, and so the point of that was just to say that the compliance with any medication regularly is a challenge, and unless something seems to be quite effective without significant harms, that... just in terms of where it fits in the therapeutic regimen is sort of more the point of that slide, I think.
- Carson Odegard: The other side of that is, there is a testimonial letter from a physician that we received where essentially, if I read it correctly, it says it is curative. So, if you have at least in their case, and so if you have children that can't control their parents and get their medications and things like that, uh, there is a potential upside. Is that correct?
- Charissa Fotinos: In the literature presented, and Hayes will have a better understanding and detail of all the studies, but there was not long enough follow-up to say it was cured. I mean, the majority of people still required inhaled corticosteroids. They still required some type of beta agonist, and at a year out, there was really very little difference in terms of symptom control. So, if your symptoms started not so great and a year later they're not so great, that, to me, does imply cure, which is not to say there may not be individual examples, but in children, asthma often resolves anyway. So, I'm not familiar with that letter to say if it was an adult or child, but that often...
- Carson Odegard: It's an adult, yeah.
- Charissa Fotinos: ...it was an adult?

- Kevin Walsh: Slide 19 is what you're referring to.
- Chris Standaert: Can you put the slides back up, the slide 19? Thank you.
- Charissa Fotinos: Mm-hmm. Yeah. This is one graphic representation that there is not significant difference in bronchodilator use at 12 months, short-acting. There were, to be fair, there were reductions in some of the studies in emergency department visits, days of work and school, though despite those changes there was not any reported difference in symptomatology, so, and that's really kind of deceiving, because it looks like it's... that line there sort of makes it look like it's (inaudible).
- Chris Standaert: Do you have other questions for Dr. Fotinos? No? OK. Alrighty, then. So, we are a few minutes ahead, but we are going to move onto scheduled and open public comment. So, at 8:50 we will check the phone lines when the public may be expecting to be able to comment. So, sometime after 8:50 is when we should check? So, somewhere in there? OK. So, we have one speaker submitted some slides and signed up ahead of time, Dr. Wechsler. We'll have Dr. Wechsler go first, but then there are six other individuals who have come in and signed in to speak. So, for everybody who comes to speak, we need several things. One, you have about three minutes. We need to give everybody a chance to talk. We will get some warning about time from the people over here. Would you please introduce yourself and your affiliations if you have one, and if you have any conflicts of interest? Somebody is funding you to come. Somebody funds your work in this regard. The committee needs to understand that, and the public needs to understand that. So, thank you. So go ahead.
- Michael Wechsler: Can I start?
- Chris Standaert: Yes, you can.
- Michael Wechsler: Oh, sorry. OK. Hi. My name is Michael Wechsler. I am the director of the asthma program and the Asthma Institute of National Jewish Health in Denver, Colorado, and I was an investigator in the AIR2 pivotal trial that led to the FDA's approval of bronchial thermoplasty in asthma. It's a pleasure to be here today, and my goal is, in my three minutes, is to try to tell you why I think that bronchial thermoplasty is both an effective and safe therapy for patients with asthma and to tell you, really, about the significant unmet need and burden in these patients and shed light on some of the new data that's emerged over the last few years.
- Chris Standaert: I don't mean to interrupt, but conflicts of interest. A number of the...
- Michael Wechsler: Oh, sorry.
- Chris Standaert: ...investigators in the AIR study had financial relationships with the company. So, if you could help us with that.

Michael Wechsler: Sure.

Chris Standaert: And your relationship. Thank you.

Michael Wechsler: Yeah. So, I was an investigator in the AIR2 study and received just research funding to participate in the AIR2 study. I have provided some consultative support to Boston Scientific, before that Asthmatics and have not received any in the past year. I am getting, having my trip for today paid for, as well as some of my time paid for, for today, by Boston Scientific.

Chris Standaert: OK. That's helpful.

Michael Wechsler: So, a few new developments in bronchial thermoplasty in the past few years. First of all, bronchial thermoplasty is now included in the global initiative for asthma guidelines. They were updated in 2014, and you saw the six-step approach that was previously presented in the national asthma medication prevention programs. Bronchial thermoplasty is now included in the GINA, Global Initiative for Asthma guidelines that were developed in 2014 as step five basically for patients who are poorly controlled with asthma. This represents approximately 10 to 15% of the asthma population. These are patients who are on a long acting beta agonist, inhaled corticosteroids, and poorly controlled. Also, in the last few years, the British Thoracic Society Asthma Guidelines have updated their guidelines to include bronchial thermoplasty to be considered for the treatment of patients with moderate to severe asthma with poor asthma control, and they said that the evidence is quite high, based on the double-blind sham-controlled studies that were developed, as well as the long-term follow-up.

Recently, there have been publications elucidating the mechanism of action of bronchial thermoplasty and it has been demonstrated that bronchial thermoplasty reduces airway smooth muscle in patients with severe asthma, and that's the mechanism by which it was hypothesized to work, is that by burning the airway smooth muscle with heat, one can deplete the... that was three minutes? Alright. A minute and a half of that was with your question.

Chris Standaert: You can keep going for another additional minute or so, yes.

Michael Wechsler: Thank you.

Chris Standaert: Please finish your slide.

Michael Wechsler: Thank you. So, I think my main point that I want to make was the durability of efficacy. We published a five-year results that demonstrated a sustained reduction in exacerbations maintained up to five years. These are patients who participated in the AIR2 study. There was approximately a 50% reduction, 44-50% reduction in severe exacerbations in a percentage of patients who had an exacerbation, and in terms of Emergency Room visits, there was a 75-90%

reduction in the proportion of patients who had Emergency Room visits, as well as a number of first events Emergency Room visits. In sum, there is also significant safety. There is no increase in hospitalizations, asthma symptoms, or respiratory adverse events over the course of five years. The bronchiectasis was not seen in longitudinal studies based on CT scans, and there was no significant structural changes that were seen out to five years in these patients. We think that the most appropriate patients are those who are 18 years and above who are poorly controlled on long acting beta-agonists and inhaled corticosteroids and who continue to have exacerbations and/or are on chronic steroids. I have significant experience in this regard. I did one of these cases yesterday. I can tell you that our patients view this as significant and view the need for this kind of therapy for our patients. Thank you.

Chris Standaert: Thank you. So, I will do my best with names. If I... yeah, you can sit down. Thank you for your comments. So, I'll do my best with names. If I mispronounce, please excuse me. So, I'm going to go in the order in which people signed up. Jiten Patel. Again, as Dr. Wechsler did, please help us with comments about financial relationships, conflicts of interest, funding for speaking, etc.

Jiten Patel: Hi. Good morning. My name is Jiten. I'm a pulmonologist in Spokane, Washington. I'm a, I think, real-time pulmonologist. I am... I sort of went off the data that I learned about five years ago. It took about two years for me to actually develop a program and now after treating 16 patients, I have a small culvert to share with you. Severe asthma is a very heterogeneous disease...

Chris Standaert: Again, conflict, please. Conflicts of interest, please.

Jiten Patel: Right. I have no conflicts of interest. Boston Scientific did pay for my flight here. I'm speaking without any need for reimbursement.

Chris Standaert: Thank you.

Jiten Patel: Severe asthma is a very heterogeneous disease typically. So, when they came to me, they usually came through via three or four pulmonary evaluations if not hospitalizations. About 52% of my patients had atopic disease. All had obstructive lung disease. As the airway becomes increasingly mottled, it becomes somewhat less broncho-reactive. So, the obstructive patterns vary from mild to moderate to even severe, but their ACT scores were all uncontrolled. Of the 16 patients I treated, they were preevaluated and went through a physical examination and a rather aggressive serologic and radiographic exclusion criteria, just to exclude any mimickers, not just of asthma, but of coughing, wheezing, and shortness of breath. So, none of my patients had bronchiectasis, considering almost a third of them were intubated. All of them were on high-dose steroids, inhaled, as well as leukotriene inhibitor plus a LABA, a long acting beta-agonist. So, they were already on step five by the time they saw me. In addition, all of them had either two exacerbations in six months or three in twelve months, defining them by the guidelines as having

severe asthma. Three of them had methotrexate, two of them had theophylline, and one of them had Xolair treatment. So, with that, I'm just going to show you some of the outcomes that wasn't very sophisticated with the four patients, but the subsequent 11 patients. They all had therapy that continued through after treatment. None had complications leading to a pneumothorax or any surgical trauma or further need for steroid therapy after I had treated them. They were on a protocol base. So, they had days minus one prednisone five days later that continues prednisone. So, I had no exacerbations with the 16 patients I did treat. They were followed at three, six, nine, and twelve months, much like the preceding studies, and they remained to be obstructed. They continued on inhaler therapy. The two methotrexate patients discontinued therapy. The Xolair patient was off Xolair treatment, and one patient was on gold treatment, was no longer on gold treatment. What I found that their ACT scores did improve subjectively. Their need for prednisone bursts lessened over the additional nine and twelve months. I do have a patient here who is going to share that experience. The theophylline patient discontinued therapy of the two of the three, and one remains on just sort of a psychotropic therapy modality because he's having a difficult time. Sorry. I felt rushed there, but.

Chris Standaert: No. Like I said, it's a short time, yeah. We need everybody to get a chance to speak. Thank you.

Jiten Patel: OK. Thank you.

Chris Standaert: Thank you. I appreciate that. Next is Roberta Stapleton. Ms. Stapleton?

Roberta Stapleton: Good morning. My name is Roberta Stapleton from Spokane, Washington. Thank you for inviting me to a historic meeting on bronchial thermoplasty. My angioplasty surgery was done between December 12th, 2013, through January of 2014, with Dr. Jiten Patel and staff. I was totally at ease with the procedure and the explanation of what was to happen was simple and very direct. Each surgery was in absolutely no pain. After the first surgery, I noticed significantly better breathing, and after each surgery, what a joy this was, like lifting an elephant off my chest. I hope these wonderful machines and doctors can be brought to more and more people with our awful disease. Breathing is a luxury. You have given me a great gift. My accomplishment was an annual walk for monies for the ALS association that I participate in. I did almost three miles of a 3K run in 2014, then to hear my grandson cheer me on when we go to the finish line. Good job, Grammy. It does work, and thank you very much.

Chris Standaert: Thank you. Catherine Richardson.

Catherine Richardson: Thank you. Excuse me. Pardon my voice. I'm Catherine Richardson. I have no conflict of interest being here. To give you some brief background, I am also a physician. I'm a recently retired nephrologist. I've had asthma for many years (inaudible) mainly by a persistent, hacking cough was difficult to treat. This became particularly worse after the introduction of antibacterial hand gels in

the hospitals where I worked. The first time I tried it, I nearly ended up in the Emergency Room. It took over two hours and a lot of Combivent to help me breathe again. I quit using it but was still confronted by this, as well as other chemicals and perfumes at work. I required medications up to and including subcutaneous Xolair every two weeks. My cough kept me awake at night for hours on end, leaving me exhausted and interfering with my work. I knew that Dr. Ryan in Tacoma started doing bronchial thermoplasty, but I had some reservations. I put it off until my situation was essentially untenable. After several bouts of pneumonia and the onset of steroid myopathy, I agree to go ahead with a large amount of difficulty, as you might imagine, getting the procedure approved by my health insurance. After four months and a last appeal, I requested that a pulmonologist be involved and finally approved it, and they were forced to pay the approximately \$15,000 that the three total procedures cost. I was very lucky in this respect. Keep in mind that at this point, Regence was already paying over \$2000 a month just for Xolair injections, not to mention inhaled steroids, bronchodilators, and other medications along with hospital admits for pneumonias with asthma exacerbations. One viral pneumonia led to the alleged severe cardiomyopathy, which subsequently has at least resolved. The procedure themselves were not difficult and as predicted I had a few days of discomfort and shortness of breath after each. I had a respiratory infection after the first one, easily treated with antibiotics. The last was in December of 2013. After a few months, I realized how much better I have gradually become. I no longer have horrible asthma exacerbations with every little hint of a respiratory infection. I have used prednisone only twice for other infections due to be immune compromised. It has been 18 months, since my last Xolair. I have stopped Singulair, only rarely need Advair, and inhaled bronchodilators are rare as well. This procedure has changed my life. I can sleep again. I can function again. As far as the health industry is concerned, they no longer need to pay several thousand dollars a month just for Xolair and other medications. Regence has spent far less for my pulmonary treatment, since the thermoplasty than it was before. The discomfort I had afterwards is something I would willingly redo for the benefit it gave me, and I highly recommend this procedure for anyone with severe asthma.

Chris Standaert:

Thank you very much. I appreciate hearing your story. We should go to the phones. Is there anyone listening on the phones? This is a meeting of the Washington State Health Technology Clinical Committee. We are now in the process of public comments for the topic of bronchial thermoplasty for asthma, and if there is someone on the line who would like to make an unscheduled public comment, please speak up so that we can have... give you the opportunity to share your thoughts with us. If there is no one on the line, we will continue with our public speakers here. Thank you. Our next scheduled speaker is Karla Marsh. Did I get that right?

Karla Marsh:

Good morning. My name is Karla Marsh, and I have no conflict of interest. It is truly a privilege and an honor to stand before you today and talk about a life-changing and life-saving procedure. For the past eight and a half years, I have been battling severe and resistant asthma. Since that time, I've spent over 150

days in the hospital and made over 25 trips to the Emergency Room. In the pursuit of answers, treatment, and a return to an active lifestyle, I visited over 15 doctors. I've been on over 30 medications and supplements, and even traveled to the National Jewish for ten days of extensive testing. I have been a nonstop advocate for my health, yet when not visiting doctors and hospitals, most of my time at home was spent on the couch or in my bed, frequently unable to walk, even a single flight of stairs in my home. I was having so many asthma flares, I was utilizing only 60% of my lung capacity at best. The conclusion of all this testing, doctor's appointments, frequent Emergency Room visits, and long hospital stays was I was repeatedly told there was nothing else that could be done, and this shell of existence would be my life, but I knew it would get even worse. My body began to experience side effects that a woman in her 20s and 30s should not experience, adrenal failure, cataracts, osteopenia, and edema are just a few of the issues that continued to get worse every month I was on the only medications that would allow me to breathe. The yearly maintenance cost for this existence was thousands of dollars out of pocket for us, we claimed over \$15,000 last year alone, and hundreds of thousands of dollars for the insurance company. After much research and more doctor visits, I found out about the BT procedures. I located incredibly reputable doctors, and they determined my severe and drug resistant asthma made me a perfect candidate and I would benefit greatly. I was filled with hope for one of the first times in years. I scoured the internet, BT boards, and all the clinical trials to see what results others had experienced. As a severe asthmatic, the results looked like an answer to prayer that I thought would never come. Compared to the costs for me to merely exist, the BT would only cost the insurance company around \$70,000. That was... just one of my three week hospital stays I did for an asthma flare cost more than that alone. I thought this made sense for anyone, yet I was wrong. After a long battle, my insurance company decided not to cover the insurance. Undeterred, I began to figure out how to do this on my own. On September 16th, I underwent my first of three procedures. When they went in, they discovered it was much worse than they thought. Areas that should have been pink were flaming red and instead of the average 70 to 80 activations, they needed to perform 124. I had the second part of the procedure on October 8th and the final portion on November 2nd receiving a grand total of 382 activations, more than 100 activations over the average. I stayed one night in the hospital after each procedure for observation purposes, was released early the next morning to recover at home. Almost immediately after each procedure, my health began a dramatic turnaround. I already felt a difference in the depth of breath I was able to get, and when the doctors listened to my lungs, they were amazed at how clear they already sounded. Instant results. My spirometer readings prior to my surgeries registered less than 500 but just ten minutes after my third surgery, I registered over 2500. Can I complete one paragraph?

Chris Standaert: One paragraph.

Karla Marsh: Thank you. My life now is on a completely different trajectory. I am back to taking my kids to school and am back to the part of the daily hustle and bustle

of being an involved mom. We even have a trip scheduled to go to Disneyland in the fall, because I can actually travel and am able to walk the park. Post-BT, I haven't been to the hospital or Emergency Room once. I have been able to eliminate and/or lessen over ten medications in six short months to the tune of thousands of dollars in savings for me and the insurance company, and most importantly, for the first time, I am successfully tapering prednisone and slowly reversing some of the side effects that would not only crease the amount of money to maintain my care but significantly shorten my life. At only 35 years old, I have a lot of life left to live and only because of the BT procedures have I been able to see and experience that bright future ahead of me that severe asthma was taking away. Thank you for your time and your valuable consideration of supporting this life-saving procedure.

Chris Standaert: Thank you. The next speaker is Dr. Narinder Shargill.

Narinder Shargill: Good morning, everybody. Thanks for the opportunity to speak here. My name is Narinder Shargill. I am the vice president of clinical and regulatory affairs at Pulmonx Corporation that is developing therapy for COPD. I was involved the BT research and all the clinical programs for asthmatics and (inaudible) at Boston Scientific and worked with the FDA to get this product approved. A couple of comments I make is that the approval of BT by FDA was based on the preponderance of evidence from three different randomized clinical trials, and certainly the clinical experience to date has validated the findings that were reported in those clinical trials. So, a 32% reduction in exacerbations, a 73% reduction in ED visits and certainly time loss from work, school, and other activities due to asthma. So, that's certainly been the benefit that BT provides. Its acceptance in global asthma treatment guidelines, as was mentioned, certainly the GINA guidelines and the British Thoracic Society Guidelines has been around for a couple years. While the ATSERS guidelines were not very favorable to its BT. I point out that Dr. Fran Chung, who was the co-chair of that panel recently co-authored the South African guidelines on severe asthma, and the guidelines state they endorse the use of BT in patients with severe, persistent asthma who remain uncontrolled, despite optimal medical therapy. So, I believe that over time, the experience that people have had in the real world setting has helped move this forward. Thank you.

Chris Standaert: Thank you. I have one more speaker on our list, and then I'll ask anybody else wants to speak after that, Noah Webster. Not speaking. Anybody else in the audience want to make a comment? Yes, sir. You can come up to the mic. Just, again, please introduce yourself, conflicts of interest sort of thing.

Travis Marsh: Hi. My name is Travis Marsh, and I have no conflict of interest. I am the husband of Karla Marsh that spoke, and I wasn't planning on speaking but after hearing the previous presentation I wanted to do a little bit of a pushback, and my pushback is this, we heard in that presentation of the potential for harm, my frustration was, I saw no real evidence. There's hypothetical potential for harm. We are scared of maybe what we don't know, etc. in the future, but you are staring at patients... what we do know, and what we do know is sitting here

today in front of you with amazing results. So, it's great to have... hypothesize of what could happen, of the potential for harm, but the reality of what is currently happening is a lot different. Also, the falter of use, the stats that were given you were all patients that have asthma. We're not talking about all patients that have asthma. We're talking about severe and resistant patients, and if we want to use those numbers of those people who actually filled their prescriptions and those people who used their medications on a daily basis, that is much higher than what the numbers were given to you, because we're talking about... we're not talking about the kid who loses his inhaler, right? I teach middle school, and they lose everything. So, I understand that, right, but what we're talking about is people that are on severe and resistant asthma on many medications. They fill their prescriptions. They are diligent about their... taking care of their health, and finally on the needs of medications after, you know when it says that... when you're getting stats saying well, you know, it's the same, completely untrue when you're looking at exactly how many medications... do they need an inhaled corticosteroid afterwards? Yes. OK, but we're not necessarily curing asthma. What we're doing is, we're taking someone who was on 60 to 80 mg of prednisone a day. We're taking people who are on numerous inhaled steroids, and we're reducing it down to one. We're taking away all these other medications, all these other treatments, all this other cost, and we're reducing it down and too... so, now we're getting to manage care where people can actually live their lives and they are not dependent on going in time after time to the hospital and, you know, you're... you're changing lives in this, and as you saw with my wife, no other hospital stays, right? She had the procedures and was not in the hospital afterwards, you know? We can't put our head in the sand on this. This is Washington State. We lead, OK, in Washington State. We can't put our head in the sand in this. We can't... we have to accept that this is a nondrug solution. My wife has just had her cataract surgeries at age 35. This is a nondrug solution. It is changing lives and this is an opportunity for us to be brave. Thank you.

Chris Standaert: Thank you. Anybody else in the audience want to make a comment? Can we check the phones one more time and then we will... so on the phone you're unmuted again. This is a meeting of the Washington State Health Technology Clinical Committee. We are talking about bronchial thermoplasty. I just want to give a last opportunity for someone on the phone to make a public comment if they would like. Otherwise, the public comment period will close, and we will move on with the meeting. OK. Thank you. Thank you, all. We appreciate the time and effort and courage in speaking.

So, we will... our next step here is our evidence vendor from Hayes.

Natalie Slezak: Good morning. I'll be presenting the Health Technology Assessment on bronchial thermoplasty for asthma. My name is Natalie Slezak, and I'm a senior research analyst at Hayes, Incorporated. I was the primary author on this report.

This slide lists abbreviations that I'll be using throughout the presentation for your reference, and there are quite a few of them.

First, I'll be presenting some clinical background information on the bronchial thermoplasty device and its use in the treatment of asthma. I will then present an overview of the scope of this report, methods used for analysis and literature search results. I will then present the findings for the evidence review and present an overview of relevant practice guidelines and payer policies and then wrap up with an overall summary and discussion.

The goals of asthma therapy are to achieve good control over asthma symptoms and maintain normal levels of activity. The severity of asthma is assessed retrospectively according to the level of treatment needed to control symptoms and exacerbations. For mild, intermittent asthma, no daily medication is advised for the majority of patients in order to relieve occasional symptoms, a short-acting beta-2 agonist or SABA, such as inhaled albuterol, is prescribed. For patients at risk of exacerbations, it's SABA plus low-dose inhaled corticosteroids, such as fluticasone, should be considered. Other treatment options include leukotriene modulators, sustained-release theophylline, or cromones.

So, asthma is a chronic inflammatory disorder. The airway is characterized by episodes of impaired breathing caused by airflow obstruction, bronchial hyper-responsive and underlying inflammation. Asthma symptoms may be triggered by factor, such as exercise, allergen or irritant exposure, changes in the weather, or viral respiratory infections. The prevalence of asthma in Americans is approximately 18.7 million adults. The prevalence of asthma varies among different population subgroups. Women have a higher asthma prevalence rate than men. Boys have a higher rate than girls, and children have a higher rate than adults. Asthma is more common among the poor than other socioeconomic groups. Stats made an annual cost of asthma in the United States is approximately 56 billion dollars, and this total includes indirect cost due to lost work days and school days and direct medical class for asthma, including asthma medications and hospitalizations.

So, for moderate, persistent asthma, the preferred step 3 treatment is a combination inhaler of low-dose corticosteroids plus LABA with a SABA as a reliever medication. Other options include increasing to a medium dose corticosteroid, combination low dose corticosteroid plus leukotriene modifier or theophylline.

For severe asthma, the preferred step four treatment is combination medium dose corticosteroids plus LABA with a SABA as a reliever medication. Other options include a medium dose corticosteroid with a leukotriene modifier or theophylline. Patients with persistent symptoms or exacerbations despite cort inhaler technique and good adherence with step four treatment should be referred to a specialist. The following add-on options may then be considered, tiotropium, omalizumab, low dose oral corticosteroids or bronchial thermoplasty.

Bronchial thermoplasty is designed to reduce the smooth muscle that constricts the airway during asthma attacks. This procedure relies on a catheter that has an expandable array of electrodes that is delivered to the airway of the bronchoscope, which allows the physician to see inside the lung. After the catheter is inserted into the airway, as shown in the figure, a wire leading out the back end of the catheter is attached to a radiofrequency generator and a lever is operated that causes the electrodes to expand. The curved electrodes are held against the bronchial walls, and an electrical current is applied to generate heat that reduces the smooth muscle underneath the lining of the bronchial passages.

Bronchial thermoplasty is typically performed in three separate sessions, at least three weeks apart, to allow shorter procedure times and to reduce risk associated with the widespread irritation of the airways in patients with severe asthma. During bronchial thermoplasty, all accessible airways located beyond the mainstream bronchi, except for the right middle lobe, are treated, and bronchial thermoplasty is typically performed by a pulmonologist with the patient under moderate sedation or general anesthesia.

The Alair bronchial thermoplasty system is regulated via the premarket approval process. It is a Class III high risk device and is subject to the most stringent regulations enforced by the Food and Drug Administration. The FDA approved the bronchial thermoplasty since April 27, 2010, for the treatment of severe asthma in adults whose asthma is not well controlled with inhaled corticosteroids and LABA.

According to labeling information, approved by the FDA, bronchial thermoplasty is contraindicated under any of the following circumstances: Presence of a pacemaker, internal defibrillator or similar implanted electronic device, known sensitivity to the drugs employed during bronchoscopy, prior thermoplasty procedure in the same area, active respiratory infection, asthma attack or alteration of corticosteroid dose in the last two weeks, bleeding disorder, need for aspirin/anticoagulants, antiplatelet agents, or NSAIDs that cannot be interrupted. The last four contraindications listed here are relative rather than absolute and may only require a delay in the bronchial thermoplasty procedure.

In addition, the FDA warns that caution should be taken in patients with the following conditions, as they were not studied in the pivotal trial, post-bronchial dilator, forced expiratory volume less than 65%, additional respiratory diseases, need for greater than 12 puffs of a SABA or oral corticosteroids greater than 10 mg per day, patients with increased risk of adverse events associated with bronchoscopy or anesthesia, intubation or ICU admission for asthma in the last two years, or more than four respiratory tract infections, three hospitalizations for asthma or four oral corticosteroid pulses in the past year.

The PICO statement outlines the scope of the report and was guided by the key questions and the available evidence. The population of interest is adults

diagnosed with moderate or severe asthma. The intervention of interest is bronchial thermoplasty. The comparators of interest were medical management, sham treatment, or no comparator, and the outcomes of interest are quality of life, asthma control, including medication use, asthma exacerbations, lung function safety, healthcare utilization, and cost implications.

The following key questions guided the development of the evidence report. Key question number 1 is, what is the clinical effectiveness of bronchial thermoplasty for the treatment of asthma? Key question 1A, is there clinically meaningful improvement for patients with severe asthma. Key question number 2, what are the harms associated with thermoplasty? Key question number 4 is, or question number 3 is, are there differential effects of bronchial thermoplasty according to clinical history or patient characteristics, and key question number 4 is what are the cost implications and cost-effectiveness of bronchial thermoplasty?

The initial literature search for primary studies to answer the key questions was conducted in the PubMed and OVID databases on October 02, 2015. Articles were selected for review if they assessed the efficacy or safety of bronchial thermoplasty in patients with moderate or severe asthma and were published in English language journals. Although bronchial thermoplasty has been approved by the FDA only for severe asthma, one of the three randomized control trials found assessed in the current report included patients with moderate or severe asthma. Therefore, we then did not just limit the search to severe asthma patients. Articles were excluded if they contained no quantitative data for assessing impact of bronchial thermoplasty, were conference abstracts, case reports, or series of case reports. Final updates searches were conducted on March 18, 2016.

This chart gives an overview of the literature search and the evidence selection process, 26 full text articles were retrieved, of which 11 studies reported in 15 articles met the inclusion and exclusion criteria and were analyzed, seven studies were found for key questions number 1, 2, and 3, and four cost studies were found for key question number 4.

Like the GRADE working group, Hayes uses the phrase quality of evidence to describe bodies of evidence in the same manner that other groups, such as ARC, uses the phrase strength of evidence. First, we assess the quality of each individual study taking into account study design, execution, and analysis using the Hayes checklist. We rate each individual study a very poor, poor, fair, or good. The aim of individual study appraisal is to determine if the study's findings are valid. We then assess the overall body of evidence for each outcome of interest, taking into account applicability, the quantity of the data available, the consistency of results across studies, and any evidence of publication bias. Bodies of evidence are graded as very low, low, moderate, or high, and the aim of grading the quality of the overall body of evidence is to determine how confident we are that the evidence answers each key question.

This slide provides an overview of what the different overall body of evidence ratings mean. A high quality body of evidence indicate that there is reliable and consistent evidence reflecting the true treatment effect and the findings are unlikely to change with future studies. A moderate quality body of evidence indicates that there is reasonable confidence that the results represented true direction of an effect; however, it is possible that the effect estimate might change with future studies. A low quality body of evidence indicates that there is little confidence in the direction of the effect due to poor quality studies, inconsistent results, or paucity of studies, and future studies are likely to change the effect estimate and possibly the direction of the effect. A very low quality body of evidence indicates that there is no confidence in any result found due to the paucity of data, and we, therefore, cannot make a statement on the study findings.

So, next, I'm going to provide an overview of the findings in order of each key question. For additional details on individual studies, please refer to the summary of findings tables in the executive summary or the full evidence tables in the appendix of the final report.

Seven studies were selected for detailed analysis for key question number one. In general, studies demonstrated that bronchial thermoplasty was superior to sham treatment or controlled treatment with some inconsistency across outcome measures. However, overall quality of the body of evidence for effectiveness of bronchial thermoplasty for asthma was considered to be low and consisted of one good quality randomized control trial, two fair quality RCTs, three very poor quality case series, and one very poor quality retrospective cohort study. Four of these studies addressed whether improvements in outcome measures were clinically meaningful for key question number 1A. All these studies assessed clinically significant improvement in asthma related quality of life. Two of three of the RCTs demonstrated that bronchial thermoplasty was superior to sham treatment or controlled treatment for improving health related quality of life, and one non-randomized study demonstrated that 50% of thermoplasty patients met the criteria for clinical improvement. Overall, quality of the body of evidence as considered to be very low and consisted of one good quality RCT, two fair quality RCTs, one very poor quality retrospective cohort study.

