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Health Technology Clinical Committee Public Meeting

May 19, 2017

- Chris Standaert: We're going to call the meeting to order and get started. So, welcome, everyone. This is the meeting of the Washington State Health Technology Clinical Committee. I am Chris Standaert, and we are here to talk about two topics today. We have selected treatments for varicose veins and chronic migraine and chronic tension type headache, nonpharmacological treatments. As a reminder for our program, we are an evidence-based committee, and that's what we work on. We look at three things, when we consider evidence. We look at efficacy, safety, and cost, and we are trying to help decide whether things that are being done or are available to be done are helpful in that manner for the people in the State of Washington who are covered by these policies. That's our charge. So, we have committee members. Our clinical experts will be present. Dr. Meissner is our clinical expert for the morning. Dr. Meissner is a vascular surgeon at the University of Washington, been there for how long?
- Mark Meissner: My whole career.
- Chris Standaert: My whole career. You're not going that far, are you? [laughs] Three years, really? So, we are honored to have him. We have our evidence vendors to help us with the evidence. We have the agency directors and representatives to help us with their perspective, as well, and we have public out in the audience and potentially on the phone somewhere. We can't see them, but maybe they're there. So, all those people will get to speak. So, if there are people in the audience or on the phone, there is a chance for public comment. You had the chance to sign up. If you missed that, we'll still give you the chance to raise your hand and say you want to speak, and we'll open up the phone lines for anybody on the phone who wants to speak to the committee. That's pretty much it. So, Josh?
- Josh Morse: We'll have a brief presentation. As Dr. Standaert pointed out, we have two topics today, the review of varicose veins and treatments for chronic migraines and tension type headaches. Just a few reminders about the meeting. This meeting is being recorded. A transcript of the meeting will be available on our website in a few weeks following the meeting. When participating in discussions, please state your name and please use a microphone, and we'll go around after this and get everybody's voice and name into the microphone for the transcriptionist.

To provide public comment during today's meeting, if you are not a person who has signed up in advance to provide a comment or presentation, please, there is a signup form outside the room.

So, a brief background about this program, the Health Technology Assessment program is located and managed out of the Washington State Health Care Authority in Olympia. 2006 legislation designed this program, and it uses evidence reports and this panel of clinicians to make coverage decisions for medical procedures or devices or tests that are selected, and they are identified based on concerns about safety, efficacy or effectiveness, and cost-effectiveness or value. So, multiple state agencies participate to identify these topics, and they are charged with implementing the policy decisions that come from this group, and those programs or agencies include the Health Care Authority that manages the Uniform Medical Plan and the State Medicaid Program, the Department of Labor and Industries that operates the worker's compensation program, and corrections participates, as well, on a voluntary basis. Agencies implement these decisions from the program in the HTCC within their existing statutory frameworks.

So, the purpose of this program is to ensure that medical treatments and devices, and the services paid for with state healthcare dollars are safe and proven to work. The program, itself, provides resources for the agencies that purchase healthcare. We develop scientific evidence-based reports on the medical devices, procedures, and tests that are identified, and we facilitate the work of this independent committee of practitioners who determine which devices, procedures, and tests meet the requirements for coverage based on safety, efficacy, and value.

So, a very high level view of the process, topics can be nominated by anybody, including state agencies. We go through a review and a public input process to prioritize those topics. The director of the Health Care Authority is charged with selecting those topics. Once they are identified and selected and have gone through a couple comment periods, we develop key questions that frame the scope of the reviews that will be done and the policy questions that will be answered, develop work plans and drafts. Those key questions are ultimately finalized and one of our technology assessment centers, these are the groups that write the reports, produce an evidence report. It goes through a public comment process, as well. The final report comes to this group and is then talked about here at this public meeting of the Health Technology Clinical Committee. Once these decisions are final, which may occur at the next meeting of this group, the agencies are charged with implementing the decisions.

So, the remainder of this year, the calendar for the Health Technology Clinical Committee includes a meeting on July 14th, which will be a phone or webinar based meeting to discuss the outcomes from today's work, followed by a meeting scheduled in November, and the topic for that meeting, at the moment, is computer-aided detection for mammograms.

We do have proposed topics out for comment for a few more days for the next cycle of reviews, and the proposed topics that are available online for review includes

surgical interventions for unilateral single-level nerve root compression with radiculopathy, extremity ultrasound, genomic micro-ray and whole exome sequencing, genetic testing or molecular pathology testing for cancers, and pharmacogenomic testing for selected conditions. There is one topic proposed for an update or a re-review and that is continuous glucose monitoring.

So, to participate in this program, we do have a website where most everything that we generate, in terms of products, reports, proposed topics, is available, and the web address is on this slide. We have a mailing list through the Health Care Authority. Anybody who is interested in finding updates from the program can sign up on that mailing list, and you'll receive regular updates on the things that we're publishing or the upcoming meetings. Anybody may provide comment on proposed topics, key questions, draft and final reports, draft decisions, and again, here at these public meetings. Anybody is welcome to attend these meetings and speak directly to the committee, and anyone is welcome to nominate health technologies for review through this process. The web address, again, is on this site, as well, as well as our program email box.

So, I would ask everybody on the committee if we could just take a moment and we'll start with Dr. Mischley and go around, state your name into the microphone for the transcriptionist, please.

Laurie Mischley: Laurie Mischley.

Gregory Brown: Gregory Brown.

Sheila Rege: Sheila Rege.

Joann Elmore: Joann Elmore.

Chris Standaert: Chris Standaert.

Josh Morse: Josh Morse.

Mark Meissner: Mark Meissner.

Kevin Walsh: Kevin Walsh.

Carson Odegard: Carson Odegard.

Seth Schwartz: Seth Schwartz.

Chris Standaert: I just want to say a couple more things before we get going. One, Josh said that, you know, when you come up to introduce yourself, conflict of interest is relevant to us. So, when you address the committee, please let us know about relevant conflicts of interest whether you represent another agency or corporation or other entity, and if anybody paid for you to travel or be here to talk to us. Dr. Meissner, we didn't talk

about that, but your disclosure would help us, as well, so people understand any relevant issues in your background. You filled out a disclosure form us, but...

Mark Meissner: I did, and my only relevant disclosure is my wife is a salaried clinical specialist with Medtronic. She is in the aortic therapy division, not in the venous division, and she has no stock or other conflicts other than being salaried.

Chris Standaert: And two other things, Dr. Rege is here with us for her first meeting. She is new to our committee. You can tell the other members a bit about your background, so they understand. So, radiation oncology, Tri-Cities, yeah?

Sheila Rege: Yeah, I did my residency training at UCLA, couldn't decide what to do, did a couple years of general surgery, actually got board certified in nuclear medicine, the PET imaging, and then switched to radiation oncology. I came to the Tri-Cities and have been there since 1997 in private practice.

Chris Standaert: We're happy to have you. This is Dr. Odegard's last actual formal meeting, I believe. You'll be here in July?

Carson Odegard: Yeah. I'll be here in July.

Chris Standaert: This is... so, this type of meeting, the decision-making process, Dr. Odegard is the last founding member of this group. He has been here since the beginning, since the very first meeting. So, it has been an honor working with you. It's been an honor to have you on the committee. You've done a tremendous service for the State. Your work is greatly appreciated.

Carson Odegard: Thank you, very much.

Chris Standaert: Yeah.

Carson Odegard: It's been an honor and pleasure to work with all of you and over these years, we've learned a lot, and I've learned so much from each and every one of you, and I really appreciate it. I appreciate both the opportunity and the challenges of what this committee has put forth. So, I wish you well. Keep up the good work. I'll keep in touch. Thank you.

Chris Standaert: We have a couple more decisions to go, though.

Carson Odegard: Yeah. Yeah, right.

Chris Standaert: You're not done yet. No. Alright. Our next order of business is minutes and our coverage determination from last meeting, and what we do is, we look at the minutes and decide whether they are OK or not. People can look at them for a bit. We only had one topic last time. I didn't get a public comment in my book here.

Josh Morse: You don't have this?

Chris Standaert: No.

Joann Elmore: We want to make certain we read the public comments.

Chris Standaert: So, we're looking at minutes at the moment. So, people have had a chance to look through them. I didn't see any corrections myself. Anybody see a correction or suggestion, please help us with that. Otherwise, a motion to approve the minutes would be appreciated when people think they're comfortable with them.

Male: [inaudible]

Chris Standaert: Do I have a second?

Carson Odegard: Second.

Chris Standaert: All in favor of approval of the minutes? Any opposed? No?

Josh Morse: Eight approved.

Chris Standaert: So, approved. Then, next we move onto our coverage determination from the last visit, which was on extracorporeal shockwave therapy for musculoskeletal conditions, and we had voted not... this is not a covered benefit or covered treatment or covered technology. We received one public comment from Robert J. Freund. Do you all have that comment? Yeah. I don't know, but it looks like a patient perspective who found the treatment helpful.

So, we went through a lot of evidence and a lot of discussion about all this. I'm looking for where the evidence took us, in terms of our issues of cost, efficacy, and safety. We're unanimous at that time that this wasn't a covered benefit. So, any comments or discussion? No? If not, can I have a motion to approve our decision?

Male: [inaudible]

Gregory Brown: Second.

Chris Standaert: Thank you. So, of the committee members who are here today who were there when we made this, those are the ones who vote, all in favor of approving our decision on extracorporeal shockwave therapy for musculoskeletal conditions.

Josh Morse: Six approve. Thank you.

Chris Standaert: And disapprove? And abstain? And two abstain, since they weren't here. Three abstain, yes. Alright.

Gregory Brown: Should we address the public comment?

Chris Standaert: That's why I was trying to offer you a chance to address it, should you have been, like, my...

Gregory Brown: Oh.

Chris Standaert: ...my comment was simply that, that I appreciate the comment.

Gregory Brown: Right.

Chris Standaert: And I appreciate that people perceive things that are helpful, maybe it indeed helped this individual, but in our review of the evidence and the totality is where we made our decision. Yeah, but you're welcome to express other thoughts if you have them.

Alright. That being said, we're gonna move on. So, we're gonna start our first topic today, selected treatments for varicose veins. Presenting for the state agencies is Dr. Emily Transue who has not addressed us before, but we're happy to have her.

Emily Transue: Nowhere to set water up here. So, hi, Emily Transue, associate medical director at the Health Care Authority. So, talking today about selected treatments for varicose veins? It's always good if the first glitch is not on me. That looks more familiar. I think I got a clicker. We're good.

So, background on varicose veins, definition enlargement of veins greater than 3 mm with tortuosity. Typically, this is associated with venous reflux and valvular incompetence. Estimates of prevalence range pretty broadly from 5% to 40%, maybe more common in women. I say maybe because actually the data on that is much less robust than I think any of us would have thought. Increases with age, as well as weight and some other risk factors. The CEAP classification is used generally for venous disease. C-, is the clinical piece of this classification. C1 is telangiectasias [superficial spider veins]. Varicose veins come in at C2 and then C3 through C6 go up through increasing levels of complications, edema, skin changes, and ulceration. There is also a division into asymptomatic and symptomatic, symptomatic being pain, tightness, burning sensation.

What are indications for treatment? So, treatment is indicated for the therapeutic management of symptoms, again, including pain, tightness, burning, and then complications, edema, skin changes, ulceration. Some patients have more significant complications. These can rupture and hemorrhage and occasionally, people will have recurrent thrombophlebitis. There is also cosmetic treatment, typically of course not covered by insurance, but I bring it up because this is a pretty big business. I tried to get numbers on how common this is and couldn't find any, but on my commute from Seattle to Olympia, I counted six billboards for venous treatment centers. So, there's a lot of this out there, and I think this is relevant, because we do want to make sure that our policies preclude cosmetic indications for treatment.

What are the goals and risks of treatment? Reduced pain, swelling, essentially reducing symptoms, improving function, and reducing complications. What are the risks? There are a certain number. Periprocedural pain can be significant, scarring, hematoma, some folks will have thrombophlebitis from treatment, and some of the modalities can result in nerve damage or skin burns. More serious adverse effects are rare, but can include DVT and PE, as well as infection.

Modalities of treatment we'll be discussing today, traditional treatment with surgical ligation and stripping, and then there are a number of newer modalities, endovenous laser ablation, so removal or destruction of the vein through laser light, and this is done with a device that's threaded into the vein. Radiofrequency ablation is similar but uses bursts of radiofrequency energy. Sclerotherapy is the injection of either a liquid or foam into the vein, which then chemically destroys the vein. Phlebectomy is use of small incisions, 1 to 3 mm and then the segments are threaded out and removed through those.

There are a few newer modalities, as well, microwave therapy and some others that are not approved in the U.S., and we won't be addressing those today.