David McCulloch: Let me just stop you there. So, why are... why are these studies even included, if you say the definition of very low is we have no confidence in any result data such that we cannot make a statement on the findings, why include them... why are they not part of the 120 some studies that were rejected? That's my first question. Second is, if... how can it be very low if one is a good quality RCT? I'm just curious to know what aspect of it made it very low quality.

Natalie Slezak: I'll get into that a little bit later, or I'll review that later, as I'm going through each individual study, but as far as why we included the very poor quality studies with a very small sample type, it was just to make sure that we are... it's a very small body of evidence. So, when we were able to go out into our

literature review, and we are able to sort of show everything that's available, that met the inclusion/exclusion criteria. So, we're just trying to show everything that was out there, but I won't get... I won't spend too much time during the presentation on those low-quality studies.

So, seven studies were selected for detailed analysis for key question number one. The overall quality of the body of evidence was low due to the few studies available on this technology, four of which were very poor quality non-randomized studies with small sample sizes. FDA approval for bronchial thermoplasty for severe asthma was based primarily on the results of the Castro 2010 study. This slide gives an overview of the direction of findings for each outcome measure, although some benefits of bronchial thermoplasty were observed compared to with control or sham treatment, results across outcome measures were inconsistent, and my subsequent slides will go more into this on a study by study basis. It's actually concentrating on those RCTs.

Asthma related quality of life was significantly improved in bronchial thermoplasty patients relative to control or sham treatment in two of the three RCTs that assessed that outcome measure. Severe asthma exacerbations were decreased in the thermoplasty group relative to control group in one of two RCTs that assessed that measure. Asthma symptoms were improved in the thermoplasty group relative to the control group in one of three RCTs. So, two RCTs did not show improvement. Forced expiratory volume in one second did not improve in the bronchial thermoplasty group compared with the control or sham treatment group in any of the three RCTs, and all of the three RCTs measured this outcome measure. Four studies did not include a control or comparison group, in which patients did not receive thermoplasty, and therefore no conclusions may be made.

So, Castro will be the first study that we go over. So, Castro 2010 was the highest quality study available and was the primary basis for FDA premarket approval of bronchial thermoplasty. Outcomes of the study were evaluated using Bayesian methods rather than traditional statistical tools. Thus, the term posterior probability of superiority or PPS rather than statistically significant will be used to describe the strength of the results. Bayesian methods used as a calculation of probabilities, and so did the hypothesis testing used in traditional statistics, and a Bayesian clinical trial uncertainty about a quantity of interest is described according to probabilities, which are updated as information is gathered from that trial. These updated distributions are called posterior distributions. Bayesian statistics can be controversial, because they require the use of a prior distribution for the treatment effect, and these may be subject to bias. Castro 2010 did not report the source of the distribution data used in the study or the use of multiple priors, so it is difficult to determine if these distributions used were appropriate.

Chris Standaert:

Wait. Wait.

- Nicole Slezak: However, it is important to note that the FDA did approve the use of Bayesian statistics.
- Chris Standaert: I just want to slow you down there, because you went very fast through that. So, my understanding of Bayesian statistics is, it's not, like you said, this isn't assuming a null hypothesis. This is more...
- Nicole Slezak: Yeah.
- Chris Standaert: ...traditional statistics, but Bayesian is sort of testing a theory, right? So, probability of that... the response... or it represents sort of a change from what you... aren't you supposed to have some baseline knowledge that you're testing a Bayesian model, yeah?
- Nicole Slezak: Mm-hmm, yes.
- Chris Standaert: But this is what, but...
- Nicole Slezak: And that comes from data from previous trials.
- Chris Standaert: ...so where, there, as far as I could see, I find this very curious they did that, because there isn't any baseline data available publically that gives them anything to test a hypothesis against. Is that... doesn't that strike you as odd in the way they structured the statistics here?
- Nicole Slezak: I'm not sure, because these are very complex calculations, and they are hard to interpret, especially if there is not... there wasn't...
- Chris Standaert: Just the choice of using Bayesian statistics in this model without a sizeable sort of database to draw from...
- Nicole Slezak: ...um...
- Chris Standaert: ...I mean it's your... your... this is, you know, your job, right, understanding statistics and the data. It's not a normal choice for studies like this typically...
- Natalie Slezak: ...um...
- Chris Standaert: ...a common choice.
- Natalie Slezak: ...well, I could say that this is the first clinical trial that I've come across that have used Bayesian statistics in my personal experience. So, I have to defer to the FDA and the FDA did approve the use of Bayesian statistics, and that's all I can say about it.
- Chris Standaert: OK.

- Joann Elmore: I found it problematic, as well, in that I've done Bayesian statistical modeling, and I advocate transparency. That's why our whole committee is transparent in our meetings, and if this paper had provided the underlying data that went into the modeling, we could evaluate its efficacy and accuracy of reporting, but this is a publication and it did not provide, at least... you need to advise us. I did not see what went into the black box Bayesian modeling. FDA may not have even asked for it.
- Natalie Slezak: They did not provide that information.
- Joann Elmore: I don't care about the FDA. I care about evaluating the evidence.
- Natalie Slezak: Right.
- Joann Elmore: And so that was the first concern I had. Bayesian modeling can be wonderful in many regards, but we need to know what went into it. So, to clarify, we do not know what went into the Bayesian modeling, it's not reported. Is that correct?
- Natalie Slezak: That's correct.
- Joann Elmore: OK. That's the first point.
- Natalie Slezak: It was not.
- Joann Elmore: The second point is that there are 14 secondary outcomes, three different time periods, I did not see an adjustment for multiple comparisons. Is that correct?
- Natalie Slezak: Um...
- Joann Elmore: They came up with a 0.95 posterior probability, but, I mean...
- Natalie Slezak: ...there was one for the primary...
- Joann Elmore: The primary, which, yeah, they had two primaries, which interestingly, was nonsignificant at six months but 'significant' at three and twelve.
- Natalie Slezak: ...the integrated score, right, that averaged across six, nine, and twelve months, but to clarify for their secondary outcomes, they did not adjust for multiple comparisons. Thank you.
- Joann Elmore: Correct. Mm-hmm.
- Chris Standaert: I had one question on severe. So, I guess you can qualify severe by symptoms but if you look at sort of FEV-1 percent predicted managing of severe is usually sort of less than 60 and this study, and the one by Cox excluded those patients.
- Natalie Slezak: Mm-hmm.

- Chris Standaert: So, it actually excluded the people who would seem to have a biologic measure of having severe asthma, but we're talking about treatment for severe asthma? Does that...
- Natalie Slezak: Yes.
- Chris Standaert: ...that bothers me a bit.
- Natalie Slezak: And in a later slide, slide 40, I will talk about that, about the different patient selection criteria across the different RCTs, but yes, that's a good point. OK?
- So, the primary outcome measure of the Castro 2010 study with the between group difference in the asthma quality of life questionnaire, integrated score average at six, nine, and twelve months. A meaningful improvement was defined as a posterior probability of superiority greater than 0.964, although scores were greater in the thermoplasty group than the sham group, this difference just missed the PPS plan of 0.964. The placebo effect in this study was larger than the study authors had anticipated. The mean change in AQLQ score was 1.16 in the placebo group compared with 1.35 in the control group.
- Kevin Walsh: For clarification, can you tell, what's the absolute possible score in an AQLQ? This is a relative value. I'd like to know what the absolute difference is.
- Natalie Slezak: I believe it's 4.
- Chris Standaert: I looked up the scale. Maybe our clinical expert can help us. I believe it's a seven-point scale, and there were 32 questions, and they are all scaled one to seven and they averaged them all. So, it's a one to seven scale is what it is and the scale has a minimally... when I looked at the paper on the scale, it said the minimally important difference is 0.5.
- Natalie Slezak: Mm-hmm.
- Chris Standaert: Dr. Markezich, if you can comment on that, perhaps, on this scale and the clinical relevance. Wait, before you... maybe you should introduce yourself and help us if there are any conflicts of interest or other things so people understand. This is the first question we've had for you.
- Amy Markezich: Sure. Sure. I'm Amy Markezich. I'm a pulmonary critical care physician at Overlake. I have no relevant conflict of interest other than I do perform this procedure on a clinical basis, but I receive no funding. Yes, the AQLQ is primarily a research technique that's used... or a research scale that's used. It is a seven-point scale and a 0.5 difference is considered to be clinically significant. It uses a number of... 32 overall questions to gage the severity and effect on quality of life on asthma.
- Kevin Walsh: So, this 0.2 difference, it's not significant, even though it's called an improvement?

Amy Markezich: That is correct. The change from baseline was not statistically significant, and it was a 0.19 change on average improvement. It was not statistically significant. They did not reach their intention to treat target of posterior probability of 0.964.

Gregory Brown: Is there a minimum clinically important difference in this scale?

Seth Schwartz: 0.5.

Gregory Brown: 0.5, OK.

Natalie Slezak: And so, as a secondary outcome measure, the study also analyzed the proportion of patients that achieved minimum clinically important difference of at least 0.5 on the AQLQ, 78.9% of thermoplasty patients achieved this difference compared with 64.3% of the sham patients, and this difference did reach the pre-specified success criterion.

Castro 2010 also found meaningful improvement in the thermoplasty group compared with the sham treatment group for these other secondary outcome measures, severe exacerbations, Emergency Room visits, and days lost from work, school, and other activities due to asthma; however, no meaningful improvements were found for these measures at one-year follow-up: Morning peak expiratory flow, total symptom scores, symptom-free days, rescue medication use, unscheduled physician visits and hospitalizations, and asthma control questionnaire scores (ACQ scores).

An additional year of uncontrolled follow-up for 166 thermoplasty group patients evaluated with traditional statistical tools show no statistically significant changes within this group from one to two years follow-up in severe exacerbations, asthma symptoms, Emergency Room visits, or hospitalizations. Uncontrolled follow-up of thermoplasty group was extended to five years in another study and found no significant increase or decrease in respiratory adverse events or need for hospitalization. An important limitation of these follow-up studies is the lack of follow-up in the sham treatment group.

So, Cox 2007 randomized patients with moderate or severe stable asthma to bronchial thermoplasty or control treatment. Control patients received continued asthma maintenance medication. All patients underwent attempted withdrawal from long acting beta agonist for two weeks at three, six, and twelve months. The primary outcome measure of the study was frequency of mild exacerbations during a two-week period of abstinence of LABA at one-year follow-up. Data on exacerbations were self-report data that were collected using daily diaries. Exacerbations were defined as either reduction in the morning peak expiratory flow of at least 20% below the average value baseline, need for at least three additional puffs of rescue medication, exceeding the average use during baseline, or nocturnal awakening caused by asthma symptoms. Improvement in exacerbations was significantly greater in the

thermoplasty group than in the control group. Statistically significant improvements were also observed with a secondary outcome measures of mild exacerbations with LABA and scores on the AQLQ, as well.

In addition, statistically significant improvements were also observed with the secondary outcome measures of the asthma control questionnaire, symptom-free days, symptom scores, rescue bronchodilator use, and morning peak expiratory flow. In contrast at one-year follow-up, no statistically significant improvements were found for severe exacerbations, airway responsiveness, or FEV-1.

Chris Standaert: Quick question on that study, too.

Natalie Slezak: Sure.

Chris Standaert: So, two things are curious to me. One, they repeatedly took people off of their medications for two weeks, every six weeks, three months they removed them.

Natalie Slezak: Mm-hmm.

Chris Standaert: But that was their primary treatment option for the control arm, yeah? And they just removed their medications for two weeks repeatedly through the study and they count exacerbations, and exacerbations are ascertained from daily diaries in which someone has actually recorded events.

Kevin Walsh: But they're set up for exacerbations.

Chris Standaert: There's a bit of a, you know, identification... all these issues of recall and identification and there's no... they're not monitored. They're just reading their diary. Anyway, so I just want to point that out. So, that's in the study design, which I found curious.

Natalie Slezak: Mm-hmm. A second report of this study extended follow-up to five years for 82% of thermoplasty patients and up to three years for 44% of controlled group patients. So, it was controlled follow-up for three years for at least a portion of the control patients and thermoplasty patients. At three-year follow-up, airway responsiveness significantly increased 1.3 doublings for the thermoplasty group versus a decrease of 0.4 doublings for the control group; however, at three-year follow-up, there were no significant differences between the thermoplasty group and the control group for some other outcome measures, other respiratory parameters, oral glucocorticoid use, worsening of asthma, Emergency Room visits, or hospitalizations. So, the only difference was with airway responsiveness.

Pavord 2007 randomized 32 patients who had severe asthma, two thermoplasty or maintenance medication control groups. The primary outcome measure of the study was occurrence of adverse events, which is discussed in the results for key question number two, safety. The study did not appear to be sufficiently

powered to detect between group differences for FEV outcomes. Compared with the control group at one-year follow-up, thermoplasty was associated with statistically significant improvements in several outcome measures, including the AQLQ, the asthma control questionnaire, and rescue bronchodilator use; however, there were certain measures that were not statistically significant, including forced expiratory volume in one second, morning or evening peak expiratory flow, symptom-free days or symptom scores, and airway responsiveness.

Uncontrolled follow-up of 14 thermoplasty group patients found that in years two to through five, respiratory adverse events, hospitalizations, Emergency Room visits, and asthma maintenance medication usage, and respiratory parameters were essentially unchanged compared with the first year after thermoplasty treatment. It is of note that outcomes during follow-up years two to five were collected only once per year and therefore may be subject to recall bias.

In addition, there were four very small, very poor quality, nonrandomized studies. Results from these studies were mostly positive. However, because they do not include control groups that did not receive thermoplasty, no conclusions may be drawn. Further details on these studies are available in the summary of findings table in the executive summary, as well as evidence tables in Appendix 4.

Three RCTs and one retrospective cohort study addressed further improvements in outcome measures where clinically meaningful. All four studies included the AQLQ and their assessment within subject change of 0.5 on the AQLQ is considered to be the minimum clinically important difference or MCID with higher scores indicating improved asthma-related quality of life. Two of three of these RCTs found that the between group differences in favor of thermoplasty met this MCID; however, the third study, Castro 2010, which this was its primary outcome measure, did not find that the between group differences met the MCID. However, when they looked at the proportion of patients in each group that did meet the MCID, they found that more thermoplasty patients than the sham patients met that criterion.

One very poor quality retrospective cohort study assessed clinically meaningful improvement in asthma related outcomes. Clinical improvement was defined as achieving at least one of the following, reduction by at least one severe exacerbation or hospital admission, improvement in the ACQ or AQLQ score by the MCID, or reduction in asthma medication. So, they compared data from some of their clinic patients, and they compared that to 15 patients that had been enrolled in the randomized control trials. They compared data between those two cohorts. So, there was no cohort that did not receive the bronchial thermoplasty. At one year follow-up, five at the time clinic patients, and 11 of 15 RCT patients met the criteria for clinical improvement.

In summary, the overall quality of evidence for clinically meaningful improvement is a very poor quality due to the very little data available.

Overall, the results for key question number two on safety suggests that the majority of events associated with bronchial thermoplasty occur during the treatment period and are transient in nature. So, the treatment period is all three sessions of the bronchial thermoplasty procedure plus six weeks following the last procedure. Three RCTs reported on the rate specific adverse events occurring during the bronchial thermoplasty treatment period. Thermoplasty was associated with statistically significant increase compared to the control or sham group in dyspnea, wheezing, chest discomfort, night awakenings, sputum discoloration, cough productive cough, bronchial irritation, and nasal congestion. Serious adverse events during the treatment phase included exacerbations requiring hospitalization, partial collapse of the left lower lobe, pleurisy, atelectasis, respiratory tract infections, and hemoptysis.

All seven of the analyzed studies reported on the rate of hospitalizations that occurred during the thermoplasty treatment period. The RCTs found that 0-4% of control patients compared with 5-27% of thermoplasty patients were hospitalized during the treatment period. Only one of the three RCTs found that the rate of hospitalization was significantly higher for the thermoplasty group than the control group, and that was the Pavord 2007 article, and that was only with the primary outcome measure of safety. The rate of hospitalizations in the thermoplasty patients among the nonrandomized studies range from 0-62.5%. In general, the rate of hospitalization appear to be higher in studies that enrolled patients with more severe asthma. The percentage of patients hospitalized ranged from 0-5.5% in studies that enrolled patients with mild and/or moderate asthma. It was 5-62.5% in studies that included patients only with severe asthma. The study with the highest rate of hospitalization of 62.5% was a very small case, a very poor quality case series that had a small sample size, and they enrolled patients with severe asthma with obstructed airflow. So, they had an FEV-1 less than 50%.

Chris Standaert: Quick question. You tell me one had statistical significance, but in the Castro study, they said 60... in the... they had a sham. So, in the active treatment group, 16 subjects required 19 hospitalizations acute versus three hospitalizations in two subjects in the sham arm. They don't give me a statistic, but that's... so they didn't do... either that's not significant or they didn't do the... give you statistics on that, because those are pretty high, 19 to 3?

Natalie Slezak: I'd have to check my evidence table before I would give you a definitive answer.

Chris Standaert: OK. Just curious.

Natalie Slezak: I can...

Gregory Brown: Can I ask you a different question? Did I just hear that you said in the last study you were talking about mild or moderate asthmatics were included?

Natalie Slezak: Yeah. So, that was...

Gregory Brown: So, the FDA, the FDA approved only for severe asthmatics. So, this study...

Kevin Walsh: This study is of moderate asthmatics.

Gregory Brown: ...so this is an off-label study? Is that correct?

Natalie Slezak: So, one of the RCTs enrolled patients with moderate or severe asthma, but there was one very poor quality case series that included mild or moderate asthma, and I'll throw up the slide in a few slides, like, showing the different classifications... or severity across studies.

Thomson 2011 extended follow-up to five years for 82% of thermoplasty group patients and at three years for 44% of control group patients that were enrolled in the Cox 2007 randomized control trial. This study found that there were no between group differences in worsening of asthma, hospitalizations, or Emergency Room visits. In addition, no serious adverse events due to thermoplasty occurred during the five-year follow-up. Uncontrolled follow-up of 14 thermoplasty patients that were enrolled in the Pavord 2007 RCT found that in years two to five, rates of respiratory adverse events, respiratory related hospitalizations, and Emergency Room visits were essentially unchanged. No serious adverse events due to thermoplasty occurred during the five-year follow-up period.

Uncontrolled follow-up of 85% of thermoplasty patients that were enrolled in the Castro 2010 RCT was extended to five years and found no significant increase or decrease in respiratory adverse events or need for hospitalizations. In addition, CT findings were unchanged, except for development of bronchiectasis in three patients.

The literature search found no studies that were specifically designed to assess differential effects of bronchial thermoplasty. The analyzed studies varied considerably in the patient selection criteria, which I'll get more into in the next couple of slides, which may have had an impact on study outcomes. In addition, several studies conducted post-hoc analyses investigating characteristics or prognostic factors that may have affected study outcomes. These data were of very poor quality. Therefore, all findings should be considered preliminary in nature.

So, this slide shows that the inclusion and exclusion criteria varied across all the randomized controlled trials. Of note, not all studies enrolled only patients with severe asthma, for which the bronchial thermoplasty device is FDA approved. Two RCTs enrolled patients with severe asthma and one RCT, the Cox 2007 study, enrolled patients with moderate or severe asthma. All three studies required different minimal dosages of daily inhaled corticosteroids and other medication requirements, and the acceptable FEV-1 varied across studies. The

actual mean forced expiratory volume among the thermoplasty patients ranged from 63% in the Pavord study to 78% in the Castro study. So, that would be actual mean.

Inclusion and exclusion criteria also varied across the four nonrandomized studies. So, these were all very poor quality studies. Three studies enrolled patients with severe asthma, and the earliest case series, Cox 2006, enrolled patients with mild to moderate asthma. Medication requirements varied across studies, and the actual mean forced expiratory volume in one second ranged from 52% in the Doeing study to 82% in the Cox study.

Several studies conducted post-hoc analysis comparing prognostic factors that may have affected clinical outcome. One RCT found that patients that required high daily doses of beclomethasone exhibited greater improvement in respiratory parameters and scores on the asthma control questionnaire. Another RCT found that patients with less favorable AQLQ scores at baseline were more likely to improve to clinically indicated degree following thermoplasty, and a follow-up study found that patients that met the minimum clinically important difference for the AQLQ had fewer asthma related adverse events and healthcare utilization during long-term follow-up of two to five years.

Four studies were found that compared the cost of the usual care with bronchial thermoplasty or assessed the cost-effectiveness of bronchial thermoplasty. One of these studies, Menzella 2014, was conducted in Italy, and the other three studies were conducted in the United States. Two of these studies were either conducted by employees of Boston Scientific or received financial support from the device manufacturer, and authors of a third study received grants or other monies from various pharmaceutical companies. One study did not report a funding source; however, Castro was an author on that study. All studies used data imputed from multiple sources; however, for efficacy and safety outcomes of bronchial thermoplasty, all studies used clinical data from Castro 2010. In these studies, although bronchial thermoplasty was found to increase costs in the short term, it was found to increase cost savings or quality adjusted life years (QALY) in the longer term.

Menzella 2014 performed a budget impact analysis to project the cost of a hypothetical cohort of adult patients with severe asthma in an Italian Regional Health System. Although thermoplasty added approximately 24,000 per patient for standard care during the first year, thermoplasty would produce net savings of approximately 1 million for the entire regional healthcare system during year three, and 23 million after year five as a result of reduced healthcare utilization. This study did have several limitations. The imputed data were derived from multiple sources, including an expert clinician's panel in Italy, available clinical data, and data from the published literature. Although several data points were based on data from Castro 2010, the hypothetical bronchial thermoplasty patients that were used in the Menzella study had a forced expiratory volume

less than 60% whereas in the Castro study, they included patients with a forced expiratory volume of at least 60%.

Chris Standaert: Those patients were excluded from the Castro study. They used data from the Castro study and applied it to patients who were actually excluded from that study to calculate their response.

Natalie Slezak: Yes. Mm-hmm.

Chris Standaert: OK.

Natalie Slezak: And, and so in addition to that, this was conducted in Italy, so it may not be applicable to settings in the United States.

Three studies estimated the cost-effectiveness of thermoplasty from a payer perspective. Cangelosi 2015 conducted a cost-effectiveness analysis of thermoplasty in poorly controlled severe asthma patients that required high-dose combination therapy and had been admitted to the Emergency Room at least once in the past year. Thermoplasty increased quality adjusted life expectancy by approximately 0.18 QALY compared with high dose combination treatment in severe persistent asthma patients, driven primarily by the decrease in exacerbations. These findings resulted in an incremental cost-effectiveness ratio, or ICER, of about 5700/QALY at five years. Study limitations included that the imputed data were derived from multiple sources, including the treatment database, red book, and data from the published literature. Although several data points were based on data from Castro 2010, the Castro study did not separate data by those patients who required an Emergency Room visit in the last year. So, it might have been a different population, as well.

A second study found similar results.

Gregory Brown: I'm sorry. Can you, were the QALYs calculated with EQ5D or SF6D or do you, by chance, remember?

Natalie Slezak: I would have to check to make sure.

Gregory Brown: OK.

Natalie Slezak: But I think so, but I would have to check.

Gregory Brown: Very good.

Natalie Slezak: I have my papers over there.

Gregory Brown: OK, fair enough.

Natalie Slezak: And a third study compared bronchial thermoplasty with usual care and omalizumab in moderate to severe allergic asthma patients and found that

bronchial thermoplasty increased QALYs by 1.6 versus usual care and was very similar to what was found for omalizumab. In a lifetime analysis, the ICER thermoplasty compared with usual care was approximately 13,000 per QALY. Omalizumab compared with bronchial thermoplasty was approximately 3.2 million per QALY, and omalizumab compared with usual care was 548,000 per QALY. Study limitations included the imputed data were derived from multiple sources and although this study was focused on allergic asthma patients, no clinical studies had been conducted examining thermoplasty exclusively in this patient population.

As mentioned earlier in a previous presentation, no CMS national coverage determination was identified. Several payer coverage databases were searched for mention of bronchial thermoplasty. AETNA and Regence group consider bronchial thermoplasty to be experimental and investigational for the treatment of asthma and Group Health states that the use of bronchial thermoplasty does not meet the Group Health medical technology assessment criteria.

Four guidelines were found that mentioned the use of bronchial thermoplasty for asthma. The British Thoracic Society states that thermoplasty is a possible treatment option in select patients with severe asthma already on maximal treatment. However, you should be limited to a few specialist treatment centers. A taskforce supported by the European Respiratory Society and American Thoracic Society states that the available evidence on bronchial thermoplasty is considered to be of very low quality, and they strongly recommend that thermoplasty be performed only in patients with severe asthma and only in the context of the clinical trial or a systemic registry. The global initiative for asthma states that bronchial thermoplasty is a possible treatment option in select patients with uncontrolled asthma that have been referred to an asthma specialty center. The long term safety and efficacy of thermoplasty are unknown, and carefully controlled trials are important as a large placebo effect has been seen in current studies. The National Institute for Health and Clinical Excellence Guidelines states that for patients with severe asthma, thermoplasty has been shown to provide some improvements in symptoms in quality of life and reduction in exacerbations and hospitalizations. More evidence on long term safety is needed and therefore, thermoplasty should only be applied in the context of clinical trials or registries.

In general, the evidence for bronchial thermoplasty for treating asthma was mostly positive and suggests that bronchial thermoplasty may provide some benefit in improving asthma related quality of life and asthma symptoms in the short term. However, there were some inconsistencies across studies for outcome measures. In addition two of the three RCTs, demonstrated that asthma related quality of life improved to an extent that was clinically meaningful, relative to the control group. However, the body of evidence is of low quality due to the small number of studies available on this technology, small sample sizes in most studies, varied patient selection criteria across studies, and insufficient evidence concerning the long-term efficacy of bronchial

thermoplasty. Current evidence suggests that bronchial thermoplasty does not pose major safety concerns in the short term. The majority of complications are mild or moderate in severity and occur during the treatment period. The most prevalent complications reported in the studies were dyspnea, wheezing, chest discomfort, and cough. However, some serious adverse events have been reported. The body of evidence for safety is of low quality due to the small quantity of data available and insufficient evidence on the long term safety of bronchial thermoplasty.

Patient selection criteria varied considerably between studies and RCTs were selected in the patients that were enrolled in each study. All three RCTs also used different primary outcome measures and protocols, which likely contributed to the inconsistency in findings across outcomes. Although bronchial thermoplasty is indicated in patients with severe asthma, one RCT was found that included patients with moderate or severe asthma. Therefore, we did not limit our inclusion criteria just to severe patients. Because the body of literature concerning bronchial thermoplasty for asthma was small, it is difficult to determine whether efficacy or safety of thermoplasty varied by baseline, variable such as asthma severity, medication use, pulmonary function, or other characteristics. More data on differential effects of baseline characteristics are needed to better identify patients that may gain the most benefit from bronchial thermoplasty. The literature search identified three cost-effectiveness assessments for bronchial thermoplasty for asthma from a payer perspective. In these studies, although bronchial thermoplasty increased costs in the short term, it is found to increase quality adjusted life years in the longer term; however, these studies did have several limitations.

Further research, especially randomized control trials and long term cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of bronchial thermoplasty in patients with severe asthma. Additional studies designed to systematically investigate differential effectiveness and safety according to patient characteristics and previous treatment histories are also needed, as are additional studies investigating the impact of bronchial thermoplasty in quality of life and functional status. So, thank you. I'll be available for questions when I have all my articles in front of me and can answer those questions.

Chris Standaert: Stay there for one second. Stay for one second. Does anybody else have questions for Dr. Slezak now? We certainly will have a chance to ask a question as we go through. Yes, Dr. Elmore.

Joann Elmore: I'd like you to go back three slides to your first summary. No, not that many, just your first summary, final summary slide.

Natalie Slezak: Summary slide, OK.

Joann Elmore: OK. I want to follow up on these two bullets, and let me choose the easiest one at the bottom. You say current evidence suggests that it does not pose major

safety concerns in the short term. However, I feel that perhaps, uh, during the break, I'd like for you to look up the Castro article, because they had 8.4% hospitalized versus 2%.

Natalie Slezak: Mm-hmm.

Joann Elmore: And to me, when a patient has hemoptysis requiring hospitalization with embolization, that is a concern, and I want us to first do no harm. So, I would ask you to look into that at the break, because I'm not certain I agree with that statement, that bullet. That's the first point. So, perhaps after you've reviewed your materials you can come back. Then, for the first bullet, a question and a comment. I guess let me reiterate your definition of low quality evidence, and this is mostly for, I think, the overall audience, as well.

Natalie Slezak: Mm-hmm.

Joann Elmore: Low quality evidence shows that you have little confidence due to poor quality studies and your low quality evidence shows that you think that future studies are likely to change the estimates and possibly the direction.

Natalie Slezak: Mm-hmm.

Joann Elmore: Alright. So, given that, I also heard you use words describing the quality of the studies, good and fair.

Natalie Slezak: Mm-hmm.

Joann Elmore: And I did not see a definition of that taxonomy, and I question how a study can be labeled as good quality, only one of them was good. The rest were fair, how it can be labeled as good when you do not have access to the statistical methods used to come up with the results. Sure, it's published. Sure, the FDA may have approved it, but what went into the Bayesian modeling? If we don't have that, how can we call that a good study?

Natalie Slezak: Well, we start... so randomized control trials start with a rating of good.

Joann Elmore: Mm-hmm.

Natalie Slezak: And since we couldn't say that those statistics were inappropriate, we don't have any evidence of that, we cannot downgrade based upon that, and so that's why we did not downgrade based upon that.

David McCulloch: With respect, you absolutely can downgrade it. Absolutely. I mean, you cannot constantly say it's a good well-designed study, so.

Chris Standaert: I'm going to echo the other point about the safety issue that, you know, if you look at these studies, Pavord... they only studied 30-something patients. So, 15

of the thermoplasty subjects, there were seven hospitalizations immediately, and there were zero when they are controlled.