Modality uses and limitations, some of these are used in certain circumstances and not in others. So, for example, laser and radiofrequency can't be used when there's an aneurysm or when the vein is over a certain size or extremely tortuous, in which case they cannot thread the device into the vein. Foam sclerotherapy is often used for very large veins, liquid for smaller ones. Phlebectomy is relatively rarely done on its own. It's more often used as an adjuvant. So, another modality would be used to destroy the primary vein, and then this can be used for the smaller tributary veins.

Key questions we'll be addressing today, as Dr. Standaert mentioned, efficacy of these new therapies, particularly relative to ligation and stripping, safety, is there varying effectiveness and safety for different subgroups of patients and what are the cost implications?

So, why are we talking about this? This is a pretty substantial book of business. Here you see the UMP and Medicaid trends for expenditure. This is something that's been slowly coming down in the UMP group, going up in Medicaid, but amounts to about a million dollars a year between the two. Numbers in L&I and in Department of Corrections are very low, so those were not included today.

Looking at the same numbers by utilization by population, again you see things going up in Medicaid, coming down in UMP. We think this is because there used to be very restricted access in the Medicaid population. That has now become more available. It used to be relatively open in UMP and now somewhat more defined policy, so kind of converging on the same utilization points in both populations.

Which modalities are these impacting? So, here you see the Medicaid data relatively small and steady strip across the bottom of ligation and stripping, and then the newer modalities are the ones that are really increasing in a pretty broad spread against the different modalities, a little bit less sclerotherapy and more of the others.

Same numbers in the UMP population or same breakdown. Again, you see utilization gradually decreasing. You can see, or maybe you can't see, the tiny yellow strip at the bottom, really, really rare to see surgery in this group, just a patient or two each year. So, most of that utilization is in the newer modalities.

Costs are difficult to assess for a couple of reasons. Frequently, people will have more than one procedure done at the same time, since they are associated surgical and facility costs, it's a little hard to figure out how to divvy those out. So, costs are harder to assess than they might be. This is using median data around people who only had one procedure at a time. So, that's kind of a somewhat selected group, but that's how we tried to get a summary data. So, you can see here, none of these are super cheap. Ligation and stripping on the left is overall a little bit more, and then kind of a broad spread across the others, not a huge trend cost across the years. This shows 2012 to 2016, not a huge shift in treatment cost per modality during that time.

Same analysis, looks a little bit different in the UMP population. On the left, the ligation and stripping, again, based on various small numbers, which is why that's so variable. Here we see that phlebectomy is sort of the next most expensive, a little bit cheaper for laser and radiofrequency and quite a bit cheaper for sclerotherapy in this group.

Current agency policies, all of the state agencies cover these procedures but with prior authorization.

Before we get to the literature, I want to talk a little bit about its limitations. I think this is going to be a frustrating analysis today, and I want to talk a little bit about why. First off, the techniques really preclude effective blinding. To do a good sham procedure of ligation and stripping, you'd be cutting fairly large holes in someone's leg. So, you will find that almost all of the studies are rated relatively poorly, and a lot of that is because of the lack of effective blinding. There's also a real lack of standardized assessment measures on either efficacy or safety. So, it's very difficult to combine study data and to hard end points, because they're all looking at different measures. Maybe even more frustrating, there is often a lack of functional assessments. There's a generally poor correlation between physiologic assessments and symptoms and quality of life scores. So, how well you occlude the vein does not necessarily correlate to how well somebody's symptoms improve.

Second slide on limitations, probably not a good sign. Many of these have a lack of information about the inclusion criteria. There are not a lot of subgroup analyses. Costs, as I mentioned, are difficult to calculate, because of the facility cost issue for use of multiple modalities, and then some of these can be done either in the office or the operating room, with obviously quite different cost scenarios. Phlebectomy, specifically, has very limited information and it's probably because it's rarely done alone as a standalone procedure.

So, now that I've warned you about the data, let's actually kinda look at it. So, this is information that Hayes will present in much more detail, but just to create kind of an overview. So, these are looking at statistical rather than clinical significance on differences for a variety of efficacy outcomes. Green are situations where the newer modalities are better than ligation and stripping. Yellow is where there is no significant difference. Red are where the newer ones are worse. So, the ones that I've pulled out here are primary occlusion of the vein, recurrence of symptoms, improvement in the CEAP score, quality of life, and reintervention. As you'll see, laser looks better for

primary occlusion, pretty much the same across the board. Sclerotherapy comes in with higher reintervention. Otherwise, most of them are statistically not that different or have conflicting results. Again, we just don't have data around phlebectomy.

I think it's useful to look at some absolute data and again, we didn't have absolute summary data because of those differences in outcomes. So, this is just a single study that I pulled out because it was relatively well done. It looked at multiple modalities. So, this looked at ligation and stripping, laser and foam sclerotherapy, and it included some really relevant functional outcomes. So, this one refers to the Aberdeen Varicose Vein Symptom Score, AVSS. I'm not sure why there's only one V. This is not our Aberdeen but the other one. This is one of the commonly accepted modalities. It does not have a threshold for clinical significance. The scale goes from 1 to 100, and most symptoms come in at... most patients start around 20. So, that, at least, gives some perspective to these numbers.

So, looking at occlusion of the vein for ligation and stripping and laser, you have almost 100% full or partial occlusion, actually full occlusion, at a year. Foam sclerotherapy, quite a bit lower, 51% total occlusion and 81% partial occlusion at a year, but then if you look at the AVSS score, ligation and stripping comes in at 8, laser is actually better at 9.5, and foam sclerotherapy is the same as ligation and stripping in spite of those much lower physiologic assessment results. Retreatment, also a relevant measure of how many people had significant symptoms that required further treatment, 7% for ligation and stripping, very low at 1% for laser, and higher at 15% for foam sclerotherapy. So, again, these aren't summary numbers, but they kind of put things in perspective.

So, that's efficacy, how about safety? So, again, these are clinical... these are statistical significance rather than clinical and relative to ligation and stripping. Looking at serious events DVT/PE, as well as nerve damage, infection, postoperative pain, delayed return to work, others. So, here again, you'll see across the board in general, the newer therapies are better on the safety side than ligation and stripping. Laser, pretty much, better across the board. Some concern with radiofrequency ablation, that there may be a slightly higher risk of DVT and PE, some conflicting numbers around some of the others, but overall, these are better tolerated than ligation and stripping.