Natalie Slezak: Mm-hmm.

Chris Standaert: And the Cox study during the immediate post-treatment period, there were 407 adverse events in the thermoplasty group and 106 in the controls. I mean, to say that's not a concern, I'm not, I agree, I'm not totally sure I agree with the language. So, you can, that's not what you think when you look at it.

Natalie Slezak: OK.

Gregory Brown: Can we go to slide 43?

Natalie Slezak: I can't see the slide number from here. Is that?

Gregory Brown: No. So, this is on the cost implications and you said there were four studies.

Natalie Slezak: Mm-hmm.

Gregory Brown: Um, two studies were supported by Boston Scientific. One study was in Italy but funding from pharmaceutical companies, and one study did not report but used Castro data and so if I understand your summary, Castro was industry funded, correct?

Natalie Slezak: Mm-hmm.

Gregory Brown: So, all four of the studies were industry funded. Is that a correct conclusion?

Natalie Slezak: Yes. Thank you.

Gregory Brown: OK. Thank you.

Chris Standaert: Any other questions at the moment? You'll have a chance to ask more questions, as we go through our discussion later. No? OK. Thank you. Alright. So, we are ten minutes out. We're going to take a break, and we'll just go back down the schedule and start back up at 10:20. OK? Thank you.

It is 10:20. If the committee could take their seats, we will resume. So, the next section we have here is the committee question/answer section where the committee discusses their data and then we will work through the decision process.

So, people are familiar with our intent, when we get to our decision, our committee is charged with finding the best outcomes and value for the state and the patient, and we focus on question, three questions: Is it safe, is it effective, and does it provide value and improve health outcome? Alright. So, we can start either with questions that people have come up with over their 20

minutes, as they process this, and they want to ask one of those... they want to ask our evidence vendor or our clinical expert. Or, we can go through general comments. Does somebody have an additional question they've been pondering, a question they didn't find answered well enough before? Tony, would you like to help orient us as to how we can think about this a bit. I know Mike has a question.

Michael Souter: I have a question for the clinical expert. When I'm thinking about the question that's been used to construct the minimal observable difference, the minimally clinically significant difference that has been... a lot of emphasis has been placed on that. How often in this field of asthma treatment is this used as a comparator between patient groups, because, you know, when you use these skills it's common to employ them to demonstrate changes within a patient. How confident are we that this is actually a reasonably... I've been talking to an empty chair.

Chris Standaert: Now that you're all warmed up. OK. She's here now. You can actually ask her. So, Dr. Souter has a question for you.

Michael Souter: I have a question for you.

Chris Standaert: Everybody else knows it. So, we'll wait to see how you think.

Michael Souter: I have a question about the use of the AQLQ score and just as to how often that is used as a discriminatory of efficacy between different asthma treatments and just to help me understand that field, because this is obviously not my own field. The... when using clinical scales like this, and I am stunned the AQLQ is one of these that was originally designed to measure improvements within a patient's care. So, as to demonstrate improvement or worsening one way or another, but how often is it actually used to measure improvement or effect comparisons across treatment groups?

Amy Markezich: So, if I understand correctly, your question is not just within the patient, as far as the patient's change but differences between, let's say a treatment group and a control group.

Michael Souter: Just in the way that was affected. Say, for example, in many of the studies are being referred to the AQLQ, using that kind of minimum difference of 0.5.

Amy Markezich: Right.

Michael Souter: But, you know, what I'm just trying to understand is that if a frequently employed device, when looking at the treatment of asthma, do people commonly use that type of scale?

Amy Markezich: It's a, yeah. As I said, it is primarily a research tool, just because it is a large number of questions. I think the difficulty comparing it between treatment groups is that it's all self-reported assessments of patients' quality of life, or

areas of their life that are effected, or symptoms management. So, it is more... considered to be more useful to look at a change in the AQLQ score from, you know, the same patient over a long period of time. It is, as far as the utility of it, it's generally considered useful because as had been mentioned before, the FEV-1 and other measures of lung function are not really a good indicator of asthma control and asthma severity, just because asthma is such a... is more of an inflammatory disease. You can have an FEV-1 of 90% and still have very severe symptoms. So, it is one of the most common tools that is used in research studies along with asthma exacerbation rates, as well as use of short-acting bronchodilator therapy. In the clinical practice, it's not used as often, just because it is a cumbersome tool. It's a lot of questions for patients to answer. So, generally, in clinical practice we use some of the more easier tools or more quick tools in order to assess patients' asthma control. I don't know if that answers your question.

Michael Souter: If I'm understanding you correctly, it's not unusual, then, to see... we would see a research study comparing two treatments for asthma and for them to use the AQLQ.

Amy Markezich: Exactly.

Michael Souter: OK. Alright. That's fine. That answers my question.

Chris Standaert: Carson?

Carson Odegard: Yes, I have a question for Dr. Amy. When... it's a procedural question, just to kind of clear my mind as far as the procedure is concerned. When you go in with the scope and... are there four sites of treatment that are done each time for the three treatments? Are there four sites of treatment? Or do you pick other sites for the second treatment, and... to try to get a...

Amy Markezich: Mm-hmm.

Carson Odegard: ...is it done ... is it all done in the same area?

Amy Markezich: Good question. We... so on each specific treatment, we will focus on a certain lobe of the lung. So, and I'll just pick for the sake of argument... and the first treatment is generally the right lower lobe. So, we go in, and we usually try to go in with the smallest bronchoscope that's available so that we get into the smallest airways, and we basically will treat every airway and every bronchus that is visible to us within that lobe. So, the number of activations is highly variable, because everyone is different, as far as how many branches and how much you can actually see, but once you treat that lobe, you don't go back there to retreat. So, that lobe is done. Then, the next procedure is focused on the left lower lobe.

Carson Odegard: OK. Thank you. And one more question. What is the typical recovery time of the soft tissue of the smooth muscle over a period of time, because I'm trying to

compare control groups against treatment groups, and so what's the natural history of recovery of the tissue itself?

Amy Markezich: In general, what we find is that... we give high-dose steroids immediately after the procedure for a few days after the procedure, and that's just to help to prevent asthma exacerbation. In general, it's felt to be about six weeks for recovery for that tissue, and I think that that's why it was chosen, as far as the treatment period to be within the six-week period. We reinspect patient's airways after... so, on the second and third procedure, we will reinspect the previously-treated airways. We do the procedure. It has to be done at least six weeks after... there has to be at least a six-week period where you don't treat the patient, and when we reinspect those airways, they generally look pretty good. They don't look erythematous. They don't appear to have any visible damage. We don't biopsy, because we don't do this procedure as part of a research study.

Carson Odegard: So, does the tissue come back at a certain point in time where it's got muscular strength that was the original strength, or does the procedure last long enough to where the tissue is holding that treatment?

Amy Markezich: Well, I know that on... other studies have looked at where they biopsy airways after this procedure, and there is less bronchial wall smooth muscle that is seen on biopsies after these procedures. So, it does appear that it is less, but as far as biopsy-proven less smooth muscle tissue, visibly, it's very difficult to see. I do know that just in my practice, you know, I do have some patients that I've treated who are extremely hyper-reactive. You touch the wall of their airway, and they immediately constrict, and when we reinspect those airways two months later, they're not doing that same reaction. So, it's... that's the only visible sign that we have on gross inspection.

Carson Odegard: Alright. Thank you.

Chris Standaert: Have you personally done that two years or five years or seven years later?

Amy Markezich: No. We will only do a bronchoscopy if we have a clinical reason to do it. So, I have not had any patients that I have had to repeat a bronchoscopy a year or two later.

Chris Standaert: OK.

David McCulloch: Please clarify, either to the clinical expert or the evidence vendor, in the few studies we have that were randomized control clinical trials, I don't know how many of them actually did a sham bronchoscopy for the same amount of time... one yeah? Did those patients also get high-dose steroid after the sham procedure in the clinical trial?

Amy Markezich: I don't know if you want me to answer the question or?

- David McCulloch: Sure.
- Amy Markezich: I know that on the AIR-2 study, which was the procedure versus the sham procedure, everyone received the same amount of steroid treatment, both as a... for the preprocedure, as well as immediately after the procedure.
- David McCulloch: OK. Thanks.
- Tony Yen: I have a hard time interpreting this literature, because it seems like, at least from the quantitative data that we have over here, that the FEV-1 is not what we would consider clinically as severe asthma. Am I correct about that, because like for example, I think that the Castro study, as well as the Cox study, which were the larger... had the larger amount of patients, the FEV-1 is over 60% and I don't know if in true clinical practice that's what you would follow to say this is a person that would benefit from this type of therapy, or do you quantify the severity of asthma before you actually proceed to doing this type of therapy?
- Amy Markezich: So, when I'm looking at asthma severity, FEV-1 is a consideration, but it's not the primary consideration in looking at how severe someone's asthma is. We do use that to help to figure out how severe or how much medication the patient needs to be treated with initially. Usually, when I see patients as a first consultation, they've already been seen by other pulmonologists or other asthma allergists, and they're already on, usually, high-dose inhaled steroids, as well as multiple other medications, and a lot of times the FEV-1 can't be used, because a lot of these medications can increase the FEV-1. So, what we look at is how many medications are these patients on, or how many medications are these patients requiring, as well as where they are along on the step therapy, as well as how symptomatic they are. So, if they still are uncontrolled, and they have already had maximum medical therapy, or they're receiving multiple medications, that would put them in the severe category, regardless of what their FEV-1 is. Now, the one time I do take into account FEV-1 is if it's too low, and there's a concern about safety of the procedure. So, there are variations among clinicians as to what their low FEV-1 cutoff is. In general, most clinicians would feel that less than 30% would be too low, 40% has also been used as a cutoff, as well as 50%, but most general cutoffs in clinical practice have actually been less than the 60% that was in the Castro study.
- Chris Standaert: I mean, in the Castro study, I mean, the average FEV-1 predicted is, like, 78, 79. I mean, it's not anywhere near the numbers you're talking about, and that didn't change much at all, and certainly not significantly. It didn't change.
- Gregory Brown: Moderate.
- Chris Standaert: Castro had... didn't... he called them severe based on symptoms, I think, yeah? They did?
- Kevin Walsh: Medication.

- Chris Standaert: Medication?
- Kevin Walsh: AQLQ score.
- Chris Standaert: Yeah, four weeks before entry, AQLQ score 6.25 or lower where 7 is like a normal... 7 is, like, the best. So, 6.25 would not exactly seem to be severe on the AQLQ.
- Tony Yen: That's why I'm left with some discomfort over here. It seems like bronchial thermoplasty is actually probably most effective in people with severe asthma, but yet the literature that we have ahead of us, I seem to feel that it's not... we are not dealing with truly severe asthmatics, or am I, I don't know. I'm welcome to any other interpretation of the literature over here.
- Chris Standaert: I have the same feeling. I'm struggling for the idea that it's effective in severe asthma, because I'm not sure that's studied in the data we have.
- Tony Yen: So, we don't have any subset data from there, at least that's presented to us right now.
- Natalie Slezak: I can say that the Castro study, 86% of the thermoplasty patients and 88% of the sham control patients met ATS criteria for severe refractory asthma.
- Seth Schwartz: Can you comment... this is for our research people. Can you comment on the medication adherence in the two groups in the Castro study, or in any of those three randomized trials whether there was any questions about medication adherence or whether they... or how they fact that?
- Natalie Slezak: They didn't discuss adherence to medications.
- Gregory Brown: Presumably... it does say everybody continued with the same treatment of corticosteroids and long acting Beta-2 agonists. So, that's the point of the randomization so that the compliance is equally randomized in both arms, so.
- Seth Schwartz: What I'm struggling with here is the effectiveness versus efficacy issue, which is that if we have a, you know, an abnormal environment where people have a higher propensity to be compliant with their medication use versus what happens in the real world, then an intervention that doesn't necessarily require that is going to look less effective in this situation than it would in real life. So, I'm just trying to get a better understanding of how well this... what's happening here mirrors what is really happening with these patients in real life.
- Gregory Brown: That's the issue with every randomized control trial is that people that sign up for a randomized control trial are different than the rest of the population.
- Seth Schwartz: No. I understand that, but I'm trying to understand the scope of that problem in this scenario, because what we heard was data that it sounds like maybe compliance in the real world is 20 to 30% and in this group it's 100% and that's...

then that's really off. We've also heard patient testimony that in the group of severe asthmatics that compliance is much higher than that. So, I guess the question is, do we have any information to bridge that discrepancy. Maybe I would ask our clinical expert if you have any concept of what the medication adherence rates are typically like in the severe asthmatics.

Amy Markezich: Generally, for the patients, and I'll just say when I'm considering a patient, trying to assess a patient and their asthma severity and what other treatment options are available to them, one of the first things I do is make sure they are compliant with the medications. There is a lot of confusion among patients in the real world, as far as what medications are considered the long-acting controller medications, what medications should be using as as-needed, and I spend the majority of my time working with... on education with the patients. That said, even with that, I probably would say that the noncompliance rate is maybe... is definitely less than, and I don't have... I should say I don't have any data to back this up, just in my experience, it definitely seems less than what is reported, as far as the 30%. It may be more around the 10, more around 10%, and that may be related more to just general confusion over when medications should be taken.

Seth Schwartz: So, just to be clear, you're thinking that 10% of the patients are noncompliant, and 90% are compliant?

Amy Markezich: If you were to put me on a... if you were to push me on a number, yes.

Seth Schwartz: I totally understand that you're... you're winging it. I'm saying because the...

Amy Markezich: This is not based on data whatsoever.

Seth Schwartz: ...I get it, but the pharmacy data is the reverse. The pharmacist data would suggest only 30% of people are compliant and 70% are not.

Kevin Walsh: No. I thought the pharmacy data said 20% of people weren't filling the prescriptions.

Seth Schwartz: Maybe someone can fill in what that data was. I thought it was... I thought it was only 30% were filling... were filling their ...

Kevin Walsh: Weren't... were not.

Amy Markezich: And I think where the issue is, is that we have, unlike other diseases where there's pills that patients take and they can put them all in pill containers. We have multiple inhalers. Most of my patients who are very severe are on, you know, even three or four long-acting inhalers, as well as one short-acting inhaler, and it's difficult for a lot of patients to keep track of.

Seth Schwartz: Yeah, slide 14.

- Gregory Brown: 20% did not fill their initial prescription.
- Seth Schwartz: Right, but then the next one is mean proportion for days covered in 12 months, and then it says for the leukotrienes only 30% were actually covered, meaning they had medication to be... is the way I interpret that. They only medication to cover themselves for 30% of days for the ICS and the LTRAs combination, only 25% had it. Maybe I'm not interpreting this correctly, but that would be helpful. Does that make sense?
- Natalie Slezak: I assume that's in all different types of asthmatics from mild to severe.
- Seth Schwartz: That's probably true, and that's why I'm trying to get the difference between what this means versus what's actually happening and so I know we're kind of winging it. I'm just trying to get a better understanding of what we're actually talking about.
- Gregory Brown: I guess the other thing that my perception is, is that if you have severe asthma, you're much more likely to be compliant just to function, whereas if it's mild then you can kind of wing it and I'll use a p.r.n. inhaler when I need it.
- Seth Schwartz: That may be true, but if you're on ten medications, it may be harder to follow through.
- David McCulloch: Maybe the reason you've got severe asthma is because you're noncompliant with taking the medications. That is certainly true in the field of diabetes.
- Louise Kaplan: There are also so many variables related to if somebody has underlying allergies and their allergies are worse at certain times of the year, and then their asthma is worse at certain times of the year. So, they're going to say well I don't really need my medication in the winter. I really need it in the summer, or vice versa, and some people will say, oh, I only use the inhaled steroid during these months because otherwise, I don't even use my albuterol. So, there's so much variability with medication use. I don't think we can just say that one study really reflects the wide variety.
- Chris Standaert: Questions or comments? People think about the cost data. You had some questions about that. It's tricky, yeah.
- Gregory Brown: Four studies all funded by industry.
- Chris Standaert: And, you know, using data on the wrong patients. So, applying data on mild to moderate asthma to severe asthma. Switching it around is problematic.
- David McCulloch: It's uninterpretable.
- Chris Standaert: It's uninterpretable.
- David McCulloch: Yeah.

- Chris Standaert: And the cost numbers are curious, too.
- Seth Schwartz: I'm struggling with this, too, because I'm trying to think of what the cost drivers are for the nonsurgical arms of these... or the noninterventional arms of these patients, and it seems like the biggest costs are going to be hospitalizations and Emergency Room visits. I think the one piece of data that we've seen, which is pretty consistently decreased in the thermoplasty group is Emergency Room visits for exacerbations. That is more statistically significant in several of the RCTs. So, I don't know what that means, but that was striking to me, as far as thinking about the cost differences. We didn't see, necessarily, a dramatic decrease in medication use, but if they're using the Emergency Room less, that might be a cost driver.
- Chris Standaert: So, hospitalizations weren't decreased, which I found odd. It looks like they're not... and, you know, in the Castro study, they said they had...
- Joann Elmore: Long-term hospitalization. It's not acute.
- Chris Standaert: ...five people got hospitalized six times. In the control group, they had four people hospitalized twelve times, but the control group was compounded by one person that got hospitalized nine times. You take that person out, it's, you know, these rates are low, but they're not... it didn't seem to lessen the rate of people winding up in the hospital.
- Kevin Walsh: I think that's, it seems like there's a difference between hospitalization versus Emergency Room visits.
- Chris Standaert: Yeah, there is, yeah.
- Kevin Walsh: And I guess I don't know what happens in reality, how common is it. I mean, we can ask our clinical expert this. How common is it for someone with an exacerbation to be treated in the Emergency Room and discharged versus admitted for severe asthmatics?
- Amy Markezich: Extremely common. I know at my institution, patients will arrive in the Emergency Room. They get treated an IV dose of steroids, get a nebulizer, sometimes an antibiotic, and then I'll see them the next day or two days later, or they establish with our clinic. Many times they do not get hospitalized.
- Chris Standaert: OK. So, this says 8.4% of the treatment group was hospitalized and 15% of the sham. I think this is after, but I don't think that counts the hospitalizations from the procedure. This is during the post-treatment phase, and that met their statistics, but like Joann said, they didn't do a multiple outcome correction essentially, some sort of Bonferroni-like correction.
- Louise Kaplan: I'm wondering if either our clinical expert or Dr. Fotinos could answer a question about trends over time. So, we have a very small number of people in this state

who have had this procedure paid for by the state and Dr. Fotinos, your first slide is giving us background information about the number of people who are hospitalized each year and those that die in Washington, and I'm just wondering, state-wide and maybe sort of nationally, that seems to me to have been a downward trend over time with better asthma care. So, it... I'm just wondering if you can confirm any numbers that might indicate, you know, substantively different outcomes and what triggered this question is, many years ago the state initiated a disease management program that included asthma and the cost numbers were equivocal, but there was some trending but nothing statistically significant in terms of improvement. There was trending, but I'm just wondering what the trends or significant differences have been in terms of hospitalization and deaths from asthma.

Charissa Fotinos: In terms, I mean, looking at the Washington State data, there has been a slight increase in asthma incidence. In terms of hospitalization, I... if you can give me a couple minutes, I can pull that up. I'm just looking at 2012 data. Some of this I got... it's not yet published, but I know I got it from the DOH folks, because they haven't had the staff to publish last year's, but I can get you that. In reference to... Josh pulled me in to comment specifically on the study that looked at compliance. This was a Harvard study that took patients from Kaiser, Harvard, Pilgrim, and a number of... let me find them, a number of other insured companies and just, again, tracked their prescription fills over time. They found that folks who were non-white had slightly less high rates of compliance. They don't speak to... they mention Charleston scores at baseline... Charleston scores, excuse me, at baseline, but otherwise, they don't speak specifically to the severity. They do talk about baseline number of hospitalizations, which is about 4 to 10%. Patients with combined LABA/ICS requiring the most, and then Emergency Room visits were about 12% across each of those groups. So, at baseline, reasonably consistent in their presentation, but I can't pull out that subset of folks who are most severe to know if they're compliance is different. It makes some intuitive sense but it doesn't speak to that, and I will look at the trend for you right now, because I can just, I need to get back to it.

Kevin Walsh: Seth, can you show me... you're saying that you think that there's an improvement in Emergency Room visits after thermoplasty compared to the control group. Can you show me which study you got that from, because I'm looking at several studies that don't seem to.

Seth Schwartz: Well, Castro study slide number 25 said Emergency Room visits were 0.07 versus 0.43 per patient annually. So, that's like a... what is that a five, six times decrease.

Chris Standaert: It says 0.13 versus 0.45 for whatever that's worth, 8.4% of subjects versus 15.3% of subjects.

Seth Schwartz: Subjects per patient annually. I'm not sure how they calculate it. I don't know. I'm just going by the slide here.

- Chris Standaert: Emergency Room visits for respiratory symptoms per subject in the BT group was 0.13. The number of Emergency Room visits per subject was 1/10, 0.13, 1/6, and in the same group was 0.45. So, it's still a low percentage going to the Emergency Room, 0.13 per subject. I see that. I just see this whole list of things. So, on... in the Castro, they have this whole table of scores and nothing changes, AQLQ, symptoms, activity, emotional, environmental, change from baseline, FEV-1 percent predicted, FEV-1 post bronchodilator, total symptom score, percent symptom-free days, rescue medications, and percent days rescue medication used. No difference whatsoever. Like, all of those are the same.
- Kevin Walsh: In Thompson...
- Chris Standaert: It was a huge number of what seemed like fairly good outcomes all total, I mean, not even... like, totally unchanged.
- Kevin Walsh: ...(inaudible) study used the Cox data and they're reporting Emergency Room visits at one, two, three, four, five years out. In year one, 4% of the thermoplasty group had Emergency Room visits, 0% of the control groups. By five years or by three years, it was 5%, 5%. I'm, I see the Cox data but when you look at other studies that are looking at other data, it's not consistent. It's not there.
- Chris Standaert: Right. People, are we ready to move onto our tool? Yeah? I think people had a fairly... it seems like we talked about all the different aspects of our data. We've covered safety concerns and efficacy concerns. Did you want to ask for her use of that language on that slide that there was no...
- Carson Odegard: I just have one question to our vendor, or anybody that's read this in the Castro article. Why did they... they do this extension arm follow-up, and we do see significant improvement in hospital visits and severe exacerbations from a year before and then to the end of... all the way through to five years, but in slide 26, it says that there is no significant increases or decreases from one to two years, and they never list. It just says no meaningful differences seen from one to two years, but yet from two to five years, or at the end of the fifth year, there is a significant drop. So, I was just wondering why that wasn't, why that one to two-year follow-up wasn't recorded, or why the data isn't there, or they just noticed that it was insignificant. Do you know?
- Natalie Slezak: Sorry. Can you repeat that? You're asking from year one to year five?
- Carson Odegard: Yeah, the two-year follow-up.
- Natalie Slezak: To two-year follow-up?
- Carson Odegard: Just on severe exacerbation and...
- Natalie Slezak: The Castro 2011 is one year, from one to two years follow-up.

Carson Odegard: So, they're saying there was no increases or decreases from the one-year follow-up data. From the data that they found after one year.

Natalie Slezak: Right.

Carson Odegard: So, at the two-year, there was nothing.

Natalie Slezak: Right.

Carson Odegard: Nothing?

Natalie Slezak: Yes. And then...

Carson Odegard: OK, but then at the five-year extension... on this extension study...

Natalie Slezak: ...mm-hmm.

Carson Odegard: ...they see a significant drop.

Natalie Slezak: There were no significant increases or decreases in respiratory adverse events or need for hospitalization.

Carson Odegard: So, then how would they go from 52% severe exacerbations 12 months before to the fifth year at 22, instead of 22%?

Natalie Slezak: Are you looking at the Castro study?

Carson Odegard: I'm looking at the uncontrolled 86%.

Natalie Slezak: The Weschler study?

Carson Odegard: No. That's...

Natalie Slezak: Castro?

Carson Odegard: ...it was the Castro study.

Natalie Slezak: Castro 2011?

Carson Odegard: Yeah.

Natalie Slezak: The two-year follow-up?

Carson Odegard: Yeah.

Kevin Walsh: Those aren't... the outcomes that they're reporting there are just for the BT treated group. It's not a comparison between...

- Carson Odegard: No. I know that.
- David McCulloch: So, I mean, it... that is among the most disingenuous studies presented today. It is... you have taken a select group, I mean, you can get that improvement by regression to the mean by the fact that those people were severe at the start of the study, unless you have the comparison of what happened in the sham treated group, it is absolutely misleading, as in the data that should not be published, but constantly is.
- Chris Standaert: I suppose, from the clinical expert, is there some concern of a long-term problem we haven't seen? I wondered this. So, in, like, the orthopedic world, when you take a thermal catheter and you fry things, they tend to shrink, right? The collagen tends to... so the idea of IDET, which is a disc treatment, which doesn't work, but that's the idea of it, and they use this thing for multi (inaudible) shoulder, right? You go fry the shoulder capsule and shrink it. So...
- Gregory Brown: Fry a nerve, it doesn't hurt anymore.
- Chris Standaert: ...yeah. You fry a nerve it doesn't hurt anymore, but it seems like in this case, you're frying bronchials, which you wouldn't really want to shrink, like, over time. So, do they scar? They do other stuff, and soon they become less... I mean, theoretically, if you (inaudible) two things, you're going to induce scar. It's going to be less pliable. Is one of the concerns over ten to fifteen years, these people's airways will become less pliable and less functional. Is that a legitimate long-term... I mean, isn't that what was brought up by NICE? Isn't that a legitimate concern?
- Amy Markezich: Right. I think in the general sense, we almost want it to be less pliable, because we don't want the bronchial reactivity, and that's the one thing that we do find, you know, it seems like it causes, as you don't have the smooth muscles there anymore to cause the constriction. Now, a lot of these patients do already have preexisting fixed airway narrowing. So, they already have remodeling of their airways. I think on one of the, I think the five-year study, they did do CT scan imaging of these patients and did not find any evidence of any interstitial lung diseases or other effects from the procedure. So far, we have not seen any effects. We do pulmonary function testing on our patients afterwards, and we have not seen, you know, although as with the studies, we do not see any improvement in their PFTs, which is expected. We also don't see a decline in their PFTs, but we're not following... I mean, we've only...
- Chris Standaert: We're not 20 years out yet, either.
- Amy Markezich: ...yeah, we're not, we're not 20 years out, and there is no way to know that at this point.
- Chris Standaert: Question.

- Michelle Simon: This is kind of a background question. So, generally, this is done in a series of three treatments. Is that right?
- Amy Markezich: That's right.
- Michelle Simon: If we look at the state utilization data, it looks like... it's hard to see that anyone has actually done a whole series through. I don't know, you must have been participating in some of these patients. Can you tell me why they would not complete the series?
- Amy Markezich: Well, one thing I'm wondering is, um, the series is listed by year, and there are definitely patients that will start in November or December. So, then they don't complete until let's say February. So, they might be listed... there might be one patient that's listed for two years. So, it looks like they haven't completed the series. So, that's the only thing I can think of it might not match.
- Michelle Simon: In your experience, generally, patients complete the series?
- Amy Markezich: Mm-hmm. Yes. Every one of the patients our institution has ever treated has completed the full series.
- Chris Standaert: Move on to our document or discussion, decision tool? OK. So, if you go to our decision tool in your booklet, we start going through this in a structured way here. So, on page three it says what are the key factors and health outcomes and what events is there? We want to know is, have we... we talked about a lot of these, but have we identified key safety outcomes? The ones listed, infection, hospitalization, wheezing, discomfort, bronchial irritation, and bronchiectasis. These are the things that we should be would be worried about that people saw our concerns for them in the literature we saw. OK? Any questions or comments on safety, or are people happy about what we talked about? We're good?
- So, efficacy is effectiveness, the same question. Do we have the right outcomes here? Are there other things people are worried about? We have days lot from school, sick days, mortality, which I didn't see anywhere really, Emergency Room visits, lung function, medication use, severe exacerbations, asthma control, and quality of life. We saw evidence on... we didn't see mortality anywhere.
- Natalie Slezak: There were no deaths due to thermoplasty.
- Chris Standaert: OK. So, no more data. OK.
- Gregory Brown: I would add hospitalization.
- Chris Standaert: Yeah. That's a good point. Is that the long-term hospitalization or does it not seem to change that they identified? Yeah.

- Joann Elmore: And I like how we list severe exacerbations, because I notice no difference in some of the studies, but then they listed their primary outcome was mild to moderate exacerbations.
- Chris Standaert: Right. Yeah, with no change in the severe.
- Joann Elmore: No change in the severe.
- Chris Standaert: On special populations, we didn't see a lot of data by population. There's some gender brought up in the studies to some degree, as ethnicity, but I didn't see it broken down by gender or ethnicity. Predominance female, predominance Caucasian in Castro, certainly.
- Michael Souter: It seems to me the only populations you'd be concerned about in special populations there would be the different phenotypes of asthma, I mean, of which there's a fair amount whether you're talking about people are primarily atopic, whether they're, you know, a consequence of some kind of occupational exposure. There's other things. I mean, there's... again, I would ask our clinical expert about that, but there are some fairly distinct phenotypes there. I don't think we've seen anything to reflect any analysis of those phenotypes.
- Chris Standaert: I mean, there are ways theoretically to help you break down the population a bit to find out.
- Gregory Brown: I think just the numbers of any of these are so small. A group analyses isn't going to happen.
- Chris Standaert: OK. And do you see distinct clinical sort of phenotypes that one would consider if you're thinking about how to treat asthma?
- Amy Markezich: In a way, yes. I think the patients who are atopic actually tend to have more treatment options available to them. So, when I'm trying to determine their... a patient's particular phenotype, I'll look at what their IGE level is, whether they have positive rash or skin testing for allergies, because if they do and they have a high IGE, then omalizumab or other would be an option for them. See if they have eosinophilia, because there is a newer medication, mepolizumab, that's now approved for eosinophilic asthma. So, I'll consider those as additional treatment options, but this procedure is something that I would usually consider for patients that do not fit those categories or who have tried those medications and then failed them.
- Chris Standaert: But the disadvantage is those categories aren't called out for us in any way.
- Amy Markezich: Right.
- Chris Standaert: Which might certainly be a future research consideration to break it down that way to find out.

- Michael Souter: That's all I was meaning. I just didn't think there any was any point in pursuing subcategories when we didn't actually have...
- Chris Standaert: We don't have anything on them.
- Michael Souter: ...anything on that.
- Chris Standaert: It is worth nothing that, though, yeah. Cost outcomes, we have cost, cost-effectiveness, but our meh, yeah.
- David McCulloch: I'm really struck of 151 nonduplicate published studies that were screen, 11 made the cut. Of those 11, seven are low-quality and four a very-low quality.
- Chris Standaert: Alright. Then other relevant societies and other things. This is not... we don't have an NCD. There is no Medicare decision on this. The number of these recommendations say it should be done under basically study settings.
- Gregory Brown: I am actually very struck by the consistency of the recommendations from the clinical practice guidelines. I mean, they... the first one British Thoracic Society, in selected patients with severe persistent asthma already on maximal treatment; and the European Respiratory Society recommend be performed only in adults with severe asthma and only in the context of a clinical trial or systematic registry; Global Initiative for Asthma, highly selected adults with uncontrolled asthma despite recommended therapeutic regimen in referral to asthma specialty centers; and for NICE their conclusion was special arrangements for clinical governance, including consent to research. So, every one of them is essentially saying high-selected, maximum treatment in a specialty center with some sort of registry or clinical oversight.
- Chris Standaert: With a broad brush of approval there, yeah. OK. Let's move on to our vote unless you have other questions or comments. So, we will get to the issue of our second vote and conditions, all that sort of thing. Our initial vote is on the things we just talked about, effectiveness, safety, cost-effectiveness. These will be your yellow cards. So, the way we vote, we consider the technology assessment, the information provided by the administrative reports and/or testimony, submission, and comments from the public, which are appreciated. The committee is given the greatest weight to the evidence that it determined based on objective factors to be the most valid and reliable. Given that, we'll start with effective. Is there some evidence under some or all situations, that is some or all, that the technology is effective, and you have unproven, less, more or equivalent.
- Josh Morse: 11 unproven.
- Chris Standaert: Safety.
- Josh Morse: Six less, excuse me, sorry. Six less, one equivalent, and four unproven.

- Chris Standaert: Doing the math in your head there. Cost-effectiveness. Same answers.
- Josh Morse: 11 unproven.
- Chris Standaert: Alright. So, we'll move on to our vote, and we have three basic options. We cannot cover. We can cover unconditionally. We can cover under conditions. It's always worth considering whether people want to consider conditions. I think in this case, I'd be curious my own sense whether someone wants to consider conditions.
- Gregory Brown: I actually would like to.
- Chris Standaert: OK.
- Gregory Brown: Conditions basically being what's specified in all the clinical practice guidelines.
- Chris Standaert: Well, they are somewhat different, and so.
- Gregory Brown: Right. So, so, the condition I would propose is severe asthma, uncontrolled on maximal medical therapy essentially, at and then treatment at a specialty center/registry.
- Chris Standaert: Well, what we are unable to do as a committee is this issue of requiring it be done in a research setting. So, this comes up often, because we all think this way. That's why we're here, and it's important, and, you know, it's interesting. Clearly, from my standpoint, there's a clearly a clinical need that needs to be researched here and assessed that I'm not totally certain has been, but the... if we choose not to cover something, it is implicit in that decision that the state still has the authority to pay for it under a research study or protocol or registry that it sees appropriate. So, we don't regulate or control that. We can't tell them not to do that. We can't mandate they do that. When we say not cover, they have then the option of if somebody submits a research proposal to them they think is reasonable, they have the option of paying for it under that setting. So, as... when we had our recommendation, the medical director, that's what she said, not covered, but then it's implicit in all those decisions that the state maintains that option.
- Gregory Brown: Can I ask our expert a question? How many centers in the state do bronchial thermoplasty?
- Amy Markezich: I believe there are three in Western Washington and one in Eastern Washington.
- Gregory Brown: OK.
- Amy Markezich: Is what I believe.

- Gregory Brown: OK. So, let me then, then I will remove the last part of that. I would just say severe uncontrolled asthma on maximal medical treatment at a specialty center.
- Michelle Simon: I would say that I would not be supportive, necessarily, of us talking about conditions. We just had a vote where it was unanimous that it was unproven for efficacy and unanimous unproven for cost-effectiveness and half of us think it's less safe. So, based on that vote, I would say we go forward, perhaps, consider a no-cover.
- Chris Standaert: We can, oh go ahead, Mike.
- Michael Souter: I find myself very conflicted about this, because we're not talking about disease, which, if you don't treat it... and none of our comparisons have been made in effect to no treatment. The treatments which are not offered that we have compared this treatment to do themselves carry consequences and even despite those treatments, we still 100 people who die a year from this condition. I would fervently support the idea that we would be able to get, you know, kind of an academic inquiry into this and kind of develop a registry, but as you've said, and we've seen multiple times before, and this has been the kind of a longstanding frustration during my tenure in this group, and as we're stepping off today, I know others will feel the same, that it is really a great source of frustration when we see something that might possibly work but we don't have a mechanism to be able to kind of allow that to happen. So, we've always been boxing with one glove here in this circumstance. I do feel that we have consequence... our decisions have consequences upon people who don't necessarily have access to academic centers, and so when we say, well, you know, we should do this within the confines of research study. That's something we all understand in the abstract, but I do get concerned at what our abstract decisions across populations do to individual patients where they're going to be treated, and I know that somebody needs to make these decisions in the abstract to make policy questions, but I think it is hard. When you're dealing with somebody with this disease, it does have very real consequences and a very real morbidity if left poorly treated or untreated, and I would not be comfortable at the idea that we're removing this completely without some form of rescue ideally within the confines of a registry, but I think that is just something that, you know, I see on a regular basis. I come across patients who have gotten severe noxious brain injury or are dead as a consequence of uncontrolled asthma, and I don't like to think that we have added to the burden of getting to an appropriate rescue in those circumstances. I think that, you know, there's still a lot of work needs to be done in kind of developing this. We need to, you know, encourage everybody, and I think that frankly, you know, I wish that, you know, manufacturers would spend as much or more on developing research studies as we do flying people here to talk to us, but, you know, that's just again another frustration I feel.
- Seth Schwartz: I'm struggling with the same thing that Richard is struggling with. I think what we've seen is a number of studies that are problematic in terms of their ability

to show us anything. They have not been conclusive in showing a benefit of this technology, and yet at the same time, we're struggling with who was actually in these studies, and are they the people that we really think might benefit from this procedure and no, it hasn't been proven that that's the case, but I think there's an inkling in there, at least the way I'm looking at this data. I don't think there's nothing there, but I just can't figure out how to understand it. So, I'm... when we think about either no cover or cover with conditions, I'm trying to think about how, in my mind, we would, we would restrict this to that very small patient group that really does not have another option, that medical therapy at its maximal contingent is not helping these people anymore. I'm not quite sure what that would even look like, but.

Kevin Walsh: I disagree with you. I think that the FDA made a decision based on a study that used Bayesian statistics. So, we don't even, I mean, we're... we're clueless about how much this data was cherry-picked to begin with. I understand the issue. I have asthma. I've taken care of asthmatic patients who have expired. I get it. I think our charge is to pay for what works, and it's... the onus is on the people who produce the technology to prove that it works, and the possibility that maybe it will help a subgroup when they haven't bothered to demonstrate that, to me means it hasn't been shown to work.

Chris Standaert: But when is the process point. If we had... actually if some people want conditions and some don't, we basically put up conditions and then of your options of voting is no cover so that the conditions do not apply. If the majority vote no cover, even though three or four want conditions that we have, the majority no cover decision will go through. So, we can get there. So, we don't all have to agree that we want conditions. I think if enough people want them, they're worth putting on the board and trying to narrow down. So, if people are... if people who want them are comfortable with them, whether they want that or they don't want that. I mean, I struggle with the same thing Kevin is struggling with. So, I... there's clearly a dire clinical need for people who have severe asthma that something... it'd be great to have another treatment option for them. What I struggle with is seeing that this is an effective intervention in those people, and there are significant... these are big numbers of hospitalizations and other things early on, and I struggle for the data that says that in that patient with that need that they've really looked to figure out that this helps them. That's what I struggle with. Joann?

Joann Elmore: Four quick points. One, being short of breath is scary. We care about patients. We want to do the right thing. I think all of us around the table are in agreement on that. Two, many of us noted definite harms associated with the procedure, being hospitalized immediately afterwards. It may only be 2%, 3%, 8%, but we do care about safety for these procedures, and in my read of these, there were definite safety issues that I think need to be studied. Three, in looking at potential efficacy as Michelle articulated, it was unanimous unproven. I think the literature... I wish it was better. We all wish it was better. We want to be able to help these patients, but it is inadequate from all of our perspective on that early vote to say that it is efficacious. The final point, number four, is

that when I first got on the committee, I think I was problematic, because I kept saying, let's add a condition because I want to study it, because the studies are all terrible, because I really care about this. This is important clinically, and we need to help these patients. So, let's add a condition that it be studied, and that just doesn't work. So, when we vote for non-conditions, to not cover, it still can be investigated, and it still can be up to the Washington State staff to cover, and I think that's an important point, because I think we need good quality studies, because we all care about patients with this disease.

Michael Souter: Let me just make the point that I am not convinced that we actually have good quality of equal access across our community when our only recourse for some patients is to go to an academic center, because that's what we're... that's what you're saying. Yes, OK. Well, we've got... your rescue in this circumstance is to go to a study, and I think that's fine if you're in a metropolitan area. I don't think it's as good as if you're working... as if you are living in a very rural environment where you may not have the facility to be able to travel in those circumstances.

Chris Standaert: I agree with you, access concern. I also (inaudible) the issue of effectiveness and efficacy, but these are the studies we have showing data that isn't convincing or by presumably the people on the planet who are best with this procedure, and have done more of them than anybody else on the planet, because they're the investigators, and you... this is a... this is the issue you have when that then extrapolates out to the population and people do it... I mean, and that's why the guidelines, I think, say that despite the difficulty in travel, you know, there's only so many... some things can only be done at so many sights because the frequency of the application and the technical challenges and the level of depth of expertise and clinical support to make it go safely is just not widespread. So, I don't think that's infrequent. It's unfortunate, but I don't think it's infrequent. I still have a data issue here, though. So, we can put some conditions on the board so people can see me. Again, those interested in conditions can talk about them and narrow them down.

David McCulloch: Please, no. I mean, how could you possibly come up with conditions? I mean, let's at least take a straw vote to see how many even want conditions, because that would be a, to me, a fool's error trying to come up with a rational condition.

Chris Standaert: We could go the other way and...

Michael Souter: I don't necessarily agree with you. I think that, you know, what I heard from Greg initially, it appeared to me to be a plausible condition that you failed all else... you know, everything else, and you're, you know, you're in a kind of fairly critical state.

Gregory Brown: I think, actually though, I agree with David. I think if we make a vote right now on, you know, cover with conditions, and if that passes, then we can do it. If the vote is no cover, then there's no point in...

- Michael Souter: I know what you're saying about the logistics of it. I'm just making the counterpoint to what David said, and I understand his passion for the intellectual rigor on this, but I couldn't necessarily say that we couldn't make conditions on this.
- Chris Standaert: When you have voting on conditions when you don't have any conditions is really problematic, because you don't really know what that is, and then that's our formal vote.
- Gregory Brown: That's why he said a straw vote.
- Chris Standaert: Right. So, but in a straw vote, we're not going to be in a position, so... I've heard three people say it. So, if people want to put up what they think to consider for conditions so they can be on the record saying this is what I supported, I think that's perfectly fair. It's a majority. So, if nobody here wants to do it, wants to go, we can just do a straw vote and then people can think about it. Why don't we try a straw vote? So, and you can abstain. So, if we abstain, that means more people want to discuss. So, people interested in discussing conditions more and putting conditions on the board, how many do we have? We got four. People who are not interested in that. So, we have five or six. So, we should put conditions on the board and let people be heard and let them express their opinion.
- Joann Elmore: And conditions usually are evidence-based where it's been shown to be efficacious and safe.
- Chris Standaert: Well, now, I don't know about that. Conditions are... we've gone through that. Conditions are where people think the overall situation puts them in a clinical scenario where they think it should be, it's reasonable to be covered.
- Michael Souter: If everything we did was evidence based and was clear-cut, we wouldn't be here. We're here to exercise clinical judgment because we practice in arenas where judgment is required, and that's part of our charge, again, as well.
- Chris Standaert: I need a condition advocate to say something. Carson?
- Carson Odegard: I'll throw something in. Is there a way to have an open door for some of these patients that absolutely need this procedure and have access to something, to have access to not necessarily an educational facility but access to some facility that the state could say yes, we will cover this.
- Kevin Walsh: I have to ask a question.
- Gregory Brown: Well, we have one in Eastern Washington. I'm assuming that's Spokane. Is that an educational facility?

- Kevin Walsh: I have to ask a question. You are talking about life-saving therapy. There is no evidence looking at that clinical condition, that subgroup, that state of severity of asthma. We heard three anecdotal reports of people whose asthma was much more severe than the study groups who seem to have beneficial outcomes, but there's nothing, we were not given any information about that group of people. So, I'm puzzled by the basis upon which you're generating this condition, because I don't, I don't see anything that looks at that condition, and I understand that you're saying something is doing better than nothing, and I'm saying based on what?
- Carson Odegard: That's why I'm bringing it up, because I would vote... my straw vote would probably lean towards no cover, but for those patients that we have concerns about and they don't have access, then I don't know if there's an avenue through the agency where they can do that. If we vote no cover, it's no cover.
- Chris Standaert: The answer is, the pulmonary community has to pull together and decide they're going to define their study group and talk to the state and acquire funding, and study it. That's what... essentially what you're leaving them with, and if they feel strongly enough about it, and if it really works in that population, they'll find it, but they have to build the study to get after the population they're concerned about and approach the state about funding or, you know, coverage as part of a study, or whatever to make the study go. When you do this, it's fairly routine for a study to then go to the payers and say, we're comparing X to Y. Will you pay for this in this study so we can run our study and see if it works, but that's up to the state? So, we always leave that option.
- Charissa Fotinos: May I clarify something? If the decision, if there is a noncover benefit, the provider can request an exceptional to rule, which, on an individual basis can be reviewed and a different determination made, if a service is covered, it only becomes covered if it meets the criteria for medical necessity, which is sometimes hard to sort out based on what you're looking at. So, just that distinction.
- Carson Odegard: That answers my question.
- Chris Standaert: If somebody is really convinced, they can go to the state and appeal. The providers can talk to the state and appeal and see if they will cover it under some circumstances, if they are convinced that's what their patient needs.
- Josh Morse: I need to clarify that, though, and maybe Dr. Fotinos can follow up and confirm this, but I believe that applies for Medicaid.
- Charissa Fotinos: Only Medicaid, yeah. Thank you for that clarification.
- Seth Schwartz: And I think in answer to Kevin's question, I mean, I think, I'm struggling with all the studies. I think there's obviously significant quality issues in a lot of these studies, and I'm, and I'm... I think there's probably a significant placebo affect

here, which is another thing I struggle with in this Castro study, but I think the Castro study probably best represents the benefit that this intervention potentially has to really offer, and I think it was not designed well or is not justified well in the way they looked at their primary outcome, and obviously the Bayesian statistics are a struggle to understand what they even mean in this setting, but when I look at the secondary outcomes in that group. So, if I'm thinking that paper alone, I think there's some real stuff in there that, that makes me question whether this is significant. So, when you look at... I don't really know, you know, how well AQLQ captures what we really care about, but if you look at the primary and secondary outcome of how many patients achieved and made a minimally-clinically significant impact, it was almost a 15% difference that was significantly statistically significant for them, 78, almost 80% of patients versus 64% had a minimally clinically-important difference. So, if you span that into the statistics of the entire group, maybe it wasn't significant, but for those patients, it was. So, I'm, again, I'm not saying this is compelling evidence. I agree that we're not... it's not yet proven to me that this is significant, but when we're saying one of the struggles is trying to figure out who in this group really benefits, we're seeing that some people are benefiting.

Kevin Walsh: But then in another study, they weren't shown to benefit.

Seth Schwartz: Right. I know, but I... but I'm struggling across the board with these studies, because we have these four randomized trials. Only one is actually comparing what this intervention really does versus other things. So, the other group, and the other, in all the other randomized trials, they are not... they're randomized but they're not blinded. One group got the intervention and one group didn't. So, I don't know, I don't know how to compare those groups. So, I'm struggling with that. So, again, I'm not... I'm in the same situation as the rest of you. I think this is unproven technology, but I think that there may be this subgroup that has the potential to benefit. So, I'm struggling to simply not say... to say across the board no one gets this. Maybe that's the right answer. Obviously, the group is... it seems like leaning that way, but I'm still struggling with that, because I'm seeing some element of benefit in the best randomized trial that we have, even though it's significantly problematic.

Chris Standaert: So, unfortunately, the blinding wasn't totally successful. Its people who are treated guessed much more commonly that they got treated. I mean, they knew, because they...

Joann Elmore: They knew.

Chris Standaert: ...they got hospitalized. So, I still need, we need somebody who wants a condition to give us a condition, and then we have a place to go.

Carson Odegard: I would take the wording straight out of the British Thoracic Society clinical practice guideline. Patients with severe persistent asthma already on maximal treatment and treatment should be limited to a few specialist centers.

- Chris Standaert: OK. She's typing. Can you run that by her one more time?
- Carson Odegard: So, patients with severe, persistent asthma already on maximal treatment and treatment should be limited to a few specialist centers in carefully selected patients.
- Christine Masters: I'm sorry, limited to a few (inaudible) clinics?
- Carson Odegard: Few specialist centers in carefully selected patients, which is the above, I guess.
- Chris Standaert: Of course, I wish I knew what that last half of that sentence was.
- Carson Odegard: Well, we can get rid of the carefully selected patients. I think it's that clause above. So, I guess one of the things that struck me, and I know it's anecdotal, but if you start including mild and moderate it washes out the effect in the more severes. So, in that group of most severe patients that can't be controlled, I agree with Seth. I think there's potentially some benefit there, and I heard one patient that thought it was so beneficial that they paid out of pocket, and near as I can guess, they paid \$15,000 out of their pocket, and to say anybody in any of these state programs that don't have those resources, we're not going to cover your care, I'm not willing to do that on every single person, no matter how severe their asthma and no matter how hard they've tried to control it with medical means.
- Chris Standaert: Well, do other people want to comment on those conditions, particularly the people who are interested in conditions? It's a very vague last four words?
- Michael Souter: I think the carefully selected patients can be construed as being the same thing as patients with persistent, severe asthma. I mean, we're saying the same thing there.
- Carson Odegard: We can take out the last four words. I agree.
- Michael Souter: The question is, what constitutes the competent specialist center? And I don't know whether there's any (inaudible).
- Kevin Walsh: I want to ask a question. I don't... I'm a little bit confused. So, you're saying, I don't want to make a decision based on people's financial status. So, people who can't pay out of pocket, I don't want to deny them that care? Is that what you're saying?
- Carson Odegard: I'm saying that if you have a patient who is having cataract surgery at 35 because they have to be on chronic steroids, if they have all these other treatments that have significant side effects and I sit down as a pulmonologist and have a shared decision making with the patient and say, look, you're... we've tried everything, you've been on multiple medications. Nothing seems to be working. This is another option. We don't know whether there... there are side effects that we don't know, but I think it's a reasonable option.

- Kevin Walsh: But I'm sorry, you were saying you did not want to deny this care to people who did not have the financial means.
- Carson Odegard: Right.
- Kevin Walsh: But it's OK to deny to people who don't have the geographic accessibility, because you're limiting it to a few specialist centers, and right now it's offered four places in the state. So, you're not saying, it's OK if you don't live in the right place, but if you don't have enough money, we want to make sure you have access to care, if you live in the right place.
- Carson Odegard: I don't under-... I guess I don't understand why you can't travel to one of those centers.
- Louise Kaplan: I will just comment that when we considered ECMO that was only available in three facilities in the state and that didn't seem to deter us from decision-making. So, that was an issue. I think I raised it. You know, if you live in the Seattle area, you have access to ECMO or if somebody flies you there. So, in this situation, this is not an emergent procedure. It can be a scheduled procedure, and quite honestly, living in Olympia and having practiced in Elma, people will travel from Aberdeen to Seattle, and people leave Olympia and go to Seattle all the time, and people will even go down to Portland if they have... the care that they are seeking is best offered in that location. It does affect people who, quite honestly, may have Medicaid coverage but don't have money for gas in their car. So, we're always dealing with these factors that are beyond our control, but I don't think because it's only offered in four places we say we can't consider it. I think the question I have is, when you limit it to a few specialist centers that seems to be limiting the opportunity for other centers to develop their expertise to offer this procedure, and then become part of this opportunity to provide the care. That's separate than how I feel about it, but I'm not sure that we have to have that.
- David McCulloch: So, you're suggesting we should encourage two or three pulmonologists in Yakima, Tri-cities, everywhere to, you know, do a few to keep their hand in. It might work.
- Louise Kaplan: I didn't say that.
- Chris Standaert: She didn't say that.
- Louise Kaplan: I said that people develop the expertise. I mean, all these centers that offer it now didn't offer it at one time. So, they became centers where it was offered through a process. So, I'm just saying, if you say only limiting it to a few, then what if you have centers of excellence that could also offer it?

- Chris Standaert: Well, there are definitely... I mean, you can learn a procedure by going to a weekend course. So, I don't know how you learn this, but, you know, that's how a lot of things are learned. That doesn't make you a center of excellence.
- Seth Schwartz: I think we're struggling with this for the wrong reasons. I think the concept is that we want to limit this to places that have expertise and the capability of taking care of these patients that would have whatever complications arise and go through a sensible process and are reasonable to treat. So, I think the word few is useless in here, because who cares whether that's 2 or 20 if the people are capable of doing this well. So, I think I'd get rid of that and just say, limit it to centers with adequate experience and capability of taking care of...
- Chris Standaert: Slow down and help her concretely and then she can get exactly what you're saying. So, start at the first word, and then you will get where you want to go.
- Carson Odegard: So, just eliminate few. Eliminate A. Make specialists specialty, and delete with carefully selected patients. Does that accomplish?
- Seth Schwartz: Yeah, I mean, and if you want to say more, you can say...
- Gregory Brown: Does the state have the authority to designate centers of excellence or specialty centers?
- Charissa Fotinos: We can define that for a benefit in Medicaid. We don't have certification authority to speak of.
- Gregory Brown: No, not certification, but I mean...
- Charissa Fotinos: We can define something, as a center of excellence based on different parameters for Medicaid.
- Seth Schwartz: I think the question is a bigger one, which is, is this operational at its current level, or do you need more than specialty centers?
- Charissa Fotinos: This would be hard to implement, because there's no definition of specialty center. It, does this...
- Seth Schwartz: So if we added in, with experience in this technique and capability of managing any associated complications, would that be more operational for you?
- Charissa Fotinos: I think the challenge is, how do we figure, whether it says specialty centers or whether it says ability to manage complications, the ability to know if that, in fact, is the case is the challenge. You could have an ambulatory surgery center that says we do this and we're fine, and how would we... I mean, from an implementation standpoint it's hard, because it's hard to know what to trust. You just say, yeah, we can do this. So, do we say, OK? You said you could, so we'll let you do it. I mean, that's... and that's... I'm not trying not to answer the

question. It's just... specificity helps, and if it can't be there, then we do the best we can.

Chris Standaert: Dr. Markezich, is there some external governing body. So, you weren't here for ECMO and ECMO may or not be a thing, but there is an external governing body with a built-in registry that sort of goes over ECMO centers, and that gave us an option for that. Is there such a thing for this procedure?

Amy Markezich: There is not a centralized registry for this procedure.

Chris Standaert: Not the registry, but a certifying body that says... somebody, you know, waves a wand over you and says you're good, you can do this and you have, you know, you can build a center that needs... some various agencies will certify that you have what you need to take care of a procedure, because you have the right backup specialists. You have a pulmonologist. You have a thoracic surgeon on call. You have the things you would need if things go awry, which you may not have in other sites, but there is no body that does that for this type of thing?

Amy Markezich: There is no body. There is a training course provided by the company and then each individual hospital will determine it would be safe to proceed with the procedure.

Chris Standaert: Right, based on individual hospital criteria, which we all are familiar with, which are highly variable.

Amy Markezich: Mm-hmm.

Chris Standaert: Yes. So, the people who want conditions, are they happy with these conditions, or does somebody who want conditions want to change the wording. It should be persistent instead of persistence, but. Do you have a comment?

Amy Markezich: Would it be helpful to the committee for me to review the criteria that I use in determining who might be appropriate for the procedure?

Seth Schwartz: I'd like to hear it.

Amy Markezich: So, the patients that we determine might be appropriate, one is we have to confirm that they do have asthma and alternate diagnoses have been ruled out for those patients, such as emphysema and other interstitial lung diseases. We also ensure compliance and good inhaler technique, and we assess and optimize treatment of other comorbid conditions that can be worsening the disease, such as GERD, sinus disease, sleep apnea. In addition, those patients then are maximally managed for their asthma, and they're considered for a monoclonal antibody therapy, such as omalizumab or mepolizumab. If they're not candidates for monoclonal antibody therapy, and they're already, they already meet all those conditions, then we would consider bronchial thermoplasty. If they are candidates for the antibody then we do a six-month trial, and if they fail that trial, then we would consider other therapy.

- Seth Schwartz: So, actually more strict. I think I like the more restrictive concept here. I think the problem I have with patients with persistent severe asthma already on, I would say, having failed all other medical therapies. That might be... kind of get you there.
- Chris Standaert: And already failed all other medical therapies is what he said. From there, where you are, having already failed other medical therapies.
- Seth Schwartz: Having failed all other medical therapies.
- Chris Standaert: Dr. Markezich, I appreciate your response. From my standpoint, everything you said is nonexistent in what we read. So, we have the data we have, and it sounds like you have a great study in mind is what it sounds like to me.
- Amy Markezich: If only I could get the funding.
- Louise Kaplan: May I ask a question? Just back to your point in terms of implementation. If it would be helpful if this conversation can do so to describe what failed would look like as well, rather than leaving it up to our interpretation if it continues to, just so it's... it's a request. It's not a... if that's possible.
- Tony Yen: Photocopy Dr. Markezich's criteria. It seems to be clinically very reasonable. Can we just copy that or use that as the basis of the criteria, if we're going to have conditions?
- Chris Standaert: They can do whatever they like to have done up there. It depends if that's what a number of people agree with. If there's not much of a consensus for that, we could do it, but.
- Seth Schwartz: Well, I think the challenge here is that... I think most of us who are thinking about this option of with conditions are not thinking we want this to be widely available. We're thinking we want this for this very selective group of people who really don't have any other options. So, I think what we just heard there captures that operationally much better than what we're trying to come up with here. So, and since it may be that other people aren't going to vote for that anyway, it's maybe irrelevant, but I would...
- Chris Standaert: Do you not find it problematic... I mean, she talked about things that are nowhere... I mean, the medications, the approach, the sorting out. I mean, that wasn't done at all in these studies...
- Seth Schwartz: No. I agree with that.
- Chris Standaert: ...we have.
- Seth Schwartz: I agree with that. So, I think with things like specifying monoclonal antibodies and all that kind of stuff, I agree. I don't think we necessarily need to get into

that, but I think you could somewhat capture that with saying all other medical therapies, but I think the challenge is defining failed. I think... and I was just trying to sort of operationally say that, which is...

Michael Souter: Well, then why not suggest something like suffering significant complications or consequences of their current medical therapy, of their current maximal medical therapy. I mean, that's the kind of population we're trying to deal with. The people, like some of the cases we've heard today of people who have suffering significant disadvantages of what we are offering them as the mainstay of treatment.

Amy Markezich: Generally, the definition of failed treatment is remaining uncontrolled. So, requiring rescue therapy more than twice a week or requiring steroids for asthma exacerbations more than twice a year. That's the general accepted...

Michael Souter: Does that bleed down anywhere...

Amy Markezich: ...definition of failing therapy.

Michael Souter: ...with, you know, with the American Thoracic Society or anything like that? Is there a definition that the ATS uses for failed therapy?

Amy Markezich: That is the definition that ATS uses, yeah.

Michael Souter: Then, I think why don't we just keep it to, you know, patients who have then got failed therapy as defined by the American Thoracic Society.

Chris Standaert: I'm curious why the Castro study excluded people who had four courses of steroids in a year.

Michael Souter: This is not about... we're not trying to (inaudible)...

Chris Standaert: (inaudible)

Michael Souter: ...evidence basis for something that, you know, to guide this condition. This condition is driven because we, like Seth says, I feel that there is a signal there in a small group of patients. We don't have an adequate data set to be able to kind of refine that or guide us in any way, but we just, you know, feel uncomfortable, because we are clinicians and know what it's like to have to kind of treat patients in these circumstances. We want some kind of slim avenue whereby, you know, people who are in desperate need can, they can have access to some, you know, last respite of care.

Chris Standaert: Well, on here, you... so having failed all other medical therapies, as defined by...

Michael Souter: The American Thoracic Society.