Again, to give some absolute numbers, just to kind of give a little color to that relative change, here, this was a study of 233 patients. DVT and PE very rare. None were seen in this group, and across the board, these were, these were quite rare. Infection, they only saw minor infections, small numbers in both ligation and stripping and laser. I will call your attention to pain score discharge. So, significant in the ligation and stripping group, about 2.2, less than half that in the laser group, but a little bit under 1, and practically none with foam sclerotherapy. Another quite significant difference, sick leave 12 days for ligation and stripping, average of only eight days for laser, and a single day for foam sclerotherapy, so some pretty significant differences. Hematoma also lower, as you go down. Skin pigmentation more common with sclerotherapy. That's a sort of known side effect of the procedure. Paresthesias quite rare in all of the groups.

Cost data was presented but again, was very limited in the literature. This is, again, kind of pulling out one study that was able to differentiate multiple groups, and I think this just really confirms what we saw in our own local data, none of these are cheap. Ligation and stripping generally somewhat more expensive, and the others kind of come in at different points, particularly depending on whether they were done in the office or in the operating room.

Subgroup analyses, there just really weren't any, which was very frustrating.

Looking at the eligibility criteria, there wasn't data on the differential eligibility for surgery versus the less invasive procedure. So, who might qualify for a minimally invasive procedure, who wouldn't qualify for surgery? Typically, the inclusion criteria were people who were referred for surgical treatment, whatever exactly that means. Presence of varicose veins, presence of symptoms, sometimes included symptoms that were severe enough to interfere with either mobility or ADLs. Then, there were a number of standard exclusions, including pregnancy, active infection, DVT, or severe distal arterial disease. If you don't have blood supply to heal, you don't want to go messing around with these things.

Comparisons, what are other people doing? So, Medicare has no National Coverage Decision. Local Coverage Decision, basically it's covered if there is significant symptoms, including impaired mobility or complications, including ulceration, edema, bleeding, dermatitis, and people have to have failed three months of conservative therapy, typically including compression hose and elevation. Regence, this is out of date, as of yesterday afternoon when we got their new policy. I think there are Regence folks here today. Apparently, they did a pretty extensive revamping of their policy this year, because this is an area where they see a huge number of requests for prior-auth and put a lot of time into them and have a lot of appeals. So, they actually simplified their policy somewhat this year, but essentially, they are requiring functional impairment or significant complications, again failure of conservative therapy, and they have a number of documentation requirements around ultrasound showing venous incompetence, photographs. Initially, they had very specific anatomic criteria for each procedure type, and that's been simplified in the current policy.

So, our overall assessment here, we feel that this is a procedure where there's medium safety, high efficacy, and medium cost.

And what are our recommendations? So, our recommendation is that all modalities be covered with conditions and prior authorization, that we use the indications and eligibility criteria that we saw in most of these studies, so the presence of varicose veins, obviously, three months of conservative therapy with compression and elevation that don't resolve the symptoms, and symptoms that are sufficient to interfere with instrumental ADLs or the presence of complications. Again, this is really about making sure that we're approving this in people where it's medically necessary rather than cosmetic. We would include the standard exclusions, pregnancy, infection, peripheral arterial disease [DVT]. As we saw earlier, really the new modalities have comparable to, for some of them, less efficacy than ligation and stripping, but those tend to also correlate with sort of increasing tolerability. So, the ones that work less

well are better tolerated. So, our assessment is that this really creates a role for patient choice and patient selection and that the evidence is not sufficient to say one over the other is appropriate in all circumstances. Any questions? Yeah.

Gregory Brown: So, did we see any of the discussion regarding things like healing of ulceration or reduction in episodes of ulceration? If that's one of your indications, did we see it in any of the outcomes?

Emily Transue: No.

Gregory Brown: OK.

Emily Transue: It really wasn't measured, and again, one of the real frustrations of this data is that the reason that these procedures are being done is typically not assessed in the outcomes.

Chris Standaert: Somebody could correct me if I'm wrong on the committee, but I don't think we've ever made a decision where we say covered under prior authorization with no other anything, right? So, if it's just going to be prior authorization, there's no need to bring it to us. We're supposed to define... for the people on the committee, we are the ones defining the parameters of that use so that that whole need for prior authorization isn't really there and isn't so subjective or so variable or so whatever. I thought the intent of our committee was to use the evidence to do that. So, from my standpoint, that's a curious suggestion for us, because you don't usually suggest we do that.

Emily Transue: And that's a Michelle Simon-phrasing on my part, as I'm sort of new to this process. So, I would say cover with conditions and the conditions would be those inclusion criteria. Or Dan, do you want to?

Dan Lessler: Yeah. That's exactly right. So, when you guys provide us with conditions for coverage, those then become the basis for prior authorization. So, that's what was intended there.

Emily Transue: I apologize.

Chris Standaert: Do you have a question or comment.

Mark Meissner: I was just wondering, I thought that was very nice. Dr. Transue, my question is how the requirement for compression stocking enters in there, because there really is no data presented at all, and in fact, there, not to bring extra data into it, but if you do the back of the napkin calculation, it increases cost quite a bit. The positive predictive value of a response to compression is very high. The negative predictive value is very low, probably about 5% in some of the literature out there, and if you calculate the cost of an additional clinic visit to assess response to compression, it comes out at about \$250 and add the price of the stockings in at \$90 a pair, it really becomes in the end an expense that really has no benefit for patients at all. That would be... I thought the review was very balanced and overall accurate, but to include a criteria that the evidence doesn't really support is a little bit problematic, I think.

Emily Transue: And I think that's a very relevant question. It was frequently sort of included in the groups that were being looked at, but I think there is a valid question to be drawn about whether that's a useful criteria.

Chris Standaert: I think we can talk about that and what's in the scope of our evidence and what isn't. I mean, it's a chronic condition. It's a longstanding condition, usually, by the time you get to surgery. I just had a question. So, I'm curious, when I see multiple different modalities using multiple different devices with varying degrees of expansion or contraction over time, I wonder several things. So, one, and Dr. Meissner, you can help answer this, too, I suppose, are the only people who can do this vascular surgeons, or are they being done by podiatry? Are they being done by other specialists of various sorts, and issues of access to various devices? People may choose to do what they can get to under their scope of privilege and what they can get to under their sort of ability to acquire the device moreso than what may be the more effective of the various options out there in the whole sphere of things. We're looking at multiple different treatment modalities that may or not be all compared head to head here to try to figure out what works and what doesn't. So, can you help me with that, at all?

Emily Transue: I'm hoping Dr. Meissner.