- Chris Standaert: The American... OK. So, we need to get this to a point where people are happy with this so we can vote, essentially, at some point.
- Seth Schwartz: Get rid of the already on maximal therapy.
- Michael Souter: And then can we... you got rid of the treatment centers, but can we just say something like treated in specialty centers, which have the infrastructure to deal with acute complications, because that what you... you were trying to get at, Seth, is you don't want to, you know, an ambulatory office.
- Chris Standaert: In... where you were, in specialty centers with appropriate training and capability to manage the procedure and its complications.
- Michael Souter: I like that.
- Chris Standaert: OK? Perform the procedure and manage complications.
- Michael Souter: Something other than... appropriate training and what else did you say, appropriate training and?
- Chris Standaert: Appropriate training and procedures with the ability to perform the procedure... yeah, with the ability to perform the procedure.
- Seth Schwartz: In specialty centers with appropriate training. Get rid of the first 'and procedures' after that. So, on that line, again, you want to get rid of 'and procedures.' Just appropriate training.
- Chris Standaert: Get rid of the word procedures. There you go. I think it's appropriate training in the procedure with the ability, yeah. Appropriate training in the procedure, OK, before with, in the procedure, with the ability to... get rid of perform the procedure, just put manage complications, with the ability to manage complications... to manage complications. Yeah, there you go. Now, get rid of that. Further comments or edits on the condition? Again your choices when you vote, regardless of what that says up there, will be no cover, which means it's not covered, again, leaving the research aspect open to the state. There is cover unconditionally, which means conditions be damned, it's covered. Or there is cover with conditions, which will apply specifically to what is standing on the board. So, if anybody wants something different on that sentence, they should say so now, because that's what we're going to vote on.
- Gregory Brown: I would get rid of already. I mean, having failed.
- Michael Souter: People... and acute and severe complications. I don't know, I mean. Acute or severe complications.
- Chris Standaert: If a lung goes down, we (inaudible).

- Michael Souter: We don't... we don't want it to be done in an office. We're just trying to find some way to encapsulate that.
- Chris Standaert: How are we doing? Comments or edits on that?
- Carson Odegard: The second with.
- Christine Masters: OK. Tell me exactly what you wanted.
- Carson Odegard: The first line after procedure and...
- Christine Masters: Without?
- Carson Odegard: No. No. Leave it.
- Chris Standaert: Add the word 'and' before the word 'with,' in between procedure and with. There you go. Yeah? Yeah? OK. So, unless there's another comment, we're going to move onto our vote, and again, your options are cover, which means cover unconditionally. It doesn't say unconditionally, but it means everything. There is no cover, which means that doesn't apply, it's not covered, and there's cover with conditions, which means that.
- Joann Elmore: And again, you know, I work at Harborview. I care about patients who are vulnerable. I don't care about money. If I have a really end-stage patient, and they have nothing else to offer them, even if we vote no cover, you know, we can still talk with the state? OK.
- Josh Morse: Yes.
- Charissa Fotinos: For Medicaid, yes.
- Joann Elmore: Right.
- Chris Standaert: OK. It's time for our vote.
- Josh Morse: Seven no cover, four cover with conditions.
- Chris Standaert: The majority is no cover. We have to make sure we are consistent with Medicare, and Medicare does not have a decision on this. So, we are clearly consistent with something that doesn't exist, and that we looked at and considered medical society guidelines and other similar related documents, which we did, and they varied. Some were required studies and other things that we couldn't do, study settings and research settings. Think we're done?
- Josh Morse: Yes. Thank you.
- Chris Standaert: We're done. Thank you, all. So, we'll have lunch, and then we start at 12:30. We will start autologous platelet rich plasma injections.

Our clinical expert is not here yet, but we will get going anyway. We have a complex report here. So, we're going to start talking about autologous blood or platelet rich plasma injections. We're going to start with the Washington State Agency Utilization and Outcomes presentation.

Chris Standaert: So, Dr. Johnson, you're on a mic. So, just introduce yourself for the recording and the whole thing.

Shana Johnson: Oh, thank you. Hi. I am Shana Johnson, and I'll be presenting the Agency Medical Directors comments on the evidence report for autologous blood and plasma-rich plasma. So, platelet-rich plasma and autologous blood is an emerging therapy. A lot of the excitement behind it is its promise as a regenerative therapy. It's touted mechanism is local delivery of high-dose growth factors and other bioactive proteins.

In today's evidence report, they looked at a variety of musculoskeletal conditions, for which these injections have been studied, including tendinopathies, plantar fasciitis, acute musculoskeletal injuries, and osteoarthritis.

The current state agency policies for this is noncovered for Medicaid, PEBB, and Labor and Industries. The Department of Corrections, it's on prior authorization; however, I don't believe it's ever been requested.

Looking at it as an emerging therapy, the medical directors concerns regarding safety, efficacy, and cost are considered at a medium level.

The next couple of slides look at agency utilization. Since this is a noncovered service, this is more for completeness. There have been less than 15 claims over the last three years, and the majority of these are nonpaid, likely because it's a noncovered service.

Chris Standaert: Let me ask you a quick question. So, it's not covered, but you've done it. So, as far as I know, and we can, well maybe I'll mention this to Dr. Harmon in a second, but it doesn't have a category 1 CPT code does it? It has a tracking code.

Shana Johnson: It has a 0232T, injection of PRP any site.

Chris Standaert: So, a tracking code is a category 3 CPT code, which does not have an RVU assigned to it is what that is, so.

Shana Johnson: OK.

Chris Standaert: That's what I... so that's what that is. So, it doesn't have a category 1 code like most other things we talk about. So, I'm just curious how you even... this is just people's... somebody just called the agency director, and they said, OK we'll pay for it?

Shana Johnson: No. These are... these claims, the majority here, they're... they were submitted. They were not paid.

Chris Standaert: Oh, OK, just submitted. OK.

Shana Johnson: Yeah. There were a couple that got through, like one fee-for-service managed care claim got paid somehow, a couple of Labor and Industries got paid somehow, but the majority of these are unpaid.

So, looking at the reasons for why these few claims were submitted, the majority were for treatment of a variety of tendinopathies, osteoarthritis, and acute injury, but are pretty widespread among diagnoses.

The Center for Medicare and Medicaid services currently only covers platelet-rich plasma injections in the setting of chronic nonhealing wounds and in that case, in accordance with their clinical trial policy. They don't speak of any indications regarding musculoskeletal use.

Looking over to the private payers, both AETNA and Cigna consider these injections to be experimental and investigational.

Clinical guidelines show mixed recommendations. The most common place it is recommended is to support its use in chronic lateral epicondylitis, of which four guidelines recommend its use, including the American College of Occupational and Environmental Medicine. The American Academy of Orthopedic Surgeons in 2013 made no recommendation regarding platelet-rich plasma injections and its use in osteoarthritis. Other musculoskeletal indications, such as the ones I showed you on the first couple of slides are either not commented on or not supported.

There have been a variety of health technology assessments on this emerging therapy. The National Institute for Health and Clinical Excellence performed an assessment in 2013 on elbow, Achilles, and patellar tendinopathy; 2013 on plantar fasciitis; and 2014 on knee osteoarthritis, and they felt that the evidence of efficacy was inadequate for all of the above. HEALTHPACT out of Australia found that there was low-quality evidence for knee osteoarthritis. The Canadian agency for Drugs and Technology and Health felt that there was insufficient evidence to guide recommendations for its use.

In recent years, there have been multiple systematic reviews suggesting platelet-rich plasma injections for benefit in knee osteoarthritis. In these reviews published in 2014 and 2015, they concluded that platelet-rich plasma injections are more effective at improving function compared with both hyaluronic acid and saline at six months, in the 2014 review and at 12 months in the 2015 reviews.

Chris Standaert: One question there?

- Shana Johnson: Yep.
- Chris Standaert: So, I'm well aware of systematic reviews that say the exact opposite, that it's strong evidence against the use of these things. So, how did you pick those to tell us about?
- Shana Johnson: I'm sorry. Could you say that again?
- Chris Standaert: I am well aware of existing systematic reviews that say there is strong evidence against the use of platelet-rich plasma injections. They are conflicted, but you just showed us three positive systematic reviews. How did you pick those, and did you do a systematic search for systematic reviews and...
- Shana Johnson: Sure.
- Chris Standaert: ...give us a representative sample?
- Shana Johnson: Yeah. So, I got the systematic reviews from the evidence report from the evidence vendor, and I focused on reviews that were in the last three years, I guess, because they would have the most up-to-date studies. The two that I didn't speak specifically of was Kearney in 2015, which showed a slight pain benefit in Achilles tendinopathy over the short-term, Morris in 2014. This was a Cochran review that did say insufficient evidence to support use of platelet-rich plasma injections for treating soft tissue injuries, but I thought it was harder to draw conclusions, because they just used a wide range of musculoskeletal conditions. So, I wasn't really sure what to take away from that conclusion, but those were the group that I saw in the evidence report, and if there are more there that need to be repeated for completeness sake, I'd be happy to pull up the evidence report and speak to those.
- Gregory Brown: If I may just interject. I talked to Josh about this briefly, but I've been involved in a network meta-analysis that we're doing through the evidence-based quality and value committee with the American Academy of Orthopedic Surgeons, and we looked at injections for hyaluronic acid, corticosteroid, platelet-rich plasma injections, and placebo and then a number of oral, including acetaminophen, ibuprofen, naproxen, diclofenac, oral placebo. Anyway, the conclusion of that, which isn't published, which is why I couldn't submit the manuscript, basically was that platelet-rich plasma injections was better than HA, which was no better than a placebo injection... injectable placebo, but it was worse than naproxen, ibuprofen, corticosteroids.
- Chris Standaert: You're talking for knee osteoarthritis.
- Gregory Brown: For knee osteoarthritis.
- Chris Standaert: And it's unpublished data that isn't in our report.

- Gregory Brown: Correct.
- Michelle Simon: Short-term or long-term or what's the follow-up on that?
- Gregory Brown: Basically, the only time period that we could find to analyze was four to six weeks.
- Chris Standaert: About my question, I didn't go looking for it. I was just looking at the articles, and I found this system review by Devoss from 2014 (inaudible) against platelet-rich plasma injections for tennis elbow. So, I don't know why it didn't show up anywhere, but that just literally just popped up in my... I didn't go looking for it. It just showed up in a search while I was looking through my articles. OK. Go ahead, I'm sorry.
- Shana Johnson: Sure. So, the evidence report looked at the specific musculoskeletal conditions in the chart above, and the strongest data was for elbow epicondylitis and knee osteoarthritis. There were also a couple of positive studies for rotator cuff tendinosis; however, although the elbow epicondylitis and the knee osteoarthritis had multiple positive studies, it is of note that the quality of the evidence noted in almost every study cited was noted to be low. So, keeping that in mind, looking at elbow epicondylitis, the outcomes were the same or better with platelet-rich plasma injections or autologous blood versus control group. In the vendor report, platelet-rich plasma injections versus control was considered both anesthetic and steroid. There were two RCTs that just looked at anesthetic while quite a few looked at steroid, and I bring this up just because I think there are some people that believe... and there may be some data that support that chronic injections with steroid can result in a weakening or a problem with a tendon over the long-term. So, it could be, in some of these studies that look at pain over six months and twelve months, that instead of comparing the platelet-rich plasma injections to an active control, which I think is what it's meant to do, you could argue that repeated steroid injections could be a negative control. So, I think that's important to keep in mind. With that being said, over the short-term, pain and function were similar, platelet-rich plasma injections versus control, but pain and function were better with platelet-rich plasma injections over the intermediate, that's I believe three to twelve months, and long-term, greater than twelve months. -Autologous blood versus control also did better than control, but the control is steroid, and platelet-rich plasma injections versus autologous blood showed that the platelet-rich plasma injections did better over the short-term and the intermediate term, intermediate term being up to twelve months.
- Briefly looking at the knee osteoarthritis data, only knee osteoarthritis showed evidence of benefit with platelet-rich plasma injections. In this case, they had platelet-rich plasma injections versus hyaluronic acid, as well as platelet-rich plasma injections versus saline. Over the short-term, there was no difference in pain or function versus the hyaluronic acid, but over the intermediate and the long-term, platelet-rich plasma injections showed better functional scores, which I thought was a positive outcome over a twelve-month time period.

Platelet-rich plasma injections versus saline showed platelet-rich plasma injections was better over the short and the intermediate term.

So, putting together the results from the evidence report, the clinical guidelines, health technology assessments, and previous I think I already said this, health technology assessments, we make the following recommendations: Platelet-rich plasma injections and autologous blood to remain noncovered for the following conditions, specifically looked at in the report, Achilles, patellar, rotator cuff tendinopathy, plantar fasciitis, acute injuries, TMJ, and hip osteoarthritis. Consideration of platelet-rich plasma injections for a covered benefit for the following conditions: Chronic lateral epicondylitis after failure of conservative therapy with some limitations noted in B and C, and for knee osteoarthritis after failure of conservative therapy with some limitations noted in B and C. Alright. Any more questions?

Chris Standaert: I have a question. So, you said, I mean, we'll get to the data and we can talk about the data and the level of the quality of the data that actually exists, when you mention that.

Shana Johnson: Right.

Chris Standaert: But even in knee osteoarthritis, you're saying it's better than HA or saline. Saline shouldn't do anything, and HA really doesn't do anything in a population...

Shana Johnson: Right.

Chris Standaert: ...in this population basis. So...

Shana Johnson: So, it was better than...

Chris Standaert: ...it just seems like...

Shana Johnson: ...placebo, I guess, would be the worst case conclusion, then, correct?

Chris Standaert: ...but it should be compared to something that works, but you know...

Shana Johnson: Well, I guess we don't have it.

Chris Standaert: ...but that... that's where my question of, you know, I don't know that leads the... the person that leads to the conclusion you came to that we should just use it. So, anyway, I'm just curious about that.

Shana Johnson: Well, I guess because the outcomes showed improved function over a six and a twelve-month time period, I think when you look at musculoskeletal interventions that are out there, I think it's very hard to show improvement in function. So, the fact that this showed improved function impressed me.

- Gregory Brown: Well, add then, the previously unpublished study we just discussed, we looked function and pain. We also looked at statistical significant and clinical significance, and the only clinically significant improvement was in function with naproxen, essentially. None of them were clinically significant for pain or function, other than naproxen.
- Shana Johnson: Was that over six weeks or six months?
- Gregory Brown: Four to six weeks.
- Shana Johnson: OK. Just of note that the benefits found here were over the long-term, not the short-term. They were seen at six months and twelve months, just for clarity.
- Chris Standaert: Other questions for Dr. Johnson? I'm sure we'll ask more questions as we go along.
- Shana Johnson: OK.
- Chris Standaert: OK? No. We will move on. Dr. Harmon is here, our clinical expert, so I will introduce her. This is Dr. Kim Harmon. Dr. Harmon is a professor at the Department of Family Medicine and the Department of Orthopedics and Sports Medicine at the University of Washington, and from my experience, she is quite familiar with this topic. I just want to clarify one thing and you can introduce more if you would like. Conflict of interest issues, here is the disclosure form, but you have a fair amount of funding to study platelet-rich plasma injections and do musculoskeletal ultrasound, like, over a million dollars you listed, but you didn't check that in your research funding.
- Kimberly Harmon: So, my funding is from an ultrasound company, but it's not necessarily to do platelet-rich plasma injections, and it's not grant funding. It's a gift.
- Chris Standaert: But you had two platelet-rich plasma injections studies with over half a million dollars in funding.
- Kimberly Harmon: Right. None of that funds me.
- Chris Standaert: It funds the study, though. It funds...
- Kimberly Harmon: Correct.
- Chris Standaert: ...you to do the research on the platelet-rich plasma injections.
- Kimberly Harmon: Correct.
- Chris Standaert: Yes. OK. OK. Just clarifying. So, do you have... I couldn't talk to you before. So, from our standpoint, what we need is, you know, you're our clinical expert. So, if we have questions about how this is done and what is done, what's the clinical

context of the issues of what is platelet-rich plasma injections, which we haven't talked about, the committee will find your expertise helpful in sort of making it, you know, going through the literature and deciding what to do.

Kimberly Harmon: OK.

Chris Standaert: Yeah. So, they will ask you and, yeah?

Kimberly Harmon: Great.

Chris Standaert: Does anybody have a question for Dr. Harmon before we go any further? No? OK. So, we'll move on to our evidence report. Oh yeah, so our public comment first. So, we had nobody send us a public comment before, and we have nobody who came to sign up for public comment, unless one of the two of you wants to say something? We have time to check the phones.

Josh Morse: It's 12:50.

Chris Standaert: Yes. It's 12:50 exactly. We can check the phone. So, for the people who might be on the phone, this is a meeting of the Washington State Health Technology Clinical Committee. We were discussing autologous blood or platelet-rich plasma injections. So, if anybody on the phone would like to make a public comment, we are in the public comment period of our meeting, and we welcome your comments if you would like to do so. We'll give you a minute to respond. Sounds like no one on the phone is looking to comment to us. OK. We will move on.

David McCulloch: Can I just note that the committee has become technically adept. We no longer need to listen to that charming voice telling us that we're muted and unmuted. This is an advance.

Gregory Brown: It also probably means deaths in the state due to tennis elbow.

Chris Standaert: OK. So, we're going to move onto the evidence vendor, Dr. Hashimoto.

Robin Hashimoto: Hello. So, I'm Robin Hashimoto with Spectrum. You've probably noticed that we have quite a large amount of evidence to go through today. Can you guys hear me OK? And I have a very large number of slides. So, I... depending on how you guys think it would be best, it might be good for you just to ask questions along the way, as we get through kind of each indication, because there is just a lot to get through. So, feel free to stop me.

OK, so I'm just going to give a brief background on the topic. So, platelet-rich plasma injections/autologous blood are blood products that can be injected into a site of injury. They're both obtained from the patient undergoing treatment, and the idea behind their use is that the platelets in both of these contain growth factors that stimulate the healing process. Compared with autologous blood, platelet-rich plasma contains a higher concentration of platelets, and in

the studies included in this report, platelets were concentrated NPRP anywhere from about 2 to 8-fold beyond that of whole blood.

So, there are a number of indications for platelet-rich plasma injections and autologous blood injections. For this report, the interest surrounding their use was for the treatment of tendinopathies, plantar fasciitis, traumatic musculoskeletal injuries, osteoarthritis, and low back pain. So, the conditions for which we found evidence are all listed here, and you'll note that found zero studies on low back pain.

So, the preparation and injection of platelet-rich plasma injections or autologous blood is relatively straightforward. It's done on an outpatient basis. So, anywhere from about nine... these slides are kind of hard to see, but about 9 to 60 mL of blood is collected from the patient. At this point, anticoagulants may be added. In the case of platelet-rich plasma injections, platelets are then concentrated, and this is typically done through centrifugation. There are a number of products available to help assist in this process. That being said, preparation of platelet-rich plasma injections is not standardized and the final concentration of platelets can vary greatly from system to system. So, after the platelet-rich plasma injections is obtained, it may be mixed but isn't always with platelet-activating agents before being injected into the patient. During the injection procedure, the patient might be injected with anesthetic beforehand, and then the injection itself may be visualized using ultrasound in order to ensure correct needle placement. However, imaging use is not standardized. In the case of tendinopathies and local injuries, platelet-rich plasma injections or autologous blood are injected in and around the affected area, and then for osteoarthritis, platelet-rich plasma injections are injected intraarticularly. The volume of the inject in the included studies ranged from 1 to 8 mL for platelet-rich plasma injections and from 1.5 to 5 mL for autologous blood. I also want to point out that for tendinopathies and plantar fasciitis, dry needling or peppering is sometimes done at the time of injection, and this basically involves inserting the needle into the tendon anywhere from 3 to 50 times. It can be done without injecting anything during each insertion or a little bit of the ejecta can be injected at that time, and this process is thought to injure the tendons, induce bleeding, and help stimulate the healing process.

Michael Souter: So, a quick question about the...

Robin Hashimoto: Mm-hmm.

Michael Souter: ...the preparation. Can... from the reading, and I'm getting from what you're saying, I'm getting the impression that there is a fair degree of variability in how this is done. With regards to this separation process, and you said there's equipment that's available, some specific equipment available to actually help do this, how many players are there out there? I mean, is it, like, is there 30 or 40 different manufacturers or is it one or two? I mean, just what degree of variability can we expect to see across the studies that have actually been done of this.

- Chris Standaert: Great question for Dr. Harmon, I imagine, yeah.
- Kimberly Harmon: So, there is a number of these different systems that make it. You can actually make it with a test tube and a syringe very easily by yourself. Most hospital systems won't let you do that. So, they require you to purchase an FDA-approved device. It's not... platelet-rich plasma injections are not FDA approved, but the actual device is. So, there's probably ten major companies that are players in the U.S. right now, and they sell the devices to make the platelet-rich plasma injections, which are one-time uses from somewhere around \$150 to about \$450 a kit.
- Michael Souter: So, that's helpful, but I guess it's, in part I'm kind of looking at, you know, do we have any sense on what the range of company devices employed is in the evidence base that we have to date. Are we talking about just a couple of manufacturers or are we talking about all the manufacturers being represented, you know?
- Kimberly Harmon: In the studies that are represented in this, there is a wide degree of heterogeneity, and that's part of the problem with looking at platelet-rich plasma. You can actually divide it into the two main categories, and one category was referred to as leukocyte poor plasma and typically has a lower platelet count and does not have white blood cells in it, and the other category is what's called leukocyte-rich platelet-rich plasma, and it has a higher platelet count, typically five to nine times, and has white blood cells in it, and there is a great deal of controversy whether you should have white blood cells in it, whether you should have red blood cells in it, what's the optimum platelet concentration, and most of the studies that have been done don't characterize the platelet-rich plasma that they're using in terms of what's actually in it.
- Chris Standaert: I've kind of run into a similar problem looking at the literature. Some of them are proprietary and some are, like, these devices that aren't FDA approved, and some are, and some describe a particular machine or device or approach, like, Endoret or whatever that are distinct, but then I was having trouble, like, am I talking about the same thing, you know?
- Kimberly Harmon: Well, most of them, I mean, most of them are making platelet-rich plasma which just means that the platelets are more than baseline, but there is so much more in blood that you can get.
- Chris Standaert: Right.
- Kimberly Harmon: And what, if anything, the blood is actually causing a healing effect is the issue, and is there anything that's detrimental in there. So, in terms... and the clinical variation, how people do this, how many times they do it, whether they do it under ultrasound guidance, the rehab that they do after it, and then just the clinical variation, and tendinopathy is not tendinopathy is not tendinopathy, and

we don't have any very good way to stage a tendinopathy clinically. So, that's the problem in all tendon studies.

Chris Standaert: Well, that's what you get when you read about it, yeah. Go ahead.

Robin Hashimoto: So, the take home is, there's going to be quite a bit of heterogeneity and variability in the injectate and in the patient. That being said, I think we can say some things.

The key questions are here. They're standard, ask about the comparative efficacy and effectiveness of platelet-rich plasma or autologous blood injections, which I also have up here as ABI. The evidence regarding the safety of these injections, the evidence of differential efficacy or effectiveness, or differential safety of the injections, and then finally we asked about the evidence of cost-effectiveness of these injections.

So, I'm going to go over the inclusion criteria. We included patients with the indications that I've already listed, musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, low back pain, patients with skin wounds, bone fractures, maxillofacial surgery or dental conditions were all excluded from the scope of this systematic review. Intervention of interest is pretty clear. I will note that studies that use the injection in conjunction with other procedures, like surgery, were excluded from the scope. That was done (inaudible). Then, the comparators of interest, we didn't place any restriction on them.

The ones that were identified in the included studies are all listed here. The comparators that were most commonly used were steroid injections for the tendinopathies and some for osteoarthritis, and then hyaluronic acid was used in quite a few studies for osteoarthritis. We also had studies that did just dry needling alone. We have some saline injection studies, dextrose prolotherapy injections, exercise, extracorporeal shockwave therapy, and TENS. We did have one cohort study that compared I think it was platelet-rich plasma to surgery.

David McCulloch: I wouldn't call any of those things conservative therapy, just between you and me.

Robin Hashimoto: OK. So, as I go through this, the majority of... well, it should be all of the five will be labeled with the comparators of interest so we can dig into that. So, the primary outcomes of interest were pain and function, and that's what I'm going to focus on today. We looked at both, in terms of success, pain and function success, and that's just the percentage of patients who are responders or those who met some pre-specified threshold of improvement. We also reported on pain and function outcome measure scores. The majority of studies did only report outcome measure scores. Secondary outcomes of interest are listed here. So, we've got time to recovery, return to normal activities, quality of life, patient satisfaction, recurrence, medication use, and additional procedures. In general, those weren't well reported. I will touch on the evidence on those here. Then, finally, we stratified outcomes by duration of follow-up as short-

term, which was up to and including three months, intermediate term, which was more than three months up to twelve months, and then the last one should be long-term, which is twelve months or longer.

So, regarding study design, the focus was placed on studies with the least potential for bias. For key question one, which asks about the efficacy and effectiveness, we included RCTs, as well as non-randomized cohort studies. Today, my discussion will be focused on the RCTs, because that's where the bulk of the evidence was.

For key question two, we additionally included any case series that were specifically designed to evaluate harms that had at least 100 patients.

For key question three, to evaluate the differential efficacy and safety, we looked for RCTs that stratified results for both the treatment groups by patient characteristics of interest, really any patient characteristics, such as that shown here.

Finally, for key question four, we included formal economic analyses, such as cost-effectiveness, cost utility, cost minimization, or cost benefit analyses.

So, the literature search period ran through the end of November of 2015. We did not place a limit on start date, and as you can see, a total of 64 publications were included, and this includes 54 RCTs, 8 nonrandomized cohort studies, no case series of harms, and no economic evaluations.

So, I'm going to present the results, in terms of the overall quality of evidence with the focus on the highest quality evidence available, and on the primary outcomes of interest. So, the way in which we arrive at the overall strength of evidence is based on our application of grade and AHRQ's recommendations. We grade the overall strength of evidence separately for each critical outcome and to arrive at a quality rating we start with a baseline quality of evidence with RCTs starting at high and nonrandomized studies starting at low. That baseline quality of evidence can then be downgraded based on concerns surrounding risk of bias and the different components of individual study, risk of bias were listed here. The overall quality of evidence could also be downgraded based on inconsistency of results, indirectness, and precision or publication bias. Again, this is done across the studies providing evidence for each outcome at each of the time frames that I had specified.

Then the overall strength or quality of evidence that we arrive at are shown here, and that just, you know, says a quality rating of high means we have high confidence in the estimate of effect being true. Also note for this report, we most commonly downgraded the quality of evidence due to risk of bias resulting from methodological flaws in the studies included, and then also for the risk of imprecision that resulted from small sample sizes. Does anybody have any other questions before we get into the results? OK.

So, the vast majority of the evidence was available for key question one. I'm going to start with the tendinopathies, and as you've heard, there is quite a bit of evidence for tennis elbow. So, we've got three different groups of comparisons for tennis elbow. The first is here. So, these are studies that compared platelet-rich plasma to autologous blood injections. For this comparator, we identified four trials. They range from 28 to 150 patients each and all four of these trials did the injections using a peppering technique in both of the groups and all studies were on patients with more chronic symptoms. The minimum symptom duration was three to six months.

So, these are the results for function, and if I say function, I mean function score. So, if I say function success, that means a percentage of patients who meet some threshold of improvement, same for pain. So, all four trials reported on function outcomes using continuous outcome measures. They are listed here, although I can't see them and you can't see them. The outcome measures here where a patient... the PRTE, patient-related tennis elbow evaluation, the MMCPPIE, or the modified Mayo Clinic performance Index, and then the Liverpool elbow outcome measure. So, overall, we found that pooled scores were significantly better in both the short and intermediate term. So, short-term is up here, intermediate term is here. This is (inaudible) platelet-rich plasma, and that's the (inaudible) autologous blood over here. So, you can see that in the short and intermediate to term, the pooled effect estimates were better with platelet-rich plasma and the strength of the evidence for those conclusions was found to be low. For the long-term, the strength of evidence was found to be insufficient.

David McCulloch: Just asking...

Robin Hashimoto: Yeah.

David McCulloch: ...in... you didn't... in your conservative control groups, you didn't mention NSAIDs or just...

Robin Hashimoto: Right, so...

David McCulloch: ...and these studies are... is that equally in both groups or was that one of the outcomes that must be used?

Robin Hashimoto: ...typically, and I believe it was pretty much across the board, and so those were, you know, co-interventions. So, exercise, PT, pain medication, anything like that was done equally in both groups. OK.

So, the next result for this comparator is pain, and VAS pain scores were reported by three of the trials. In the short-term, there was low quality of evidence, better pain scores with platelet-rich plasma versus autologous blood, based on low quality of evidence. By the intermediate term, the results were slightly favoring platelet-rich plasma but the effect estimate did not reach statistical significance, and this was also of low quality evidence. As for

function, the long-term evidence was insufficient quality to draw firm conclusions.

Chris Standaert: The studies you are quoting, I mean, you're saying low, but I assume... I mean, these are largely non-blinded... so the Raeissadat and the Thanasas, I mean, most of these are non-blind. The blinding is not terribly effective for the patient, particularly.

Robin Hashimoto: Right.

Chris Standaert: Somehow the blind (inaudible)...

Robin Hashimoto: I think one of them, yeah, only one of these was going to, uh-huh.

Chris Standaert: But these are low-quality studies you're looking at with a decent...

Robin Hashimoto: The quality of evidence...

Chris Standaert: ...risk of bias, yeah.

Robin Hashimoto: ...the quality of evidence, yeah, was low. These, let's see, three of these trials were at moderately low risk of bias, and one was at moderately high. Just the fact that there were even a moderately low risk of bias knocks them down a level and then I believe the other reason they got knocked down from moderate to low was likely because of imprecision, just because of the small sample sizes.