Mark Meissner: Well, as far as the first question goes, who can do this? There are, as you saw from Dr. Transue's presentation, many of these are done in the office where there is no credentialing to be able to do these procedures. I think we're fairly fortunate in Washington State, which is not true around the country, and I don't think there is a lot of overuse. In Washington State, I would suspect the vast majority are done by vascular surgeons or interventional radiologists who have the skills to do that, but the fact of the matter is, is many of these are done in the office, which I think clearly is the way to do it, because as the data showed, it's much cheaper in the office, but it does have the problem that there is no credentialing.

Chris Standaert: So, there is no real restriction on who can do this?

Mark Meissner: No. There are, and we can talk about that at some point. There are some accreditation, well one in particular accreditation agency that's been adopted in Massachusetts that accreditation is required for payment by Blue Cross and Blue Shield of Massachusetts, which does add a layer of credentialing and showing your results to become credentialed. It has not been widely adopted across the country yet. As far as the multiple modalities, I mean, all of these are functionally designed to destroy or eliminate from the circulation the main trunks, which really are the saphenous vein, the accessory saphenous vein, or the short saphenous vein. All of these accomplish it with equal efficacy, and I think the data really showed that despite the relatively low quality of it. All of these things work equally well.

Chris Standaert: OK. I guess we'll have to get into why one would pick one over another then. I mean, are there different access issues, different costs for the technology, different ability to acquire, based on your practice style or your profession?

Mark Meissner: I think, not really. I think...

Chris Standaert: Hospital privileging, that sort of thing play a role?

Mark Meissner: ...I think some of it is really based upon the introduction of the technology, laser and radiofrequency were the first introduced back in the early 2000s, so have a wide degree of penetrates and adoption. Some of the newer products, which are even beyond the scope of this review, are more recent in their introduction. I think a lot of us pick and choose which technology we use based upon how the patient presents, and as Dr. Transue said, the catheter based technologies, which are radiofrequency and laser ablation, work well for straight segments of the axial veins, the saphenous veins. They don't work well for tortuous veins or veins that have had a previous episode of thrombophlebitis, superficial thrombophlebitis, and in those foam sclerotherapy may be a better option. So, I think all of these are used by most practitioners to a greater or lesser extent based upon individual patient characteristics.

Chris Standaert: Other questions or comments for Dr. Transue?

Sheila Rege: For some reason, between 2015, like, 2013, this wasn't done much, and then all of a sudden, 2015 utilization just skyrocketed, and I'm just thinking back on, you know, when you said something about billboards. Sometimes, that has a reason, either the code suddenly has been valued really high, and so all these startups kind of come into play. Did something happen? I mean, was this reviewed by Medicare and all of a sudden the reimbursement got really super good or did some new technology come into play? I'm just wondering?

Mark Meissner: I think Dr. Transue did a nice job of explaining some of it. I think utilization, historically, has probably been low, just because of the magnitude of the procedure with saphenous vein stripping with a long return to work, a long recovery time, I think the data at some low quality does suggest patients have much less pain and return to work faster, which has not only increased patient adoption, but also patients who were referred for it, but I think Dr. Transue also mentioned that, you know, throughout the 2000 to 2010 there was very little access for Medicaid patients to this technology. It just wasn't covered. Utilization went up when it was utilized and in contrast, I do think the Uniform Plan restrictions have increased resulting in a decrease in Uniform Plan participation, but I think a lot of the increased utilization can be attributed, as Dr. Transue said, to increased utilization by Medicaid patients.

Chris Standaert: On that graph of, I don't know what slide number that is.

Sheila Rege: Twenty seven.

Chris Standaert: With a big jump. That is Medicaid.

Sheila Rege: On Page 5 here.

Emily Transue: Yes, that's...

Chris Standaert: That's Medicaid, and that doesn't, there's two. One has per 1000 population. The other one doesn't have... it just says number of treated patients, which is totally different, because the...

Sheila Rege: How about the other...

Chris Standaert: ...Medicaid population...

Sheila Rege: ...slide?

Chris Standaert: ...has expanded.

Sheila Rege: The slide before that?

Emily Transue: So, this, let's see. So, this shows number treated per 1000 in the two groups, so Medicaid going up, UMP going down and kind of converging on the same point.

Sheila Rege: I was looking at the slide, trends and utilization by modality, Medicaid.

Emily Transue: Yeah. So, this is, right. So, Medicaid is going up, and that's just the total number of treated patients in the...

Sheila Rege: Yeah, it's [inaudible].

Emily Transue: ...Medicaid population.

Chris Standaert: Yeah.

Emily Transue: Um...

Chris Standaert: So, that's the thing. That's total number. That's not number per 1000 or per population.

Emily Transue: ...right.

Chris Standaert: So, if the pop...

Sheila Rege: That just...

Chris Standaert: ...if the population went...

Sheila Rege: ...that is, OK.

Chris Standaert: ...up also, and it sounds like Medicaid expanded access...

Sheila Rege: OK. So, it's...

Chris Standaert: ...to existing procedures.

- Sheila Rege: ...Medicaid expanded access more than utilization.
- Chris Standaert: So, they paid for it, it sounds like. They decided to start paying for it so people started doing it. They started paying enough that people would do it.
- Kevin Walsh: But it's also an increase in the absolute number of people covered by Medicaid.
- Chris Standaert: Yeah, exactly.
- Kevin Walsh: Because after the [crosstalk].
- Emily Transue: Yeah, so I think this slide gives a better, I think, assessment of sort of the frequency per population.
- Sheila Rege: And that's not a big [crosstalk].
- Emily Transue: So, again, you do see an increase. I think all of us who were requesting authorizations for these back in the early 2000 somethings remember that you just couldn't get them approved in Medicaid at that time, and that's loosened up a bit.
- Chris Standaert: Other questions for Dr. Transue? She will still be over there for the morning, but we can let her go sit down if nobody has any more questions for her.
- Emily Transue: Thanks.
- Chris Standaert: No? OK. So, next on our agenda is the public comment. So, there are four people who have signed up to speak, several of whom had pre-signed up, one of whom signed up today. I want to make sure we open up the phones while we're in our window for public comment. So, our time for public comment on the schedule ends at 9:05. So, I don't like to go out of order, but I do want to make sure we give a chance for people on the phone. So, we're gonna start with them to make sure we're in their window when they might be expecting to speak, and then we can have the people in the audience speak. So, given that, is there someone on the phone who would like to address the committee regarding treatment of varicose veins? This is the open public comment period, and this is your time to address the committee. It doesn't sound like it. Nope. Nobody there. So, then we're going to go through our list here. We have four speakers. So, again, when you come up, please introduce yourself. State conflicts of interest, if you represent anyone or any organization, and if people paid for travel, all that sort of thing to get here to present to us. Our first presenter is Kathleen Gibson. Yes, to the mic please. So, again, introduce yourself. This is all transcribed.
- Kathleen Gibson: OK. My name is Kathleen Gibson. I'm a vascular surgeon, and I work at Lake Washington Vascular, which is a private practice vascular surgery group. I'm a board member of the American College of Phlebology, which is about a 2000 member group of different vein practitioners, and I'm also on some committees for the American Venous Forum, which is another society. I do a lot of clinical research. So, I have gotten research support from various players in this field, AngioDynamics, which makes a laser, Medtronic, which makes a vein glue and radiofrequency catheters, BTG, which

makes a foam. I also work in thrombosis research, so I've had support from Bristol-Myers Squibb and Behr. Those are my conflicts. So, I appreciate you taking up this issue and I think that was a very nice summary. The one quibble I have is also what Dr. Meissner said about the stockings. If you look at the NICE guidelines that the British government came up with in 2013, before that time, varicose vein treatment was very restricted in the U.K. and afterwards, they came to the conclusion that treatment of patients with symptomatic varicose veins was cost-effective, it improved quality of life. Chronic venous disease, they put it about the same kind of impact on patient quality of life as chronic cholecystitis or COPD, and they concluded that requiring patients to wear compression stockings was not appropriate, because it was not shown to be beneficial. In my mind, it's kind of like saying to someone with a hernia, you need to wear a truss. Take the truss off, it hurts again. I think our challenge is making sure that the right patients are being treated and that patients that require treatment do not face significant obstruction to get it. That plays into both your efficacy, safety, and your cost. It's not cost-effective if you're treating people that don't need to be treated. We need to be treating our patients and not the ultrasound image. A lot of these kind of measures of success say, is the vein closed. Patients don't come to us saying, I'm here because my GSV is refluxing. They come because it's impacting their quality of life, nor do they come back and say this failed because the ultrasound shows it's not closed. So, we really need to be focused and be patient centered, like you had said, focusing on the impact of the disease. I think we need to use some of the validated tools that we have out there when we're looking at our patient's severity measures and quality of life tools that we have. Treatment needs to be ethical. Some of this billboard phenomenon is scaring patients into thinking this is something that might be life or limb threatening when it's not. So, appropriate treatment is important, and I think societies need to have a role in that. Registries need to have a role in that, encouraging patient's physicians to be showing their outcome measures. I think patients with advanced disease should not have significant delays in evaluation and treatment, and that's a problem that we are seeing, particularly with Regence in our areas. Even though you've seen their coverage policy, the majority of their coverage now is restricted to the University of Washington or the Bill and Melinda Gates Foundation. Most of their other policies have a blanket carve out. We are finding barriers for stocking wearing, plans with blanket exclusions, calling certain veins as being experimental treatment when they're clearly not, requiring photographs, which there is no data that somebody else looking at a photograph says that the patient has an impact on their quality of life. Size requirements that are based on no data, and lifetime limits. So, I think that I need to wrap up, but I would say we need to be our patient advocate. We need to look at the impact on patient quality of life and not on an ultrasound image and encourage practitioners to be ethical. Treating the right patients will give us value, I think, in improving patient quality of life and why they come to see us. Thank you.

Chris Standaert: Thank you. Just a reminder, you all have... when you're addressing us, you have three minutes and you'll get little warning signs over there, as you near the end. Next is Monte Madsen. I hope I'm pronouncing people's names right. OK.

Monte Madsen: Good morning. Thanks for the opportunity. I'm Monte Madsen. I'm the medical science advisor for Medtronic, and I'm a salaried employee for Medtronic. Prior to this

position, I worked as a vascular technologist in Spokane, Washington, which is basically a diagnostician and assisting physicians in these procedures that are in our discussion today. We want to ensure that the panel is aware of some robust clinical evidence comparing radiofrequency to stripping that was excluded from the evidence review, and it was excluded because it was published before the March 2011 cutoff date. Specifically, the review excluded six randomized control studies representing a total of nearly 900 patients evaluating RFA and stripping. Given how much less invasive RFA is to stripping, the studies demonstrate that the patients receiving RFA have shorter recovery times. Some of that was depicted in the nice presentation, less postoperative pain, and fewer higher morbidity complications compared to stripping. These benefits are achieved without sacrificing treatment efficacy. Vein occlusion and treatment rates, or excuse me, recurrence rates, are comparable to stripping short and long-term. Again, a nice presentation that depicted that. Medtronic technology has had FDA clearance, since 1999. So, the key studies of that technology's effectiveness were published in the early 2000s, hence missed the cutoff date. We provided description studies in both our comments on the draft key questions and the draft report. With the exception of being published before the review's cutoff date, these studies satisfy the reports inclusion criteria, and are critical to any comprehensive evaluation of any treatment modalities. We encourage the panel to take the exclusion of these level one evidence studies into account and rely on the clinical guidelines cited in the evidence review, which takes a more comprehensive body of evidence into account. The American Venous Forum, Society of Vascular Surgery, and ACP guidelines for patients with chronic venous disease both recommend both forms of ablation over stripping and ligation for the treatment of saphenous incompetence. We also ask the evidence review group, Hayes, to acknowledge the exclusion of these studies in the report, as this will be reported at other Health Technology Assessment and other payers potentially may rely on for decision making in those venous treatments. Thank you, very much, for your time, and I'd be happy to take any questions.

Chris Standaert: Next, we have Alex Young. Again, oh, I'm sorry. You're signed up, then Dr. Brian Ferris.

Brian Ferris: Good morning, and thank you for the opportunity to speak before the committee. As mentioned, my name is Dr. Brian Ferris. I am a vascular surgeon and partner to Dr. Gibson, and a member at Lake Washington Vascular practicing on the Eastside. I am a fulltime clinician participating in clinical research, as coinvestigator, principal investigator. I also serve on medical advisory boards in the industry, including Boston Scientific, BTG, and do educational talks on behalf of the new anticoagulants for Jansen Pharmaceuticals. I'd like to comment on the initial presentation. I thought that was a very good and thoughtful presentation, and I respect the guidelines by the researchers to be evidence directed. I do think, however, the committee is missing the mark and like we talk to patients, it's a matter of informed consent. Venous disease has come a long way, and I would recommend that we consider we're far behind in contrast to how we look at things like tumors or arterial disease. The American Venous Forum has gone a long way to try and not only have a common terminology language, and I think our overall research is improving. I do think, though, that we've missed the mark in that there are randomized blinded trials, and it pertains to your discussion on foam sclerotherapy, and I think an important distinction was missed. There are two forms of foam sclerotherapy. There are physician created and then there is actually FDA

approved, and those are different therapies. The FDA approved therapy, which is called [inaudible] was evaluated in several trials that did include blinding, did include patient-centered quality of life, patient-centered outcomes, are independently verified, as well as specific to venous disease. So, I think that there is actually some patient-centered outcome data that should also be included with all respects to the restraints of trying to have the highest quality clinical evidence, level one evidence, and we recognize that as surgeons, our field, including vascular surgery, has long missed the mark, but we're making great strides to improve that. So, I would like to make that a note for the record, as well, and thank you for your time to let me address you. Good morning.