Chris Standaert: (inaudible)

Robin Hashimoto: Mm-hmm.

Chris Standaert: Yeah.

Robin Hashimoto: OK.

Carson Odegard: When you mention in those tables and you gave the reason for downgrading...

Robin Hashimoto: Uh-huh.

Carson Odegard: ...so the negative 1, negative 2s are two levels down.

Robin Hashimoto: Yes.

Carson Odegard: One level down.

Robin Hashimoto: Yes.

Carson Odegard: One bubble down.

- Robin Hashimoto: Yes.
- Carson Odegard: OK.
- Robin Hashimoto: Yep.
- Carson Odegard: Thank you.
- Robin Hashimoto: OK. So, this is the last slide for platelet-rich plasma compared with autologous blood and we found insufficient evidence of pain success, no evidence for function success, and then the secondary outcomes are just summarized here. We found no differences between groups in intermediate term surgery and no difference between groups in a composite of function success plus no surgery in the intermediate term.
- So, the next one is platelet-rich plasma versus control, and this is a larger one. So, in this case the comparator treatment was steroid injections in five of the trials, anesthetic injections in two, and dry needling in one, and that trial actually compared platelet-rich plasma plus dry needling to dry needling alone. For this comparator to alleviate any concerns about pooling the different comparators together, the results have been stratified by the different control groups.
- So, five of the trials here did use a peppering technique in both groups, and the trial size, as you can see, ranged from 25 to 240 patients. The minimum symptom duration ranged from one and a half to six months, and the majority of trials, five of them, required failure of previous conservative therapy.
- These are the results for function success. This was assessed using the DASH score. So, for this, we found low quality evidence of no difference between groups in the short and intermediate term, and then for the long-term, the quality of evidence was insufficient, and that was because we had one trial showing better results with platelet-rich plasma and another showing no difference between groups.
- OK. So, this slide shows the results for short-term function scores. So, overall for this one, we found the quality of evidence to be insufficient despite the fact that there were seven RCTs reporting, and this was due not only to risk of bias issues and imprecision of the estimate of effect but, as you can see, there was inconsistency in the direction of effect, and we were unable, by looking at different study characteristics, patient characteristics, etc., to determine what could have caused these issues.
- Carson Odegard: When you have different measures how are you normalizing between measures?
- Robin Hashimoto: For this, we did... well, this one was just the mean difference because they were based on the same scales. If the scales are in different directions, then we just

normalize, you know, subtract 100 or whatever it is, take the end burst. If the outcome measure scales are different, then we just take the standardized mean difference. So, what you're seeing here is the mean difference. This one, we've got the PRTEE DASH scores and the modified measure. So, here we have the results stratified. So, these are... this is... the top group is platelet-rich plasma versus steroid studies. So, you can see some of them show no difference between the two groups. Others favor platelet-rich plasma and then other ones favor steroid. The next group is platelet-rich plasma versus anesthetic. For that, there was still no difference between groups. The overall pooled effect is at the bottom, and it shows no difference between groups.

Gregory Brown: You said that they used the same measure, but there it says various measures.

Robin Hashimoto: Right. This has various measures, but the scales are the same. We determined whether or not it's appropriate to pool different measures just based on the different domains that go into them.

So, then by the intermediate term, we found that function scores were significantly better with platelet-rich plasma than either with steroid, such as the top group here, or anesthetic injections. So, this is the pooled estimate of effect based on low quality of evidence.

Then, we found similar results for the long-term with low quality of evidence, better function scores with platelet-rich plasma than control. So, again, than steroid or anesthetic injections.

The next result for this comparator is pain success. For this, all conclusions were based on low quality of evidence, and while there were no differences between groups in the short-term, in the intermediate term, significantly more platelet-rich plasma than steroid patients achieved pain success, and that was for actually both the intermediate term and the long-term.

The next outcome is short-term pain scores, and for this, we found moderate quality of evidence of no difference between groups, and this was regardless of the control group used... for the control injection used, and then in addition to what is shown here, we also found no difference between groups in Nirschl scores, which evaluates pain during activity. For the intermediate term, there was low quality of evidence but pain scores were significantly better with platelet-rich plasma than with steroid or anesthetic injection, and again, we found similar results for the Nirschl scores.

In the long-term, there was also low quality of evidence of better pain scores with platelet-rich plasma and either steroid or anesthetic ejection.

So, this is the last slide for this comparator. We found very few secondary outcomes reported with one trial reporting worse outcomes with platelet-rich plasma than steroid, in terms of full recovery or the achievement of no symptoms, and another trial reported fewer additional procedures with

platelet-rich plasma in the long-term, and there were a variety of different procedures that went into that estimate.

The next four slides are on autologous blood injections compared with control treatments in patients with tennis elbow. So, for this, we identified three RCTs and three quasi-RCT's. All of them compared autologous blood to steroid injections. One trial also had an extracorporeal shockwave therapy control group. Most of the studies required no previous treatment or had at least patients had not received any steroid injections in the previous three months.

So, the results for function scores are shown here. So, in the short-term, the top group, there was low quality of evidence of better function with autologous blood injections than steroid. For the intermediate and long-term, the quality of evidence was insufficient to draw firm conclusions. For this comparator, we did not find any evidence on function success.

For pain scores, there was low quality of evidence with better results with autologous blood injections in the short-term, and that's based on both the VAS pain scores and the Nirschl scores, which was pain during activity. Then, finally, we found similar results for the intermediate term. Long-term pain scores were not reported, and then results for pain success were of insufficient quality were not reported, and no secondary outcomes were reported.

So, this slide just briefly summarizes the results for tennis elbow. So, for this condition, in general, outcomes were either the same or better with platelet-rich plasma or autologous blood injection versus the control groups. Again, the control groups were mostly steroid, some anesthetic, and then a couple of extracorporeal shockwave.

David McCulloch: I don't want to belabor the point, but these aren't controlled groups. These are comparative groups, and that's... I keep coming back that this is not comparing autologous blood injection or platelet-rich plasma with some innocuous placebo control group. It's to another intervention and obviously, if those other interventions, like steroids or anesthetics, were in fact harmful, then it would... it would look as if the platelet-rich plasma or autologous blood injection was beneficial, but it may be none of these are beneficial, just compared with each other, they're more or less harmful.

Robin Hashimoto: Sure. So, you know, I refer to them as control. I did not refer to them as placebo. They are generally active controls.

David McCulloch: Right.

Robin Hashimoto: I think that's important to note.

David McCulloch: Yeah.

- Robin Hashimoto: So, for platelet-rich plasma compared with autologous blood injection, there was short-term benefit with platelet-rich plasma over autologous blood injection for pain and function based on low strength of evidence, and there was also a benefit for platelet-rich plasma in intermediate term function. For platelet-rich plasma versus steroid, anesthetic, or dry needling, although pain and function scores and success were similar between groups in the short-term, and that was based on insufficient to moderate strength of evidence, by the intermediate term, they were better with platelet-rich plasma, and that was for pain scores, pain success, and function scores, but there was no difference between groups and function success based on low strength of evidence. In the long-term, function scores and pain scores and success were better with platelet-rich plasma. For autologous blood injection versus control, there was better short-term results with autologous blood injection with respect to pain and function scores, and similar results were seen for pain scores in the intermediate term, based on low strength of evidence. So, before we move on, does anybody have any questions on this?
- Joann Elmore: I want to follow up on David's comment in that when the comparator is steroid injection, can you or a committee member or a clinical expert comment on the outcome after a steroid injection? Is it going to make things potentially worse, and if that's the case, are you then comparing platelet-rich plasma to something that will make it worse. So, my question is, and maybe Chris can answer this, the impact of steroid injections here.
- Chris Standaert: We can certainly ask Dr. Harmon. In my... there was a meta-analysis a few years ago showing long-term outcomes of corticosteroids were worse with tennis elbow. Steroids do bad things in the long-run, but you can certainly share your insight on that
- Kimberly Harmon: Typically, steroids are very, very effective in the short-term, but then they wear off and histologically, the tendon is worse off after a steroid injection, but not necessarily in terms of pain and function, which is what's being measured here. So, typically, people don't have worse pain and function scores down the road. It just, the effect just wears off and it doesn't work anymore with the vast majority of tendons with the exception of some studies that show... in lateral epicondylitis it actually does show worse function.
- Chris Standaert: It tapers off at the end yeah.
- Kimberly Harmon: What was that?
- Chris Standaert: The ones I've seen sort of tail... they go back and they regress at the end. So, the steroids may go out to a year, so the steroids have done bad things to people or they... I don't know if the steroids are doing bad things or that the outcome seems worse, but maybe it's that they felt better so early before they're actually healed that they did stop and they beat themselves up and they just wind up not so good a year later. It certainly suggests (inaudible).

- Gregory Brown: Well, certainly in the knee, there is a crystal carrier for the corticosteroid. So, with multiple injections that crystal builds up, and you can actually generate a crystalline arthropathy from the multiple injections, and when I do a total knee replacement, I can see the residual crystals in there for people that have had a number of injections. So, I mean, this is not a joint in a tennis elbow, but in a joint, you can definitely have long-term effects, very deleterious.
- Chris Standaert: I want to comment now, because this is the one we have the most studies on, but I mean, I've read a bunch of these things, and they're all over the place in terms of design, in terms of what they do. They're from all over the world. They are not blinded. They are small. And I didn't... and we've seen a lot of technologies where you take that sort of evidence and when you stratify it by quality of study and you eliminate commercial bias, you score them differently for blinding and no blinding. You score them by quality and size and metric so that you certainly see it for hyaluronic acid, but the demonstration of effect gets smaller and smaller and smaller the better and better you get, and I'm worried about that a bit reading some of this, 'cuz some of these studies, you know, there's a couple you sort of say this (inaudible), but boy there's one, the Harris study there's, like, 25 people, totally no description of what happened to... you know, what they did and it's, you know?
- Robin Hashimoto: Right. Right.
- Chris Standaert: But I assume that's all reflected in your strength of evidence...
- Robin Hashimoto: Yeah.
- Chris Standaert: ...that is where you're reflecting that.
- Robin Hashimoto: Yeah.
- Chris Standaert: Yeah.
- Robin Hashimoto: Yeah.
- Gregory Brown: So, the other thing that I'm struck by and, correct me if I'm wrong, but...
- Robin Hashimoto: Uh-huh.
- Gregory Brown: ...there were no studies comparing to a strong treatment, such as naproxen or ibuprofen or an active anti-inflammatory that may actually be much better.
- Robin Hashimoto: Well, I can't comment on whether it would be much better...
- Gregory Brown: Were there any studies comparing it against NSAIDs?
- Robin Hashimoto: No, but we did not restrict against that.

- Gregory Brown: OK. Thank you.
- Seth Schwartz: I guess the one other question I would have is, it sounds like there is a whole bunch of different things being done and is there any sense of what is currently the standard? I guess we'd have to ask our expert that.
- Kimberly Harmon: So, my practice, my entire practice nearly is tendinopathy, chronic refractory tendinopathy that everybody has tried multiple courses of platelet-rich plasma and NSAIDs and chiropractic and acupuncture and massage and everything else that they can think of, and it hasn't worked. So, I see a really recalcitrant population. So, I think that they're... your standard of care for tendinopathy when it comes in is rest, NSAIDs, ice. If that doesn't work, then physical therapy. If that doesn't work, after that, there is no clear evidence that there's anything that works, and actually, there is not a lot of clear evidence that in these chronic tendinopathies physical therapy, or anything, works.
- Chris Standaert: How do you deal with the challenge of, like, the... in your field, though, like, what are you injecting in people? So, is there... I mean, is there some type of organized effort to come up with an optimal biological sort of solution to be injecting.
- Kimberly Harmon: So, most people are looking at animal studies. The problem with this is, that most of the... most of... there's not a lot of money to do research in this, and this is incredibly expensive research to do.
- Chris Standaert: Yeah.
- Kimberly Harmon: So, there's just not a lot of money to do research in it. Most of the manufacturers of the devices are not making a ton of money from this, and they don't see a huge upside in it. So, they're not putting in the clinical trials. There is one that is in knee arthritis right now, actually, but other than that. So, the other problem is that, you know, I can't have a coulter counter in my office, because then that... so when I make platelet-rich plasma from somebody, it's going to be different depending on what their baseline level of whatever is, and I can't do... because then it takes me up into a different level of lab.
- Chris Standaert: Because then you're a lab.
- Kimberly Harmon: Then I'm a lab. So, unless it's in a study and I have a research study, you know, clinically I can't even get a good idea of that.
- Chris Standaert: There are multiple constraints between that and between coding and billing. It's multiple constraints on all that standardizing and doing all that, huh? Yeah.
- Kimberly Harmon: So, outside of a very, very large funder, it's not easy to do.
- Seth Schwartz: That's a different level than what I'm trying to understand. I'm just trying to understand who we're even talking about. So, like, in terms of the entry criteria

to these studies, who are these people? I mean, what... have they failed medical therapy? What's... are we even talking apples to apples? I'm just trying to understand who we're offering these injections to.

Robin Hashimoto: It varied by... it varied by study and by comparator.

Seth Schwartz: So, it was just so heterogeneous, you can't even generalize that?

Robin Hashimoto: Yes. That's correct.

Seth Schwartz: OK.

Robin Hashimoto: Some of them specifically required patients to have failed other treatments. Some of them said that you couldn't. Some of them said you couldn't have had any steroid injections in the past x-months. It varied quite a bit.

Chris Standaert: The duration varied a bit, too, three months. I saw some that were four weeks, some that were three months, some that were greater than.

Robin Hashimoto: Right. And that's the minimum, yeah.

Chris Standaert: Yeah.

Robin Hashimoto: That's the minimum duration of pain.

Chris Standaert: Yeah.

Robin Hashimoto: Mm-hmm. And a lot of the studies did not report mean duration of pain. So, it's hard to get a handle on it.

Joann Elmore: Seth is stuck on the who. I'm stuck on the what.

Robin Hashimoto: Mm-hmm.

Joann Elmore: Like, what is this platelet-rich plasma? There are few FDA-approved devices that make it. We don't know what goes into some of them. There is no standardization. We heard from our expert and from you that some of the publications don't even explain what goes into them.

Robin Hashimoto: Right.

Joann Elmore: There is variable amounts of platelets in them.

Robin Hashimoto: Correct

Joann Elmore: Some use lidocaine, which is thought to have an inhibitory effect.

Robin Hashimoto: Mm-hmm.

- Joann Elmore: There can be leukocyte poor, leukocyte rich, who knows about the activating agents. They can be plus or minus use of imaging.
- Robin Hashimoto: Mm-hmm.
- Joann Elmore: The volume can run from 1 to 5 mL, plus or minus dry needling.
- Robin Hashimoto: Yep.
- Joann Elmore: So, in other words, as I contemplate sort of listening to the rest of the presentations, I'm still stuck with what is it, because we vote to cover or cover with conditions, but I'm not certain what it is because of the vast array and sometimes lack of description of what is actually being done in the published studies. Is anybody else having the same challenge I'm having?
- Robin Hashimoto: Well, from my understanding, and the clinical expert can speak to this, I think that might be reflective of actual clinical practice.
- Joann Elmore: OK. Great.
- David McCulloch: Yes.
- Kimberly Harmon: Right. It is, and the question really is, is injecting anything helpful in the tendinopathy. In terms of platelet-rich plasma, it is loosely defined as an increase in baseline from platelets. So, anything that has an increased baseline of platelets, and whether that's better than blood or serum alone.
- Gregory Brown: There is an unspecified group of growth factors and an unspecified concentration.
- Michelle Simon: Given that, if we just look visually at the data for this, tennis elbow function, these slides, I mean, there is a... there is something there, it seems, at least visually looking at the scatter plots. They do kind of line up. So, it'd be nice to know what it was.
- Kimberly Harmon: You know, I'm in the business of taking care of patients and not necessarily... and the people I see have no options except for surgery and sometimes that's not an option, and some of them get better with this, and if that's because they paid lot of money, because it's cash right now, they'd probably pay it twice over because their life is significantly improved from it, but not everybody. Clearly, some people do not respond to it and for me, the challenge is picking out the person who is going to, and as of yet, and is it because of their blood type, the number of platelets they have, or some other unknown factor, but there are clearly people with no options that respond to this, and I think that that is reflected in the fact that the studies are so heterogeneous and still when you take all this heterogeneity, which is likely to regress to the mean in anything like that, there is still a trend towards effectiveness.

- Chris Standaert: I mean, I see that. Michelle, I see the same thing, but when you read them, it's like blinding, very, very few is the patient actually blinded, you know? So, it's not... they are structurally, as a collection when you read this literature, it is structurally unimpressive, in terms of how their study design and what they do and how they blind and how they assess, and how they define their patient population and whose... this whole, like, internal/external (inaudible) thing, I was wondering the same thing. Well, who are, like, I hurt when I go do this and that's sort of what they... which may be how you diagnose it. It's tricky. So, I was trying to sort out, is there something maybe there, but I don't know.
- Kimberly Harmon: There are some that are blinded.
- Chris Standaert: There are some, yeah. There are.
- Robin Hashimoto: Right, but it, you know, I don't think any of the studies met all of the criteria for a good quality RCT and again, that's reflected in the overall strength of evidence, you know. It knocks everybody down a level just to start based on these issues.
- Gregory Brown: So, could I ask our expert a different question? So, you said that most of this is being done in animal studies. Are there animal models for tendinopathy, as opposed to an acute injury?
- Kimberly Harmon: So, that's part of the problem of doing any study in tendinopathy is, there are very few good animal models, and all tendinopathy is probably not the same. So, there are several animal models, but they all have drawbacks and advantages. You can inject collagenase into a tendon, and that will give it a tendinopathy-like appearance. You can... there's a model where you put rabbits into a cake machine, because there's no other animals other than racehorses that don't stop when something hurts.
- Gregory Brown: And do those animal studies actually show any healing histologically?
- Kimberly Harmon: Yes. And there is in vitro studies, as well, and there is good, as you know, there's good models of osteoarthritis in animals. So, histologically there are some. They are varied, but there are more that show effect than don't.
- Tony Yen: Do we understand why is it that there's no benefit of platelet-rich plasma or autologous blood injection, because I'm trying to think about platelet-rich plasma as, like, a drug where some sort of dose response curve and maybe I'm just making a very simplistic assumption that platelet-rich plasma would have 'greater' concentrate over growth factors, but yet, at least with the initial data with the tennis elbow, I don't see a significant difference in terms of pain or function.
- Kimberly Harmon: Right. You know, I think the... so, in our practice, we do both autologous blood and platelet-rich plasma, and we keep validating the outcome measures, and we

see a benefit to platelet-rich plasma versus the autologous blood. However, there... it may depend... platelets are like little packets of growth factors, right, and you've got more of them if you concentrate it, but you also then potentially concentrate white blood cells. There is potentially a tailing off effect. There's some research that shows if you're at three-times the level of platelets you're better off than if you're ten. So, there's a sweet spot in terms of that, and so we don't really know. When I first got into this, I did only autologous blood because I thought if blood worked, why would anybody go to the expense and the hassle of creating platelet-rich plasma. I moved on to platelet-rich plasma personally because people are, like, can you please do it, so I don't have to fly to San Francisco. So, really, because of patient demand initially, I'm, like, you know what? This does work in terms of our patient outcomes. Again, there is a strong placebo effect paying \$900 for something, and I don't deny that, but I've been doing this for, autologous blood and platelet-rich plasma, for nine years and my clinical impression is that platelet-rich plasma works in some people when nothing else doesn't, and it works a little bit better than blood, I'd say 10 to 15% is what our numbers show.

Robin Hashimoto: OK. So, that concludes the tennis elbow portion of this report.

Chris Standaert: One condition down.

Robin Hashimoto: This is good. So, the next condition is Achilles tendinopathy. There is quite a lot. There's not nearly as much evidence here. So, for this, these next set of slides compare platelet-rich plasma to either saline injection in one trial or exercise in the other. Then, again, I'll point out that if we did see differences between the control groups in terms of the effect, and we did separate the results out. These trials were small. We've got 20 to 54 patients per trial, the minimum duration of symptoms was two to three months.

So, for function scores, so here we have the trials grouped in terms of short-term, intermediate term, and long-term, and as you can see there was low to moderate quality evidence of no difference between groups for all of those ten points.

We found no evidence for any of the other primary outcomes and all of the secondary outcomes that were reported are listed here with a comparator group listed, and in all cases there were no differences between groups. So, for Achilles tendinopathy, platelet-rich plasma appears to have similar effect to exercise or saline injections and function.

The next two slides are, again, on Achilles tendinopathy, and these compare autologous blood injections to either dry needling or to exercise, and that trial actually compared autologous blood injections plus exercise to exercise alone. These, again, were small trials. The minimum symptom duration was three months. The only primary outcome reported here was function. However, due to limitation and sample size, the quality of evidence was insufficient to draw conclusions. There was no evidence on any of the other primary outcomes. The

only two secondary outcomes that were reported were recovery and return to sport in the intermediate term, and there were no differences between groups.

The next condition is patellar tendinopathy. These slides compare and provide evidence from the two trials that compared platelet-rich plasma to either extracorporeal shockwave therapy or dry needling, and that trial compared platelet-rich plasma plus dry needling to dry needling alone.

Here are the function scores. Both trials reported no difference between groups and short-term function scores, and the overall quality of evidence for that was considered to be low. In the intermediate term, you can see that there are differing results between the two control groups here. So, we did grade the evidence for each separately, but because of study limitations and very small sample size, the quality of evidence for each was considered to be insufficient. The evidence for long-term function scores was also considered to be insufficient.

These are the results for pain. They were very similar to what we found for function with low quality of evidence showing no difference between groups in the short-term and insufficient quality of evidence for the intermediate and long-term. There was no evidence for function success or pain success, and secondary outcomes reported were no difference in short or intermediate term health-related quality of life for platelet-rich plasma versus extracorporeal shockwave therapy, and there were mixed results for pain during sports from one RCT comparing platelet-rich plasma to dry needling with no difference between groups in the short and intermediate term, but better outcomes in the long-term.

So, for rotator cuff tendinosis, two trials were included that compared platelet-rich plasma to either saline injection or dry needling. The trials were small, both included patients with more chronic symptoms. So, for this we found moderate quality of evidence of better function scores, moderate might be an overstatement in looking at this again, with platelet-rich plasma in both the short and intermediate term, but by the long-term, there was no difference between groups based on low quality of evidence. For pain scores, we found insufficient quality of evidence and no other primary outcomes were reported. For secondary outcomes, we found no difference between groups in any of the outcomes reported.

OK. So, for the rest of the tendinopathies, we found some evidence of better results with platelet-rich plasma in the short and intermediate term for rotator cuff tendinosis, but no difference by the long-term, and then for Achilles and patellar tendinopathy, we did not find any differences between groups.

Are there any questions?

Gregory Brown:

So, when we get into the inclusion criteria on the tendinopathy...

- Robin Hashimoto: Mm-hmm.
- Gregory Brown; I'm presuming that's all by MRI or?
- Robin Hashimoto: Oh, gosh, I'd honestly have to go back and look.
- Kimberly Harmon: The inclusion criteria for most of them were, like, for patellar tendinosis would just be pain at the insertion of the patellar tendon along with pain with resisted use. Often the ones... patellar tendinosis and Achilles tendinosis would use ultrasound. On the rotator cuff tendinosis, those were, I believe, MRI confirmed.
- Robin Hashimoto: Thank you. So, the next condition is plantar fasciitis. So, we found five trials that compared platelet-rich plasma to the different comparator treatments. So, those were steroid injections in three trials, prolotherapy in one, and extracorporeal shockwave therapy or conservative care in one. The trials were, again, small, and the minimum duration of symptoms ranged from four all the way up to 12 months. All of the studies that were included here were all moderately high risk of bias.
- So, the results for function scores are shown here. So, you can see in the short and intermediate term, there was low quality of evidence of no difference between groups, and we were not able to do any pooling here due to differences and data reporting. By the long-term, function scores were better with platelet-rich plasma, and that was compared to steroid injections.
- For pain in the short, intermediate, and long-term, we found low strength of evidence, low quality of evidence of no difference between any other groups. There was insufficient quality of evidence for long-term function success and no evidence for the other primary outcomes. The secondary outcomes are shown here. We had no difference between groups in short and intermediate term symptoms, but better results with platelet-rich plasma than steroids in the long-term and no difference between platelet-rich plasma and prolotherapy in the short and intermediate term in disability.
- The next set of slides compare autologous blood injection to either steroid injections or anesthetic injections plus dry needling. So, there were three trials. All of them did use a steroid control group and then two of them had additional groups. The minimum symptom duration was six months in two of the trials that reported the information.
- So, this slide shows short-term pain results, and we found low quality of evidence of better pain results with autologous blood injection compared with steroid, but the evidence for autologous blood injection versus anesthetic was of insufficient quality to draw firm conclusions.
- In the intermediate term, there was low quality of evidence of no difference between autologous blood injection and either steroid or local anesthetic plus

dry needling, though the results for autologous blood versus steroid did border on statistical significance in favor of autologous blood injections.

The only other primary outcome that was reported was intermediate term function for which there was insufficient quality of evidence of no difference between groups. There was no evidence on any of the other primary outcomes. Secondary outcomes reported included symptoms with no difference between groups in the intermediate term and repeat injections, which were the same or worse with autologous blood injections.

So, overall, for plantar fasciitis, most of the outcomes were either the same with platelet-rich plasma or autologous blood versus the different comparator groups. So, for platelet-rich plasma, short and intermediate term pain and function, results were similar between the groups, although long-term function scores were better with platelet-rich plasma than steroid injections, and this was all based on low strength of evidence. For autologous blood, short-term pain was worse with autologous blood injections than steroids, though intermediate term pain was similar between the groups.

So, next we have acute injuries. We will start with acute muscle injuries. For this, we had four trials. Three of them included patients with an injury to the hamstring muscle, and then the fourth trial included patients with an injury to either the thigh, foot, ankle, or shoulder. While patients were treated within days of the injury, the comparator group was conservative care in three trials and saline injection in one. So, these trials were a bit different in that two of them were specifically on male professional athletes and another was comprised primarily of athletes playing at the national level. So, for these, as you can see, there was low quality of evidence of no difference between groups and intermediate term pain and function.

Chris Standaert: Just a quick question.

Robin Hashimoto: Yeah.

Chris Standaert: So, the biological rationale on tendons maybe (inaudible) on this, but in acute muscle injury, don't you have lots of blood and activated platelets and all sorts of stuff when you tear a muscle? So, you go inject blood back into it?

Kimberly Harmon: Typically, people don't do blood. They'll do platelet-rich plasma and that's a very good question. So, some people will do it three days after the injuries to try and get that acute inflammatory flare that you get in the first 48 hours after injury. The other thing is, is that there's some thought that in animal models it's not actually the platelets, but it's the insulin like growth factor 1, which has been shown to encourage satellite cells to turn into myotubules. So, there's a lot of interesting theories about how this may work, and I do this all the time, and I'm not... it is not my clinical impression that this is... if my kid tore their hamstring, I would not pay a bunch of money to have them have platelet-rich plasma in it.

- Chris Standaert: Right.
- Kimberly Harmon: If they had chronic tendon injury, I would.
- Chris Standaert: Thank you.
- Robin Hashimoto: And again, these are studies of really high-level athletes that are probably doing anything they can to get back on the field.
- Kimberly Harmon: And the criteria to return to play, which... when somebody is being highly paid, is highly motivated, so that's not great criteria for a return to play in that subgroup.
- Robin Hashimoto: Right.
- Kimberly Harmon: Muscle injury studies are really, really hard because they're self-limited injuries, and it's difficult to tell at the outset whether it's going to be a one weekend treat or a 12- weekend treat. So, to do a standardized injury in a human is a difficult thing to do.
- Chris Standaert: So, we're talking about animals actually stop running when they hurt.
- Kimberly Harmon: Yeah, you can...
- Chris Standaert: They're quite different than humans. Yeah.
- Robin Hashimoto: OK. So, for finishing with the acute muscle injuries, the evidence for short-term pain and function was insufficient, and no other primary outcomes were reported. The secondary outcomes are listed here. There were mixed results in return to sports, and no difference between groups in the other outcomes, which were recovery, symptoms, and reinjury.
- The rest of the injuries are summarized here. The evidence was very limited. There was one trial, or a quasi-RCT for each, and in general, primary outcomes were either of insufficient quality to draw conclusions or were not reported.
- So, we have arrived at osteoarthritis. So, there were three different types of osteoarthritis that were identified. One was knee, and that's where the bulk of the evidence is, and then we also found some evidence for hip and temporomandibular osteoarthritis.
- So, the next 12 slides are on knee osteoarthritis and the comparison here is platelet-rich plasma to hyaluronic acid injections. There were six trials that met the inclusions criteria, and they enrolled between 96 and 192 patients each. These patients had had symptoms for at least three to six months. We tried to get a handle on disease severity based on the information that was provided and we believe... or it appeared that the disease severity was mild to moderate

based on radiographic classification only; however, that doesn't necessarily correlate with symptoms. Based on the baseline symptom severity, baseline outcome measures reported, we looked and looked but had a difficult time making generalizations based on the information provided. As you will see, there is quite a bit of heterogeneity in many of the results for this comparison, particularly for the intermediate term and we did examine potential sources of heterogeneity, but the cause was not clear.

Short-term function is shown here. Short-term function success was not reported, and the quality of evidence for short-term function scores was moderate, of no difference between groups. The evidence for that, the four spots are shown here. So, you can see that all four trials reported the different outcome measure. So, two reported the, I don't know how to say that, Laquesne Index, and then the other two reported either WOMAC total or IKDC (International Knee something Classification). As you can see, three out of the four clearly found no difference between groups. One, I believe, yes, there is a... did find significantly better results with platelet-rich plasma. That was actually the lowest quality trial of the four and patients were not blinded. So, based on all of this, again, we concluded there was no difference between groups in short-term function scores.

So, then for the intermediate term function success, it was not clear whether function success was more common following platelet-rich plasma versus hyaluronic acid injections, and this was based on low quality evidence. So, these were both good trials. There was no downgrading for risk of bias, but we did downgrade for inconsistency of results and imprecision. So, you can see one trial reported that significantly more patients that received platelet-rich plasma injections met the function success criteria. In this case, it was patients that were OMERACT-OSARI responders, and the other trial showed no difference between groups.

- Chris Standaert: You said you didn't downgrade. Both those studies, Sanchez and Vaquerizo, are on this PRGF Endoret, which is a proprietary company, and they're funded by the company, the studies were? I've looked it up. I tried finding Endoret on line, and it wasn't FDA approved in the U.S., for something else, but nothing for, like, an orthopedic thing.
- Robin Hashimoto: OK.
- Chris Standaert: Those two studies were...
- Robin Hashimoto: Interesting.
- Chris Standaert: ...similar groups.
- Robin Hashimoto: OK.

- Chris Standaert: Do you know what PRGF Endoret is, in particular? These two... are you familiar with these two studies?
- Kimberly Harmon: Yeah. I'm familiar with those studies. The platelet-rich and growth factors, it's another sort of... it's similar to a leukocyte rich platelet-rich plasma.
- Chris Standaert: So, they own proprietary (inaudible)...
- Kimberly Harmon: It's what they call it. So, the other thing is platelet-rich plasma, particularly depending on where you go in the world is called different things.
- Chris Standaert: Right.
- Kimberly Harmon: You can look at the method section and sort of tell what they're actually making and what they appear to be making in these, if I'm remembering correctly, is leukocyte rich growth factor, which is using a buffy -coat system.
- Chris Standaert: Because they have, like, their own machine and they have a whole patented thing they're using here to...
- Robin Hashimoto: These two are actually a...
- Chris Standaert: ...to extract what you're after, yeah.
- Robin Hashimoto: ...leukocyte poor, but yeah.
- Kimberly Harmon: Leukocyte poor.
- Chris Standaert: OK.
- Robin Hashimoto: Yeah, both of them were conducted in Spain. One of them had research institute funding, and the other one the funding wasn't reported. Actually, the risk of bias in one was low and the other one was moderately-low.
- OK. So, anyways, it wasn't clear. For intermediate term function scores, there was moderate quality of evidence that overall function scores were significantly better with platelet-rich plasma than hyaluronic acid injections, although you can obviously see there was quite a bit of heterogeneity in the individual estimates and in the pooled estimate with an I-squared of 94%. Again, we tried to account for this heterogeneity and couldn't figure out what was causing it.
- Chris Standaert: The Fillardo study was a blinded one, so that's the big main... I mean, Cerza wasn't blinded. That's the one on the top. Fillardo, the one that's dead middle, was a blinded. They all... they drew blood from everybody. They did the whole thing for everybody. That's the only one I saw that did that.
- Robin Hashimoto: Mm-hmm.

Chris Standaert: So, everybody (inaudible) in patients. It was actually double-blinded.

Robin Hashimoto: Yeah. OK. The next slide is long-term function, and there was low strength of evidence. It suggested that both function success and function scores were significantly better with platelet-rich plasma than hyaluronic acid.

Now, moving from function to pain, pain success was not reported for the short-term. Short-term pain, there was low quality of evidence of no difference between groups. For pain success in the intermediate term, although for this one we concluded there was moderate quality of evidence of significantly greater improvement with platelet-rich plasma versus hyaluronic acid, and I do want to point out that this one was a bit unusual in that the pooled effect estimate shows no statistical difference between groups, as you can see here. It's overlapping on that line of no effect; however, both of the individual trials did show a significant effect. So, we talked about it and made the judgment and we thought overall, the results showed that there was greater improvement with platelet-rich plasma, but that's the actual evidence.

So, for intermediate term pain, there was moderate quality of evidence of no difference between groups. In the long-term, we found low quality evidence that pain success was significantly more likely following platelet-rich plasma than hyaluronic acid injections. Then, for long-term pain scores, there was low quality of evidence of no difference between groups. So, you can see, again, as I'm going through this, there is quite a bit of variability in the individual study conclusions.

For this comparison, there were relatively few secondary outcomes reported. Health-related quality of life was better with platelet-rich plasma in the long-term and possibly intermediate term, but otherwise, there were no differences between groups and in the other secondary outcomes reported.

So, we're still on the knee. This comparison is for platelet-rich plasma to saline injections. There were two trials that made this comparison. In general, it appeared that the osteoarthritis in the majority of the patients was still in the earlier stages, although it is hard to stay definitely, and as you can see here we found low quality of evidence of better function scores with platelet-rich plasma than saline injections and no data were reported for long-term function or for function success.

We also found low quality of evidence of better pain scores with platelet-rich plasma in the short and intermediate term. As for function, no data were reported for long-term pain scores or pain success, and for the secondary outcomes, both patient satisfaction and health-related quality of life were better with platelet-rich plasma in the intermediate term.

We had evidence for a couple of other comparators for the knee, but the quality for each was of insufficient quality to draw from conclusions.

The next two slides are on hip osteoarthritis. We have platelet-rich plasma compared with hyaluronic acid injections. For this, we identified one trial, and this trial included patients with unilateral hip osteoarthritis and symptoms that had been going on for anywhere from six to 24 months. For function scores, we found low quality of evidence of no difference between the groups at any time point.

We also found low quality of evidence of no difference between groups in pain scores. No other primary outcome was reported, and the only secondary outcome reported was medication use and at all three time points, there were no differences between groups.

We found one trial that compared platelet-rich plasma to hyaluronic acid injections in patients with temporomandibular joint osteoarthritis. For this, the quality of evidence was insufficient to draw conclusions.

So, the summaries for knee and hip osteoarthritis are here. Of those, only the knee had evidence of benefit with platelet-rich plasma compared with the control group. So, for platelet-rich plasma versus hyaluronic acid, while there were no short-term differences between groups in pain or function, by the intermediate term, function scores were better, and pain success was more common with platelet-rich plasma. However, there were no differences in intermediate term function success or pain scores. In the long-term, pain and function success were more common, and function success was better with platelet-rich plasma, but there were no differences between groups in pain scores. There was evidence of benefit with platelet-rich plasma over saline in short and intermediate term pain and function, and for the hip there were no differences between platelet-rich plasma and hyaluronic acid injections in short, intermediate, or long-term function or pain scores.

OK. Now, we have arrived at key question two, harms and complications. For this, we included all evidence of harms, complications, adverse events from all of the comparative studies. We did not identify any case series that met the inclusion criteria. Again, those were case series of at least 100 patients that were specifically designed to evaluate harms. We found low to insufficient quality of evidence that... across all included studies. There was no evidence of any serious harms in either the intervention or any of the comparator groups. Regarding non-serious adverse events, there was low to insufficient quality of evidence that in general these events were very infrequent with the exception of injection site pain, which appeared to pain both during and in the short-term after the injection, and that was more common and more severe with platelet-rich plasma or autologous blood injections than the other injections. The other non-serious adverse events that were reported, and again were very infrequent, included reduced elbow movement, skin atrophy, skin reddening, minor rash, loss of pigmentation, swelling, and nausea to give you an idea.

Key question three asked about the differential efficacy and safety. We found no evidence for the majority of conditions and for knee osteoarthritis, we found

insufficient quality of evidence from two studies, one compared platelet-rich plasma to hyaluronic acid and the other platelet-rich plasma to saline, but again, the quality of evidence was insufficient to draw conclusions.

There was no evidence on cost-effectiveness. So, there were no formal cost-effectiveness/cost utility analyses, etc., that met our inclusion criteria, and those are just the summaries for the last key questions.

Chris Standaert: Questions for Dr. Hashimoto? She will certainly be available when we make our... have our discussion.

Robin Hashimoto: Yep.

Chris Standaert: No? You can take five there.

Robin Hashimoto: Sounds good.

Chris Standaert: Thank you. Alright. I'm not sure you were glad you had extra, but I'm glad you had extra time. So, we can take a break. We'll come back at 2:25, on with our schedule. OK.

We have time for discussion, questions. We still have Dr. Harmon. We still have Dr. Hashimoto to help us. Then, eventually we will get to our coverage tool, which again, we're looking for the best outcomes and value for the state and the patient, and we focus on safety, effectiveness, and value in health outcomes. So, Spectrum went through a lot of studies and gave us a lot of subcategorizations of various things, and there are multiple ways we could tackle this. I would be curious on people's sort of general sort of gestalt or where they're thinking or what they need to know or what they're wondering rather than diving into one particular thing.

Gregory Brown: I'm not wondering anything. I would like to make an observation that I made earlier, that this is a class industry... every one of these is a classic industry design where you pick your weakest comparator as your control or sham or saline or hyaluronic acid, and that's what you compare against. None of the studies compared against anything that's effective, except for the few that may have been corticosteroid, which, again, in certain applications is arguable whether it's effective or harmful. So, given that, I didn't see one application in one study for a large group of patients of any effectiveness.

Kimberly Harmon: Can I make a comment regarding that?

Gregory Brown: Yep.

Kimberly Harmon: In tendinopathy, the real control that you're going to want is somebody that is not doing anything at all, and then it becomes very difficult to blind that person, you know, to the fact that they're not getting an injection and they're exercising when somebody else isn't. So, really doing well-designed studies is difficult

because injecting saline into a tendon, you're sticking a needle in the tendon and you're disrupting the tendon fibrils and all that sort of stuff. The same thing with osteoarthritis. Saline injection is not necessarily a placebo. There is potentially an effect to that. So, the real control is doing nothing or a sham injection or something.

Gregory Brown: I would actually disagree. I would say the real control is a true double-blind study with platelet-rich plasma and naproxen where you give one active oral and placebo oral and active platelet-rich plasma and saline or, you know, red-colored whatever it needs to look like blood or what. That would be the true, to me, RCT that would show a difference.

Kimberly Harmon: I respectfully disagree. My clinic is full of people who NSAIDs and over-the-counter medications no longer work.

Gregory Brown: Right. No. No. I'm not saying that there isn't a subset of people that maybe nothing works on, but that doesn't mean that it's effective and certainly not on everybody. I have the exact opposite. I don't see people that have had multiple failures with tendinopathy. I see them when they first come in with knee pain. The flip side of that is, if we did MRIs of 100 people, I would guess the vast majority of them had some sort of tendinopathy with no pain. So, it's correlating that tendinopathy with their symptoms all the time. So, your practice is so different of the patient you see. As you say, you see multiple failed tendinopathies.

Kimberly Harmon: And the problem is, is that there's no relationship to pain to the tendinopathy spectrum and what we treat is we treat the pain, not the tendinopathic. Two-thirds of tendons that ruptured have been nonpainful before they rupture. So, clearly, the structure, function, and health of a tendon is different than how much it hurts.

Gregory Brown: Right.

Kimberly Harmon: Clearly, all of that is a problem... part of our problem as a committee is do we see that in the evidence. Does the evidence draw this out for us? You look at our inclusion criteria, are there studies of patients who have been through a decent exercise program and physical therapy and appropriate NSAIDs and time and appropriate activity restriction and splinting or whatever else they do. Is that really just... can they, you know, my own personal thing is this issue of sort of what are we putting and into whom? Like, who is this? Right? And do we see that in the evidence to help us to get this out.

Kimberly Harmon: In the vast majority of the studies that were presented, people failed all conservative treatment. So, one of the exceptions to that was the Devoss study in Achilles where they had three-months of pain. They hadn't done an eccentric exercise program, and anything was likely to work with them, and it did, both the saline and the platelet-rich plasma have both improved the same.

- Chris Standaert: I mean, I can certainly say the studies I read largely said they failed conservative therapy. That's literally what they said. So, I have no idea what that means. I just have no idea. I don't know what that... and some said they had to have one of three things, maybe an NSAID, maybe rest, maybe steroid injection, but it didn't tell you who had what. There's all that... anyway. So, are there general opinions where people lie or what they're curious about? There's a lot of data. There's a lot of stuff there. So people could have things on their mind.
- Tony Yen: What I'm curious about is, is this really truly, at least with the evidence that I can see there's... I don't see a superiority of platelet-rich plasma over autologous blood injection. I do appreciate our clinical expert's experience with maybe having better results with platelet-rich plasma, but at least with the evidence that I'm seeing in front of me, that raises a lot of questions for me. Then...
- Kimberly Harmon: I would agree with that. Autologous blood is not covered right now.
- Tony Yen: Right.
- Chris Standaert: None of this is covered right now.
- Kimberly Harmon: And I would agree that there, that the evidence is not clear. That that's my clinical impression that it works a little bit better.
- Chris Standaert: The issue we have with it is, we're driven by evidence. We're driven by what we have from the vendor and what our studies say and what they show is what we're driven by.
- Kimberly Harmon: Right, but if you're saying does platelet-rich plasma work better than autologous blood injection and neither one is covered and both work, because you don't know that either one works or doesn't work if you're comparing them to each other. As Dr. Brown has pointed out, there are very few that actually compare it to anything that is...
- Chris Standaert: Right. So, the trouble, but the... so, this is not the debate necessarily, but the thing the committee has to then determine is... so it doesn't show that it works better than something else... better than something else that would be done or is the proof of benefit there in some way. Showing everything works doesn't really help you in some ways, but that's up to the committee, so.
- Tony Yen: My question is really what are we really injecting that's really being helpful, and I think you... you teased it out pretty well that it's... at least for me, personally, it's not very clear that it is... is it the... and you know, I know there are comparators against saline. There are comparators against steroids, but like I said earlier with my comments is that, well, you know, with literature, it should show us, like, if there's some benefit to, you know, some component of platelet-rich plasma, and maybe it's not really platelet-rich plasma that's really beneficial. Maybe whole blood is just as beneficial. I just don't see... I have a

very poor understanding of, like, what is it that we're injecting that actually confers benefit. It feels a little bit, like, very murky to me right now.

Michelle Simon: We don't really know that. What we see is that between those two, there's some natural substance, perhaps, in the human-derived product, putting it back into the human body, that confers some benefit over saline or hyaluronic acid or doing nothing. So, and we don't know.

Seth Schwartz: Maybe deal with the easier side first, which is the aspects of this for which there is clearly no evidence, and I think most of us are probably pretty comfortable saying, we're not going to cover it for plantar fasciitis and all that kind of other stuff that really... there was nothing there. I think we might want to focus our discussions on the two areas where there was some element of benefit. It seems like the tennis elbow situation we can argue whether it's actually doing anything or what it's actually doing, but we're seeing a number of studies that they rated as moderate to low but there's something there that consistently show an advantage, which is better than we usually get. So, I... and I think... I'm not surprised by what Greg says that in the short-term there's not a big difference, because it seems that if you're putting something in there and the histopathology is that it somehow encourages healing, that's not something you're necessarily going to appreciate in four weeks, but over six months to a year, you might see a difference, and that's kind of what we're seeing. So, empirically what the data is saying makes sense with what the in view of the concept of what's happening is occurring. I don't know if that's really happening or not, but from a hypothesis testing perspective it makes sense to me.

Chris Standaert: Well, let's go up from there, then. So, lateral epicondylitis, there are a fair number of studies. Strength of evidence was not terribly high for anything.

Carson Odegard: I have a question for our expert. Do you... in your practice, do you use platelet-rich plasma on other tendons, as well?

Kimberly Harmon: Yeah, I use it on any tendon, actually.

Carson Odegard: Any tendon.

Kimberly Harmon: Any tendinopathic tendon.

Carson Odegard: OK. Then my question is, is just from your understanding of the anatomy, why it would work on some tendons and not on others?

Kimberly Harmon: So, we follow our patients with validated outcome measures, and my average patient is 49 years old and has had symptoms for 34 months, 3 years has tried everything, nothing's worked. We don't see a difference in the location in our outcomes, other than plantar fascia, which see an improved outcome on, and the evidence that was presented today does not support that. That's what I see in my practice. I think the real key is making a good diagnosis versus, you know,

- the direction doing something on a tendinopathic tendon rather than just... platelet-rich plasma is not magic, so.
- Carson Odegard: Yeah. That's another question that I have, because some of those tendons have underlying bursas.
- Kimberly Harmon: Mm-hmm. So, the vast majority of things that we have diagnosed bursitis as for the last 20 years, there's no bursitis when we look with ultrasound, there's no bursa. So, most... like gluteal... like greater trochanteric bursitis, I've been looking at greater trochanters in a lot of different people for the last 15 years... 10 years with ultrasound, and I've seen two clear greater trochanteric bursas. It's mostly gluteal meatus tendinopathy.
- Carson Odegard: Yeah. Right.
- Chris Standaert: Can we go back to the tennis elbow question for the committee? So, as Seth said, you see some benefit that he thinks is consistent or at least prominent enough to note. Other people agree, disagree, have other perspectives?
- Michelle Simon: I agree. I think if you look at the scatterplots, it supports some effect in the intermediate to long-term. It's kind of summarized on that slide 33, I guess, for tennis elbow anyway.
- Chris Standaert: I struggle some with this quality issue. Any idea... there are scatterplots in there, and they have a summation of quality of evidence, but they're really not weighted by quality, and that issue of sort of do we have a good study?
- Kimberly Harmon: What about the (inaudible) study?
- Chris Standaert: Do we have the study...
- Kimberly Harmon: What about the (inaudible) ??
- Chris Standaert: Hold on, wait. We need to let... let the... we'll go back...
- Kimberly Harmon: OK.
- Chris Standaert: ...to you with questions.
- Kimberly Harmon: Sorry.
- Chris Standaert: No. It's OK. So, do people see the kind of data they would like?
- Joann Elmore: I'll follow up on your comment in that it looks visually as if there might be something there, but when you do the deeper dive in the studies that are the double blind placebo controlled, those are the negative ones, you know? Krogh in the tennis elbow, Fillardo is the large randomized double-blind placebo-controlled knee, and both of those were negative. Then, for the other studies,

they're smaller. They're not blinded. There's a powerful potential for placebo effect, and I keep coming back to this issue that some of the others were compared to steroids, which might potentially make things worse and so, therefore, it would automatically look better. Then, my final concern is that there's so much variability in what is actually in the platelet-rich plasma and what is actually... how it's being done, that I'm hesitant to cover it given that I think it needs to be standardized.

Seth Schwartz: And Joann, just to jump on that, to play devil's advocate, there's no harms that we've seen at all. What does it matter? In other words, if you're capturing some generic benefit from this stuff, how... does it matter if the concentration is XYZ? I mean, we might prefer to know it because we're hearing from our clinical expert, maybe there is some effects of toe tail of this therapy, and you'd like to know that, but from a standpoint of whether this, as a whole, is efficacious, I would argue you could say it's almost irrelevant.

Joann Elmore: I thought that there actually were a few harms. They weren't as serious as this morning, but platelet-rich plasma, the article by (inaudible) knee osteoarthritis, increased pain, increased acetaminophen days three to two weeks, statistically significant. So, you know, and it's... it's not biologically, maybe that's when it's quit working, but I agree that there is less harm with this than with earlier this morning.

Chris Standaert: Certainly, there is no concern of fatality, but there's safety. There's cost, \$1000 give or take. Kevin, what do you think?

Kevin Walsh: It seems to be benefit in some studies and not in others. I'm not swayed. I mean, I'd like to see better designed studies.

Chris Standaert: These are (inaudible). What do you think?

Louise Kaplan: I have a concern about the strength of the evidence. There are so many of these studies that are low or insufficient in their strength, and I think that's a repeating theme with many of the technologies that we've reviewed. To say it's being done and it doesn't seem to be harmful is not sufficient reason to me for us to endorse this, and if there's no real benefit that can be demonstrated, then I'm inclined to say it's not yet proven.

Chris Standaert: What do you think?

Michael Souter: I'm trying to wrap my head around the biologic plausibility here for a while, you know? I mean, in essence, we're just seeing this as a kind of super hematoma, in other words, you know? Which seems to have an effect of modeling and repair on tissue, and that can sound intuitively attractive on one level, but I kind of still find that difficult to reconcile with. Practices of care where we're kind of wanting to get hematomas out from joints and from tendons and everything else. It seems as if we've got kind of a conflict there. So, when you look at the studies that are positive in the context of what are already established

practices, with kind of having blood in bad places or blood where we don't want blood, it... I'm just, well I guess I'm kind of resonating with what Joann was saying about, you know, on kind of the deeper dive of the data whether we're actually truly seeing something or whether this is just, you know, a coincidence, and I guess I'm... it's just still too much of a stretch for me to imagine that this is actually doing something useful. With regards to the question of you know, well, if it's not really doing any harm, you know, one could argue that, but you could also argue the fact, well, maybe it's distracting care away from something else that could actually be... people think they've got something that works, it means they don't have to look as hard for alternatives, you know, I kind of get... I get concerned about that.

Chris Standaert: Dr. Hashimoto, I don't... I didn't... don't recall you saying that any of the studies you looked at, which was a lot of them, discussed any biologic markers of repair. I think there's one ultrasound one that looked at something. I think steroids got worse. Tendons got bad that I saw, but in general, regrowing cartilage compared to just natural history, some bio... the proof of biological mechanism in the studies you saw, I don't see ever coming through as an outcome.

Robin Hashimoto: In term... yeah, in terms of the outcome, we didn't include anything like that. We focused only on clinical outcomes.

Chris Standaert: But it didn't come... but it wasn't in the studies.

Robin Hashimoto: I don't recall seeing it, no.

Chris Standaert: Alright. It's not typically measured.

Seth Schwartz: I mean, that, that's what you're going to see in the basic science literature and the animal studies and that sort of thing. I mean, I don't think we ever really would see that in this... as an outcome in these types of situations.

Chris Standaert: See, it'll like show a microfracture, they'll go look at the knee and look at the ingrowth of cartilage and that sort of stuff and...

Seth Schwartz: Not in the outcomes.

Chris Standaert: ...the procedures.

Seth Schwartz: Not in the randomized control studies of effectiveness. In the...

Chris Standaert: No.

Seth Schwartz: ...proven concept studies, and those were necessarily excluded from this search. So, I just think it's a... what we'd... I'd love to see that data, because I want to know what that... what it is actually doing or, you know, I think... I think we're all struggling with why is this make... how does this make sense, but we don't

know... I mean, that literature wasn't provided to us at all. Maybe it doesn't exist, but we don't know whether it exists or not.

Michelle Simon: So, to pick up on your point, do you think that you're concerned about this replacing other effective therapies, but it... it sounds like, from what the clinical expert was saying, people have tried everything by the time they get to her door three years, you know, of chronic pain and they've probably exhausted the other effective therapies, I would think.

Michael Souter: Let me just clarify. I wasn't meaning that replacing effective therapies. It is replacing a search for other effective therapies. If you think you've got something that works, it makes you less likely to kind of look for alternatives. See what I mean? And that, alternatives which may not exist as yet. That's what I was meaning, not that there's already existing suitable alternatives. It's just that if you think you've found something that works, then, you know, we're just... but it truly doesn't, and it's wasted time or a wasted resource. That's all I was meaning.

Michelle Simon: But if you think you found something that works, then you've probably found something that works, because it's pain that we're talking about here, mostly.

Michael Souter: I don't know that we have found something that works.

Chris Standaert: I also don't know that we have a study that looks at that population. Pain for three years, tried gazillions of things. I mean, I just don't... that's not... I didn't find that study myself. I found three months, four weeks, eight weeks. So, I mean, that's what I found, failed conservative care and did something, you know? Very... I struggled a lot with... I struggle with two things. I struggle with two things. I struggle with what Joann said, the... what are we putting into people. So we define platelet-rich plasma. What is it, right? I mean, they have plasma with more platelets than you should have, right, normal or whatever, right? The rest of the blood, and who is the person or target, right? You can't look at a tendon and say it hurts. People tell you it hurts. Sometimes you can't see. They also have edema and acute tear, maybe that sort of makes sense, but how do you find that thing, and why is that tennis elbow, why is lateral epicondyle different than the patellar tendon if it's a biologic thing? Why is it different? Is it just we haven't looked? It just isn't as prevalent? It just... but who is that person? So, who with tennis elbow at six months, and tennis elbow, you know what, you wait it out a year. A lot of people get better. I did it to myself. It took me a year. I got better. I hear it all the time. So, at three months, I don't know if you should be intervening, you know? And so it's... who is... who are these people and I don't know. I just have... in my own reading... I don't know. I wonder if we're a bit ahead of the science, but that's my own... what do you think, Carson?

Carson Odegard: I have to agree with you, and that was my question before about what tendons... what's the nature of the person... what's the nature of the tendon

that's being injected. And also, is there a... I don't see anything where this is ever repeated in the... in a patient. Is that?

Chris Standaert: Like a year later or whatever?

Carson Odegard: Yeah, right.

Kimberly Harmon: It's one of these things where there's a heterogeneity of protocols, particularly for osteoarthritis. Some people will do three injections. Some people will do more than one platelet-rich plasma injection into tendons. I would say most people that do this usually do one and then repeat it if people have had improvement but not all the way improved, but that's... but it's mostly one injection, and the idea, from a pathophysiologic standpoint, is to restart the healing process. You've got this degenerative tendon that has the capacity to heal but is not. So, the idea is that you will restart the healing process, and it won't need to be repeated.

Carson Odegard: I mean, it sounds very logical, and fashionable to explain it to a patient. It, you know, it sounds like, wow. This is exactly what I need, and... it's hard to decipher from the literature what is actually happening and what we're seeing are the same thing.

Chris Standaert: Why don't stents prevent MI's in stable angina? It seems like they should, but they don't. That's what we've found anyway. Let's jump to knees or joints. Are they different than tendons? People are more or less convinced by the knee?

Gregory Brown: To me, this is hyaluronic acid all over again. It was a device that was approved by the FDA 20 years ago. We spent 20 years...

Chris Standaert: For a device, which is fascinating.

Gregory Brown: ...correct.

Chris Standaert: On a device.

Gregory Brown: We spent 20 years with finally now good meta-analysis of the high quality data showing it's no effect. It's basically a placebo effect for the people that respond. So, we have a very expensive placebo. You now can open just about any major newspaper and see a full page ad where you can go to their center, and they're going to inject this and charge an injection fee, and an ultrasound imaging fee for the injection, and the fee for the device because Medicare covers it. There is no real great harm for hyaluronic acid, so why don't we just do it? Well, we've spent billions of dollars every year on an ineffective treatment. So, I... I can't imagine why we would approve this for knee arthritis, let alone any other condition.

Chris Standaert: Any perspectives on joints that may be different. We did not have much on hips or other things, some on knees.

- Seth Schwartz: I think that the data that we see is a lot less compelling on knees, as well. I mean, it's sort of hovering around no effect, and even if it's sort of... when you look at the meta-analysis of the number of papers, it's leaning towards one side, but we really didn't see any statistically-significant differences, and I think it was just less impressive overall.
- Chris Standaert: Costs, we have nothing. We have zip, because this isn't actually paid for. We don't really know what... people charge whatever they seem to want to charge.
- Kimberly Harmon: Market price is around 500 to \$2000, per injection.
- Chris Standaert: I had the patient from the Emergency Room came back two weeks ago and said she got platelet-rich plasma for \$2400 cash.
- Kimberly Harmon: (inaudible) for special surgery.
- Chris Standaert: New York City somewhere, yeah.
- Kimberly Harmon: Yeah.
- Chris Standaert: Yeah, better water, too, apparently. So, we don't know that. Our cost studies aren't... you know, one study I looked at said it was \$44, and I was, like, whoa. It's not \$44.
- Kimberly Harmon: There's somebody in town charging \$375 for it, but it's actually not a very good platelet-rich plasma.
- Chris Standaert: There you go. You get what you pay for maybe, I don't know, but data-wise, we don't have data on that. Safety wise, people didn't express significant severe... there's no... we don't have mortality. We don't have that sort of stuff. We have short-term pain, inflammation I saw in several places after platelet-rich plasma, and we have maybe steroids have their own... they're not our topic, but maybe they have their own deleterious effects long-term, but that's not what we're talking about. Alright. Should we move on to our decision tool? Or do people have more they want to discuss? Let's go to our decision tool.
- We start this with our discussion document. So, what are the key factors and health outcomes and what evidence is there? This is on page three in the back of your packet, and we start with safety outcomes is our first one. There is injection site pain and swelling, that sort of thing. Other safety concerns we should be noting that we considered or saw? No?
- Efficacy, we have function, functional success, pain, pain success, need for surgery, various composite ratings of various things, full recovery, quality of life by various measures, activity, satisfaction, medication. We didn't have measures of sort of biological repair or restoration of joint and space or other

- sorts of things. People see other outcomes that they thought were striking?
No?
- And special populations, did we get much? So, even by gender, by age, by BMI,
by...
- Gregory Brown: There was the one study about...
- Chris Standaert: OK. Early advanced osteoarthritis. Their studies were sort of global is what they were. So, we have all sorts of ethnicities represented but nobody, they weren't brought out as a subpopulation anywhere.
- Joann Elmore: I'd like to add here that I liked, on page 195, 4% risk with platelet-rich plasma of vague giddiness.
- Chris Standaert: Vague giddiness?
- Kimberly Harmon: I have not found that to be an issue.
- Chris Standaert: Is that an adverse effect or is that, like, a... if that's an outcome.
- Joann Elmore: Right after skin atrophy at 7%.
- Chris Standaert: Skin atrophy and vague giddiness. Wow. I know. I was going to say. That would seem to be a positive outcome not an adverse effect. Cost, we had nothing. Yeah, we would have liked to have data on cost, but we had nothing. So, we will start with our yellow cards. Is there sufficient evidence under some or all situations that the technology is, and this is what we're voting on? So, again, that's some or all, and if you think there are places where this is better, you vote it is more. If you think there are places... this is always tricky. If it's less, you say less. I (inaudible) predominance there. If you're unsure, you say unproven or equivalent is your fourth choice. So, for... is there sufficient evidence...
- Gregory Brown: To what? What are we equivalent to?
- Chris Standaert: Other treatment choices you might have in your milieu of being able to treat somebody, yeah. Is there sufficient evidence under some or all situations that this technology is effective?
- Seth Schwartz: Before we do this...
- Chris Standaert: Yes.
- Seth Schwartz: ...are we voting on overall or are we voting on epicondylitis or are we voting on tendons, or are we voting on osteoarthritis?