Chris Standaert: Quick question. You said you felt the committee was off the mark, or are you referring to the report, 'cuz the...

Brian Ferris: I'm sorry, not the committee, you're right, because you haven't made a decision.

Chris Standaert: Just trying to be clear.

Brian Ferris: What I mean by that is, is that I think it's a matter of informed consent. You need more information. I think this morning's presentation was good. I think it missed the mark on some additional data that, as we talk about patient-centered outcomes, there's... venous disease is as spectrum, and yes. There are clearly problems that are cosmetic. And as professionals, we would like to make sure that those patients are not before your charge before insurance company or Medicaid. We'd like to see those dealt with separately. Then there's two other buckets. There's the patient-centered symptoms, and then there's complications. Whether those complications are skin problems, stasis changes, lipodermatosclerosis, ulceration, recurrent ulceration, but there is also thrombosis and bleeding. So, I think we have to categorize those, and I think the American Venous Forum has helped us do that, and I think we're getting better, but in light of this morning's initial data review, I think that we missed the mark on some additional information that would be useful to you making a decision. That's what I think.

Chris Standaert: OK. Thank you.

Brian Ferris: Thanks for letting me clarify that, and good for calling me out on it.

Chris Standaert: Anybody else in the audience want to address the committee? No? OK. That will end our time for public comment. Next, we move on to our evidence report.

Candy Wines: Good morning. As you've heard, this presentation covers the key data and conclusions from the selected treatments of varicose veins Health Technology Assessment. The second slide in your packet is a reference slide for some of the abbreviations you may see throughout this presentation.

I was planning to start with background of the condition and the treatments of interest, but that seems to have been covered fairly well. If you'd like me to go through it again, I will, or we can skip forward. Is there a preference?

Chris Standaert: You should just go through your presentation as you submitted.

Candy Wines: OK. Sure.

Chris Standaert: Just to make sure we're all on equal footing.

Candy Wines: No problem. So, we'll start with the background. The varicose veins, or varicosities, are a common manifestation of chronic venous insufficiency. It's a category of chronic venous disease. They are enlarged, usually greater than 3 mm, tortuous vessels that develop when the flaps of the venous valves no longer meet in the midline, causing the blood to flow backwards, or reflux. Superficial venous reflux introduces elevated intravascular pressure leading to progressive distension, dilation, and tortuosity of the vein. Prevalent estimates range from 5% to 30% of the adult population and they are generally more common among women than men, as we heard earlier. There is some question in that. Chronic venous insufficiency of the lower extremities is typically classified based on symptoms using the clinical, etiologic, anatomic, pathophysiologic, or CEAP classification system. The C-, or clinical score, ranges from C0, which means absolutely no venous disease that can be seen or felt in the legs, to C6, which indicates and open and active leg ulcer. C2 denotes the presence of varicose veins, and C3-6 describes chronic venous insufficiency of increasing severity.

Varicose veins are found, most often, on the back of the calf or on the inside of the leg between the groin and ankle, but they may appear anywhere on the body. Greater saphenous vein reflux, a frequent form of chronic venous insufficiency, is commonly responsible for the development of varicose veins; however, reflux in the small saphenous vein also occurs in approximately 6% to 15% of patients with chronic venous insufficiency. Often, varicose veins initially present as a cosmetic concern, but they can become clinically important when symptoms, such as cramping, swelling, or feeling of heaviness or fatigue in the afflicted area become pronounced. Severe varicosities may be associated with dermatitis, ulceration, and thrombophlebitis. Additionally, patients may report decreased general health and overall quality of life. Risk factors include older age, family history of the condition, obesity, pregnancy, inactivity, and prolonged standing or sitting.

Goals of treatment include sealing off damaged portions of veins, reducing or eliminating pain and discomfort, improving quality of life, preventing further varicose veins formation, preventing or treating conditions, such as venous leg ulcers, and making cosmetic improvements. Risks and potential harms for traditional open techniques include complications from groin incisions, pain, scarring, and long recovery periods. Less invasive procedures may reduce postoperative morbidity, improve recovery time, and be preferred by patients compared with conventional surgical options, but these are also associated with potential risks and complications, such as hematoma, thrombophlebitis, venous thrombosis, vessel perforation, thermal injury to adjacent nerves, skin burns, and discoloration.

The treatments reviewed in this Health Technology Assessment are endovenous laser ablation, referred to as EVLA. This is removal or destruction of a vein using laser light. This is intended for the treatment of varicose veins that result from greater saphenous

vein, small saphenous vein, or accessory vein reflux. Contraindications include pregnancy, extremely tortuous veins, peripheral inflammatory artery disease, history of deep vein thrombosis, or deep venous insufficiency, nonpalpable pedal pulses, and difficulty walking. The next intervention is radiofrequency ablation. It is another form of endovenous thermal ablation that employs radiofrequency energy. It is intended for the treatment of varicose veins that result from greater saphenous vein, small saphenous vein, or accessory vein reflux, and presence of a thrombus in the vein segment to be treated as a contraindication. Sclerotherapy is the obliteration of a vein or vein segment by chemical introduction, either liquid or foam. Liquid sclerotherapy is commonly used for telangiectasias and reticular veins or small to medium varicose veins. Foam sclerotherapy can be used for larger refluxing veins. Currently, there is one FDA approved foam sclerotherapy product that uses a canister system to generate foam using low nitrogen air; however, physician compounding at the time of treatment using liquid sclerotherapy and room air has also been described. That particular approach is the one used in most of the studies identified for this Health Technology Assessment. Contraindications to foam sclerotherapy include allergies to sclerosant, severe systemic disease, acute superficial or deep vein thrombosis, local infection in area to be treated, severe generalized infections, immobility, confinement to bed, advanced arterial occlusive disease, and known symptomatic patent foramen ovale. Phlebectomy, the next one on the list, is removal of a vein segment through a small, usually 1 to 3 mm incision with the aid of instruments. It is intended for side branch varicose veins and varicose veins of the foot around the ankle and the knee. It is often performed in conjunction with other techniques, either concurrently or sequentially at a later date. Ligation and stripping, or surgery, is a traditional method of surgically closing off a vein and removing it. Variations of the procedure exist, depending on the veins targeted for treatment.