- Chris Standaert: We can go by tendons and knees separately? Well, if we go overall and then we get people saying... we can go... I'd be happy to do it any way you want.
- Seth Schwartz: We can do whatever you want. I just want to know what we're voting on.
- Chris Standaert: I would think overall, so if people think maybe tendon is better than knee, we can still talk about tendons and then we move on, right? So, but any or all, is it effective under some or all situations?
- Josh Morse: Two more, nine unproven.
- Chris Standaert: Is it safe under all or?
- Josh Morse: Six unproven, please hold up your cards, three equivalent, one less and one more.
- Chris Standaert: Cost-effectiveness. This is the most widely used card by far in this particular part of our conversation.
- Josh Morse: One less, ten unproven.
- Chris Standaert: OK. So, like with our last time where we had a predominance of unprovens there in terms of effective. So, now we get to the issue of voting, and again, as is typical, our choices are three. We cover under all conditions, so unconditionally. We don't cover, or we cover with certain conditions, and then we define what those conditions are, and the discussion that we have is usually around what those conditions may be. So, as of last time, it probably helps to know whether people are interested in conditions of various sorts, if they think we should be doing this in some circumstances, and they think they can help define those, and people can be convinced, so. People should feel free to have their say. So, you don't have to put your cards up yet, but how... with a straw vote, how many people are considering conditions and would like to hear something about various conditions or subsets where they think they might be able to define something here to cover? We have two hands, Seth and Michelle. So, help us. What would you... where would you... you're not talking unconditionally, I assume, right? You said things you don't.
- Seth Schwartz: Personally, I'm... it's only for the lateral epicondylitis thing and it would be under failure of medical therapy for... or whatever conservative therapy is. I'm not sure what the conditions would look like exactly. I think it would be kind of, like, I mean, we'd have to look... maybe we'd look at the entrance criteria for some of the better of the studies that were there, but effectively, an extended period of time of symptoms and no benefit from all other therapies, but for everything else, I'm comfortable with... I don't feel like (inaudible).
- Chris Standaert: Tennis elbow also, well epicondylitis. OK. This would be something like, I don't know, one of you all should probably start while you're thinking about it. Help her out with the typing.

- Seth Schwartz: For lateral epicondylitis, chronic for lateral, yeah.
- Chris Standaert: I think you want to put in three, six, twelve months?
- Josh Morse: If I could make a suggestion. There might be some helpful language in the guidelines.
- Carson Odegard: Yeah. There's one under Sue's guideline under... just basically says elbow epicondylitis, refractor to standard nonsurgical treatment.
- David McCulloch: So, just to be clear, we're saying under those circumstances we haven't quite defined yet, we're recommending that Washington State cover injecting some volume of some fluid some number of times at the discretion of the doctor looking after the patient. Go ahead.
- Chris Standaert: Let's go back for one second. So, Josh is backing me up here, appropriately. So, we do have... I got back to our coverage guidelines. Medicare does have a coverage determination on blood-derived products, but it's for chronic nonhealing diabetic and venous pressure wounds, which we don't... this is not what we're talking about. So, they don't have a statement on our field here. We have several guidelines from Colorado's Worker's Compensation. They thought there is evidence on platelet-rich plasma, they said for lateral or medial epicondylitis, I didn't see any medial epicondylitis, lasting for more than six months. American College of Occupational and Environmental Medicine, sorry, platelet-rich plasma for lateral epicondylitis, and that's about it. ICMS, I don't know what that stands for, need for further research. And Sue, I don't know who Sue represents. That's his own, that's a Sue in a research group, tennis elbow refractory to standard nonsurgical treatment is the language they said, and the Work Less Data Institute says platelet-rich plasma and autologous blood injection for acute and chronic elbow disorders, not specified. That's a vague thing. We do have the autologous blood injection issue, because our charge is autologous blood also. So, this goes back to if you're going to inject it, what are you going to inject question.
- Josh Morse: And you mentioned the AAOS.
- Chris Standaert: And the AAOS, yeah. The AAOS decided they cannot make a recommendation for or against platelet-rich plasma, just for the knee is what they were talking about. They didn't say much about other stuff in the statement we have.
- Gregory Brown: So, in the spirit of full disclosure, I was cochair of the workgroup that developed that AAOS guideline, so everybody's aware of that.
- Chris Standaert: That is helpful. So, somewhere in this condition, if people are talking conditions, is the condition and the blood versus platelet-rich plasma question, because they're both in our charge. Borrowing language from somebody else is often a good starting point, even if you may not keep any of it when you're done.

- Seth Schwartz: I think we should use David's words, which is you can inject anything from yourself into anybody in any part. No. I mean, but... so we saw some data that therapy may be better than autologous blood injection, but I think the autologous blood injection versus control data showed a little bit of benefit in short and intermediate term pain and functional outcomes. So, I don't know that when you separate just platelet-rich plasma or autologous blood injection in this situation. I think if we're going to do this as an exception or as a potential condition, I'd probably include autologous blood injection.
- Kimberly Harmon: There was a double-blind placebo-controlled randomized study by Kreaney that compared autologous blood injection to platelet-rich plasma and showed equivalent outcomes. The platelet-rich plasma wasn't a great, again it was low, but it was a good study, and it showed equivalent outcomes.
- Seth Schwartz: So, again, for this condition, you could say... and don't start with resistant, but just say lateral epicondylitis present for greater than...
- Christine Masters: Can you speak up just a little bit, please?
- Seth Schwartz: ...present for greater than whatever... I mean, three months is what we saw in the studies.
- Chris Standaert: Kreaney study mentioned six.
- Seth Schwartz: Yeah, or we could go with that.
- Kimberly Harmon: As a clinical person, I would say six.
- Seth Schwartz: OK. Greater than six months, resistant to all other nonsurgical therapies. Michelle, does that capture what you were thinking, too?
- Chris Standaert: Would that mean acupuncture and all sorts of stuff and...
- Seth Schwartz: Standard.
- Chris Standaert: ...standard.
- Seth Schwartz: Nonsurgical therapies.
- Chris Standaert: Steroid injections? Yeah, I don't know. It shouldn't be, but it is. All other standard nonsurgical therapies or covered. You could say covered so you don't have to deal with things that aren't covered by the insurer. By the... by the payer is what I was thinking. That way, at least you've limited it to what they can actually have that they don't have to pay for it, but I don't know. I don't know. I assume they would.
- Kimberly Harmon: Yeah, they do...

- Chris Standaert: They do is what we just heard.
- Kimberly Harmon: They do.
- Gregory Brown: They do in the operating room. I mean, an injection is a procedure. It's a procedure.
- Kimberly Harmon: I would just say the other conservative therapies and then they can leave that open to interpretation and say you have to try this or you have to try that.
- Chris Standaert: So, people who are thinking this, you've got to edit your terms. Is that some of the difficulty that some of the rest of us are having. How do you define this? So, if people think they can find the group with a space at the place that helps to articulate it.
- Seth Schwartz: I would be inclined to say standard nonsurgical therapies. I mean, I think there's going to have to be wiggle room in that, because we don't know what all those other therapies are, and we've heard in every study that people are comparing it to different stuff. So, I think what we're trying to capture is, this shouldn't be a first line thing you jump to, but if you've tried other stuff and nothing else is working.
- Michelle Simon: But if therapy has other guidelines before, I think that would work, as well.
- Chris Standaert: This could apply to autologous blood and platelet-rich plasma. Yeah? OK. Edits, comments or other conditions people want to throw up for consideration? We have knees. We have other sorts of things.
- Michelle Simon: So, recommend covering this and knee, correct?
- Chris Standaert: Well, lateral epicondylitis, sorry. I have not sensed enthusiasm with the knee. OK. So, as we move ahead. So, if people... give people a chance to think about that. If they have another comment on those, they can comment while we're talking or after I'm talking. When we vote, we get three choices. We have cover, which means condition or not, it's just covered whenever a physician feels it's appropriate to do under all circumstances. You have cover with conditions, which will apply to this sentence right there, and you have no cover, which just means it won't be covered, or this condition does not apply. It just won't be covered under any conditions, but again, under research protocols, other sorts of things, and appeals processes back to the state, people are welcome to do all that.
- Kimberly Harmon: Chris, can I make a comment from a clinical perspective?
- Chris Standaert: Sure.

- Kimberly Harmon: When I've got a patient who has had years' worth of lateral epicondylitis has tried three rounds of physical therapy and chiropractic and acupuncture and massage and nothing has worked, my choices are to send them to surgery, which has no more evidence than this does that it's effective, or to send them back to PT, which is actually more expensive, in terms of a round of 12 sessions of PT or whatever. So, as a clinician, neither one of those are good alternatives, to me this just offers a relatively inexpensive option that has a significant amount of evidence supporting. It may not reach the level of evidence that you would wish.
- Chris Standaert: Mm-hmm.
- Kimberly Harmon: But it does have evidence.
- David McCulloch: With all due respect, you're here as a medical expert to answer our questions, and we want you to answer them, not to advocate and give your valued judgment on, in your opinion, this is significant amount of evidence. It's not significant amounts of evidence, and I appreciate these people are very difficult to treat. That doesn't mean we should ask the state to cover unproven treatment because it's better than nothing, because it's probably not better than nothing.
- Chris Standaert: Again, the charge of our committee is the evidence with effectiveness, the cost, and the safety, and we have to consider all of them, and the committee weighs them and weighs the best evidence available for all of those variables with their clinical experience to make their decision. So, we're going to move on to our vote. So, again those are your three options. No cover, cover with this specific condition, or cover under all conditions. Yeah, other comments? You want to say something, Joann.
- Joann Elmore: I sort of want to.
- Chris Standaert: OK.
- Joann Elmore: I think two of you are wondering about the cover with conditions, and thinking about kind of how we review the evidence. I'm hoping that in future evidence reviews, they won't just throw all of the RCTs together, but they will, because there was an 'it looked like it was suggestive of a small improvement.' Sure, in the figures it does, but when you pull out the low quality studies, then you might be seeing things differently. So, that was not... the data were not presented to us visually in that way. We had to go digging in the individual articles, and I thought the points that the patient population, some of these weren't that sick. You may be having regression to the means. Some of these studies were not randomized. They were not placebo-controlled. So, I think that in the future, I'm hoping that we can have differentiation of the results presented to us with attention to quality.

- Chris Standaert: That certainly was my experience in reading the report and the articles, but other comments before we vote? Alright. So, based on the evidence about the technology's safety, evidence, and cost-effectiveness, of platelet-rich plasma and autologous blood, you may vote.
- Josh Morse: Three cover with conditions, so it would be eight no cover.
- Chris Standaert: OK. So, we have to then go back and say are we consistent? So, Medicare does not have a decision on this particular topic in a way that relates to what we just discussed. So, there's no worry there. More of the guidelines and not recommended for tennis elbow, but they are vague. Some do not. Some recommend more work to be done. Most payers don't pay for this already. It's experimental, so it doesn't strike me as though we are out of line with what the medical community is doing, at least the payer side of the medical community. Yes. Other opinions? OK. Then, we are done with that. We... you can't leave yet. We have to do review updates for Josh on reviews in progress.
- Josh Morse: Yes, we do have a couple of brief items of business. In the back of your binder, I'll just give you a very quick update, and then we have one other item to cover. Just on the topics that are in (inaudible) right now. So, for November, again, I mentioned this a bit this morning, fecal microbiota transplantation and negative pressure wound therapy. Negative pressure wound therapy, we just concluded the comments on the draft key questions. There may be some changes to that scope, we'll see in the next couple of weeks, and we'll, of course, publish the final. The pharmacogenetics is one that we're not too far into the scoping quite yet. We will be getting into that intensely here shortly to try and identify a couple of areas where we can focus that report and the types of treatments that are being offered and the tests that are accompanying that. So, perhaps depression and antipsychotics, I'm not sure. Those are... that's the kind of idea that we're developing to frame that report.
- Gregory Brown: On the negative pressure wound therapy, is it any more focused than that? Is it focused on chronic wounds, any wounds?
- Josh Morse: Focused on home use. So, it was outside of... and home use has a bit of an odd definition. It's not strictly the home use, because there wasn't a report that led us to select this. Home use was not defined, necessarily to be in the home. It was broad. It was basically outside of a hospital or long-term care facility, I believe. There's an existing report on that, so we're working off of that report as a starting point, and then it was wound types. I believe it was mostly chronic type.
- Gregory Brown: The only reason I ask for clarification is, definitely in orthopedics, in an acute open fracture, I would argue that's the standard of care, but that would be in a hospital setting, again, for an acute open fracture.
- Josh Morse: Yes, and I believe, yes. That was part of the scoping question, and I'm not sure those were actually included, yeah, for the acute type of injury. Is there another

question? And these slides show the timeframe, but really the other item we wanted to do was... we have some parting recognition letters and gifts for our three committee members. We're doing this now, even though you're still here. You're still on the committee until there is a replacement, essentially, but this is likely the last public meeting.

Chris Standaert: I would like to thank you for the remarkable contribution. You're all stellar.

Josh Morse: Yes, thank you, so much.

Chris Standaert: Now, you're out the door, and they hand you a plaque. That's what's happening. It's, like, yeah, nice knowing you.

Louise Kaplan: Well, the last time I went off, I got a piece of paper.

Chris Standaert: OK. We're moving up. We're moving up, see? So, that's why you can come back. You didn't get the plaque.

Josh Morse: So, thank you. You will be receiving some further updates, I think, in the next couple weeks regarding some rule making. We don't need to talk about that now. We'll do that more in the fall.

Chris Standaert: So, I would like to throw something out. So, oh, go ahead.

Louise Kaplan: I was just going to ask related to that, is that related to the legislative bill that passed this year?

Josh Morse: No.

Louise Kaplan: But the bill did pass, right? It got?

Josh Morse: The bill, yeah. I can give a couple other updates if you want to hear. So, we have had rule making ongoing for a couple of years as a result of a legal settlement that you've been briefed on in the past. The last iteration of the rules was sent out, I believe, in the fall. A new iteration was just published a couple of days ago, and we can send you a copy. We're in a comment period right now, a 20-day comment... or 30-day comment period, excuse me, for the revision to those rules. Those rules do a couple of things. They add some process for the agency to ensure that the work that is done here follows the requirements of the law and the agency rules. So, we put the procedures that have been followed into rule and some procedures to make sure that that's current for each determination. Additionally, there is a new rule that makes clear that nothing in the statute or the rules obstructs somebody from going to court to challenge an outcome from this process. This is part of the legal settlement. So, in full disclosure, I really don't know what I'm talking about, but that rule is very brief, and it just basically says nothing prevents you from going to superior court if you feel that the actions of this group have not followed the

law. So, other aspects of the rule changes include cleaning up language. There was a...

Chris Standaert: No more swearing.

Josh Morse: ...yeah. So, defining some terms, like the term... so you'll have to read the rules to see some of these terms that have not had definition but have operationally meant certain things. We've turned those into formal definitions in the rules, but again, these are not final. This is still a draft, so things can change before this rule becomes final, but that draft is now publically available. One concrete change that's proposed in these rules is that instead of being able to serve three terms on this committee, go off the committee for a year, and then come back for another term at some point in the future, that term in the future has been removed, such that the... essentially, you can serve three 3-year terms on this committee at this point when these rules become final. So, that is one pretty obvious change in the rules.

Chris Standaert: The clinical expert, frankly I was kind of experimenting with this a bit in my head. I've had to deal with this. So, as of next year, the clinical expert will be there, right? Will be at our table, will not be there, and they're non-voting. They become a member for the day, but they are non-voting. They can vote, but we're going to have the same issue of how to have them not disrupt what we want to be a well-functioning committee. I'm personally very concerned about this, and I think as a committee we should really discuss... the expert is for us still, right? This isn't an at-the-table industry representative. It isn't a slot for industry, and I think we need to screen a lot more about conflicts of interest. I think we may need to be a bit more rigid about that sort of thing ourselves. I think we need to be explicit about what kind of help we want and maybe a little more conversation on our part to define that and what we want, and we're going to have to work a little more with the vendors or with Josh to find the right people, because I think it could... obviously, we've all done this. We can see some clinical experts really want to sort of take over. Some are happy to sort of sit back. The ones who want to take over can be problematic for us, and I've tried to argue... you know, I don't mind having somebody sit at the table, as much, if they sit here five times a year for five years and they get the scope of what we do and the difficulty and the challenge, and the gravity of the decision, right? We're deciding whether people can get care or not that's covered. I mean, we get it. People who sit here for one afternoon may not get that all. They may think, well, of course you should do this or of course, you shouldn't do this. I don't understand that. So, how, as a committee, we have to think about that a bit. I think for people who are still... I'd love all of you to be... I mean, you're all going to be here unfortunately. Come September, our retreat, I would love for people to think through if they have an idea, you want to send Josh an email or me an email saying can we talk about this. Some of those things about how we integrate that is something we should really be discussing in September in what we want from that expert and how we're going to interact with them, and how we do this, because it's going to change.

- David McCulloch: I agree with that, Chris, and I appreciate the difficulty you are in, and it's very hard for experts not to become advocates because of their role. I think we may... one proposal might be we should come up with a brief standardized paragraph that you will say at every meeting, in public. Here's what, as an expert, you can do and here's what you can't do.
- Josh Morse: Well, so... let me... I'll just speak frankly. The legislature made this change. It is now the law. They have created a new member of the committee that has full committee rights with the exception of voting. They will... they have to meet the same requirements to be on the committee, meaning conflict of interest requirements, employment related to industry, but beyond that, they will be a committee member. There will not be another set of rules for that nonvoting member. Correct. And that was the intent. That is what...
- Chris Standaert: So, are we not allowed to discuss a topic and say what we might like in that clinical expert as our committee is trying to find our expert, if they...
- Josh Morse: No. I think there will be an opportunity, because I believe this... there likely will need to be some rulemaking to implement this clearly with a clear process that meets everybody's expectations.
- Chris Standaert: And there are, I mean, we have... I don't know if people ever remember reading them. When you saw in your contract, there is a code of conduct and a code of ethics, and you have to be respectful and responsible. We all sign that when we join. I mean, they're going to have to do the same thing, and they're going to have to... so we're going to need a... you know, that whole... build them a packet and say here, this... I mean, this is the real... you're... you cannot do this, so.
- Josh Morse: So, there's a clear... the new bill that became law is very clear and says any clinical expert. The expectation is that there will, because there consistently has been a clinical expert for these meetings, but if there is to be a clinical expert, that clinical expert is to be this nonvoting member. So, if there is not a clinical expert, then there will not be a clinical expert, and that nonvoting member will not be at the table, but there will not be a separate clinical expert. Does that answer your question?
- Gregory Brown: I guess what I'm saying is, what level are you pushed to find a clinical expert that's unconflicted?
- Josh Morse: Well, again, that's the... that'll be the difference between where we are now versus where we are six months from now, because we haven't applied the same criteria to identifying a clinical expert that we applied to identifying committee members. Now that said, finding committee members and clinical experts is not always the easiest thing to do to get people to commit to be here for a day or in the case of a clinical expert, half of a day. So, where the criteria land as far as that goes is yet to be determined.

- Chris Standaert: My sense is if you look at sort of zealot and skeptic or whatever, the different ends of the spectrum, we tend to be... most of the ones we seem to have tend to be closer to the zealotish side, as opposed to the really sort of skeptical, cynical side, clinical experts. We have had some who are cynical, who are sort of like, meh, you know? You guys are doing... this is... we have some of that. We have a lot more of why wouldn't you?
- David McCulloch: We want them to be rational, not cynical.
- Chris Standaert: There's different ends of the spectrum. We want that in the middle somewhere, rational.
- David McCulloch: Rational, yeah.
- Chris Standaert: Right, yes.
- Louise Kaplan: Could I just clarify then, Josh, what you're saying is the clinical expert is a rotating position so that each meeting, there will be two different clinical experts, just the way they have been, but they'll be at the table.
- Josh Morse: Correct.
- Louise Kaplan: And so they...
- Chris Standaert: There'll be two?
- Louise Kaplan: ...they...
- Josh Morse: Well, there'll be one for each topic.
- Chris Standaert: Oh, OK.
- Louise Kaplan: ...for each topic, but the implication then is that they're just coming in as a 'member' for a few hours and then they leave. So, they're not enculturated.
- Josh Morse: No, there are... I mean, there are clearly some challenges me... our... my team we will have to face and perhaps the chair and the vice chair bringing people up to speed prior to the meeting to understand the process, because they likely will have a little bit more involvement in being a slightly, like, 15 foot different position. So, we'll have to figure out a way to communicate that more clearly in advance and spec it out so that it's not... so it's repeatable, basically.
- Michelle Simon: And what problem is this solving?
- Charissa Fotinos: He didn't ask for this.
- Michelle Simon: I'm sure. I'm just curious.

- Josh Morse: So, one of the problems, and I think... what problem is this solving? That's a great question. The problem that is being solved is one where the perception of the clinical experts, perhaps, may not always be able to contribute equally. So, I think that was the takeaway that may have led to this. This has been lobbied for a long time, many years. This is not an abrupt...
- Louise Kaplan: Why?
- Chris Standaert: Well there was a move for, like, a... for an industry person on the committee.
- Josh Morse: ...yes.
- Chris Standaert: At one point, an industry-appointed person, which (inaudible), and there are a number of, you know, these... I got to tell you, it's frankly my own feeling, it's the pain fields really get pissy that their expert doesn't get to sort of talk about all the papers they brought with them and all the evidence they have, and they talk a big... they want to talk about the evidence that isn't in the report, because it got excluded because it didn't meet their criteria, and these are the people who get upset that it's not being discussed. So, then they say, well, my... our person is alienated, and they say that's the only person who, you know, has our perspective.
- Michael Souter: Can I make an observation that part of our practice is getting the clinical expert involved in the preparation of the report beforehand, and that's because they have particular, you know, knowledge bias, and a context of which to be able to decide and contribute to the key questions, but therein lies an implicit bias that they will have because they're an expert in their field. They're going to... and they're probably practicing in that field. They are going to feel a duty of care, such as to that particular practice, and I think that perhaps the way forward from this, I would suggest, lies in divorcing those clinical experts who contribute to the evidence report and the formulation of key questions away from somebody who can actually contribute to a discussion in the context of the overall field when it comes to the grouping itself, because there's less chance of an overt bias from somebody who just is a practicing cardiologist, perhaps, rather than somebody whose area of expertise is in the particular cardiologic syndrome that we're dealing with at that point in time.
- Chris Standaert: I think your point about the person who works on the report not being the person at the table is great, because I think, in my own thing... we've talked about this. How involved should we get in key questions and scoping topics, and I always have held the same perspective that I want to know... I want to... obviously say somethings are going to work or don't work. I don't want to personally dive into that and become invested in that being the right answer. Otherwise, when it comes down the pike and it was the wrong answer, I can't say that, even if I think it is. I become bias, and I would rather, even though I don't always like the questions they give me, and I don't always like where the questions take the report, I'd rather bitch about it at the end than go holy crap, I did this, too. Like, to have some ownership that I'm trying to sort of work

around, I think it keeps us un-conflicted to... we are more un-conflicted if we are not invested in what happens with the report, which I think is what we should be, and I agree. That's a great point, that the clinical expert also should be similarly divorced from sort of psychological or bias to the findings in the report that they helped shape.

Michael Souter: Practically, it might make them easier to find.

Chris Standaert: It might, yeah, because it wouldn't be quite so... just show up for the day and you can hear what we hear. You can get the report a week ahead of time, and you can read it and see what you think, and this is the evidence we have and we'll talk about it.

Michael Souter: It gives you wider pool to draw from. (inaudible)

Chris Standaert: So, a month ahead of time. Well, well give it to them a week ahead of time.

Joann Elmore: I have a question for Josh. Are we able to help you with names of possible clinicians for future reviews?

Josh Morse: Yes, I think so. You know, we've had a relatively informal process to identify clinical experts through the state medical societies through individuals that have participated before or contacted and made comment, but it's always helpful to, you know, get ideas, names. Frankly, for the bronchial thermoplasty, it was feast or famine. There were no clinical experts emerging and then suddenly there was a host of individuals available. Well, frankly, it was networking with Boston Scientific that helped to figure out, because the networking that I was doing prior to that wasn't working out, but yes. That's true. The industry often knows exactly who is performing their procedures.

Chris Standaert: In that case, you had to be trained by them or you can't do it. So, in that case, you were sort of stuck. So, if somebody asks how do you learn how to do this? You go to Boston Scientific for a week or a weekend, and they show you how to do it. So...

Josh Morse: Right.

Chris Standaert: ...they know everybody...

Josh Morse: So... so, and so...

Chris Standaert: ...they've trained, yeah.

Josh Morse: ...yeah. So, the level of... so, it will be difficult, and you'll... you've probably already put it together, it will be difficult to identify clinical experts with zero conflict, and that is why we have not tried to apply or over screen for clinical experts.

- Gregory Brown: I mean (inaudible) for clinical practice guidelines for AAOS, and our working group drafts the PICO questions, and then, you know, six months or a year later when we've gone through several thousand abstracts with our research staff, we get together again and write our recommendations. We're very, you know, specific about financial conflicts of interest, but there's all sorts of intellectual conflicts of interest that there's no way to screen for, if you will. So, I don't... I'm not so concerned about that separation, I guess. I...
- Seth Schwartz: I think that's a really valid point. I do guidelines with our academy, too, and you can't get around conflict of interest. I think that what was critical is disclosure, you know, so that everybody knows where they're coming from, so that everyone at the table knows that every word out of that person's mouth, what... how it comes up. I thought Charissa did a great job today at sort of pulling that out of the bronchial thermoplasty.
- Kevin Walsh: Or the orthopedist, because that was concerning, that she said, oh, I, you know, I've got millions of dollars' worth of remuneration, but it was from the ultrasound company, not about platelet-rich plasma, and I was thinking, well what were you doing ultrasound for?
- Chris Standaert: Why did they want to give you half a million dollars?
- Kevin Walsh: So, the other thing is, I think we have to... we're not going to be able to screen for this stuff. What we have to do...
- Gregory Brown: (inaudible)
- Kevin Walsh: ...my apologies. We have to be... I think we have to emphasize the civility with which we've tried to have these discussions with each other and the limits with which we've tried to have these discussions with each other and impose those expectations on these clinical experts.
- Chris Standaert: There are requirements that we all are supposed to meet, right? They are stricter than we've been applying to our clinical experts in terms of conflict of interest, and I think there definitely are some conflicts that, you know, you just don't want at the table, whether they say it or not. I mean, if they work for Boston Scientific, they shouldn't be sitting at our table. So, they could still drive opinion and annoyance.
- Seth Schwartz: But I think the problem we run into more is that the expert is the person that does the procedure, and there's an inherent conflict of interest there, both intellectual and financial, regardless of what they say.
- Chris Standaert: Yeah.
- Seth Schwartz: But I think we can say, that's OK.
- Chris Standaert: Right. We're going to have that.

- Seth Schwartz: I mean, we've talked about this, about members that are on the committee. You're conflicted about injections that you do.
- Chris Standaert: Yeah. Yeah.
- Seth Schwartz: So, I think it's fine, as long as there's disclosure.
- Chris Standaert: Right. No, and I think we can apply the criteria that we have to follow, and I think we can set a rule of table manners for people. They have to be civil. They have to expect things. They have to do stuff. I personally do kind of like the idea of taking somebody other than the evidence person who wrote the report, so you can get sort of an unvarnished view of, huh, I don't see that in the report or whatever, as opposed to, oh, don't you see? It said in this 0.1 person we should be doing this, and that's we get a little bit of.
- Michael Souter: Because we all, you know, at various points in time have disagreed with or been unhappy with our report as it stands, because we've got to look at that from an impartial basis. I don't think you can get that from somebody who has invested their time in crafting that report.
- Chris Standaert: So, I think that's a good idea. I think this matter of sort of... again, in September, however we interact and how we do this and what, you know, how we... maybe how we help set the table manners shows a person what we expect of them.
- Michael Souter: The three of us will be thinking of you.
- Chris Standaert: It's sort of up to us.
- Michael Souter: The three of us will be thinking of you as you're (inaudible).
- Chris Standaert: As you're lying on the beach in Maui with your black.
- Louise Kaplan: We'll be wondering if there's the pump for the IV instead of just counting drips, right?
- Chris Standaert: Right. And we'll be counting platelets.
- Louise Kaplan: Well, that's why they have the highest HIV prevalence in the world, right?
- Chris Standaert: So, again, if anybody has some other issues they think we should talk about in September, let me know or let Josh know so we can make use of that well. There are a couple of things I want to talk about that I know of already, but we can make use of that time well. Third Friday in September, whatever that is. With the phone call, it's to confirm our votes today is the main purpose. If something else comes up, we'll talk about it. If nothing else comes up, we... it's set for an hour. Last year, it took, like, ten minutes or five minutes. It's just to

confirm the vote is the main purpose. So, it's pretty quick, but that way, at least otherwise we won't vote again until November and they won't be able to put our decision into action until after November when we vote. So, if we vote in July they can start working on it. Yeah, that's the purpose. Alright. Thank you, all. We're adjourned.