Next, we'll review the policy context and objectives for this Health Technology Assessment. Treatments for varicose veins represent an area of substantial utilization in plans managed by Washington State agencies and participating agencies identified this topic based on uncertainties related to safety, efficacy, and the value of certain procedures, including chemical ablation, stab phlebectomy, and laser ablation. An evidence-based assessment of the comparative effectiveness, safety, and cost compared with traditional surgery is warranted to guide coverage policy. The key questions for the Health Technology Assessment address these concerns through effectiveness, safety, varying effectiveness and safety for subgroups, and cost implications of the interventions of interest compared with surgery.

Next, I will review, the Health Technology Assessment is structured around the population interventions comparator outcomes and study designs or PICOS shown on the next two slides. Subsequent slides provide a brief description of the literature search and quality methods employed.

Studies of adults being treated for varicose veins with endovenous laser ablation, radiofrequency ablation, sclerotherapy, or phlebectomy compared with those who received conventional surgery were sought. Data related to several clinical patient-centered adverse event and cost outcomes were extracted. Surrogate or indirect outcome, such as failure of procedure and technical recurrence are frequently

reported in the literature. These may provide some information about the technical success of the intervention, but it is unclear how directly they influence patient-centered outcomes, such as quality of life and time to return to work or other activities. Changes in symptoms or disease severity when assessed were often measured using the venous clinical severity score, or VCSS or the CEAP classification system. Studies investigating quality of life often employed more than one tool, a combination of general and disease specific instruments, and these instruments will be described in the results section in more detail. Eligible study designs were systematic reviews, randomized control trials, observational studies greater than 500 participants for key question two, and modeling studies for key question four were also considered.

A review of review methodology was employed for this Health Technology Assessment, and a comprehensive search of multiple databases for systematic reviews and Health Technology Assessment was conducted first. Following identification of the systematic reviews and Health Technology Assessment targeted searches for relevant primary data sources published subsequent to the systematic reviews were conducted. These included searches of electronic databases and manual searches of lists of citations from key publications. In addition, the national guidelines clearinghouse and websites of professional organizations were searched for practice guidelines. Payer policies were identified through searches of selected payers published coverage policies.

The assessment of systematic reviews, or the AMSTAR tool was employed to assess the quality of the systematic reviews, and the process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the grade working group. For individual study quality, the focus is on whether the findings are valid. This is assessed by considering study design, execution, and analysis and internal validity. The body of evidence for each outcome is assessed by considering five domains, the study design and weaknesses of the individual studies contributing to the body of evidence, the quantity and precision of data, applicability of the PICOS, consistency of the study findings, and any evidence of publication bias.

The next section summarizes the literature search results and data gleaned from the eligible publications. This figure shows the flow of literature through the search and review process. A total of 23 publications were identified through searches for systematic reviews and additional publications of primary data to answer the key questions. This includes eight systematic reviews and 15 publications for primary data not already included in one or more of the systematic reviews. The table in the next two slides describes some of the features of the eight included systematic reviews. There was some overlap of the individual studies included in the eight reviews; however, none of them included exactly the same set of studies because of variations in search dates and inclusion and exclusion criteria. Consideration was given to the overlap of studies when assessing the body of evidence. The review by Carroll et al included randomized control trials of endovenous laser ablation, radiofrequency ablation, and foam sclerotherapy. This review included studies of patients with any type of varices, and the two reviews by Nesbitt and Paravastu also assessed

endovenous laser ablation, radiofrequency ablation, and foam sclerotherapy. However, the Nesbitt review focused on studies evaluating the selected interventions for greater saphenous vein varices, and the Paravastu review focused on small saphenous vein varices. Pan et al evaluated studies of endovenous laser ablation only. This review included randomized control trials and observational studies.

Two reviews by Rathbun and Rigby focused on sclerotherapy compared with surgery. Rathbun limited studies to foam sclerotherapy, whereas the Rigby review also included liquid sclerotherapy. Dermody and O'Donnell assessed studies of endovenous laser ablation and radiofrequency ablation. Dermody specifically focused on analyzing data about harms associated with the two procedures compared with traditional surgery.

Fifteen publications of primary data not already included and at least one of the systematic reviews were identified. Eight of these publications presented recent or supplemental data from studies that contributed earlier data to one or more of the reviews. In addition, two U.S. based cost studies were identified. The inclusion and exclusion criteria of the individual studies varied. Some limited eligibility to patients with uncomplicated varicose veins, which means no thrombosis or phlebitis or skin changes or to patients with specific CEAP clinical classes, or to those with unilateral varicose veins while others did not explicitly state such requirements for inclusion. Most studies required confirmation of reflux by duplex ultrasound. Exclusion criteria in many of the studies included but was not necessarily limited to previous surgical or other interventional treatment, pregnancy, deep vein insufficiency, deep venous insufficiency, previous or active deep vein thrombosis, use of anticoagulants, allergies to sclerosant or anesthesia, and veins unsuitable for the techniques being evaluated. The patient characteristics included a mean age that ranged from 33 years to a mean of 56 years. More women than men were represented in the studies, and among the studies that reported the baseline CEAP clinical category, the majority of patients were C2 to C4.

The next few slides provide results for key question one. The tables indicate the overall body of the quality of evidence for each outcome and comparison with a summary of results from the publications contributing information for the specific outcome. This first outcome is technical failure or failure of the procedure. This is defined as incomplete procedure, in other words, the procedure had to be stopped, or occlusion or obliteration was not achieved or was not sustained. The results shown here generally represent early, less than six months post treatment assessment in most cases. The two-year data from one study was included in the laser ablation versus surgery meta-analysis by the Nesbitt et al group. For endovenous laser ablation versus surgery, there is moderate quality evidence that technical failure is similar or reduced with laser ablation. Two of the four systematic reviews analyzing data for this outcome either did not report the statistical significance of their results or they found no difference between endovenous laser ablation and surgery. The other two reviews reported statistical significant differences that suggest better results with laser ablation than with surgery. I just wanted to point out if you're making notes on your slides, in your packet, there is a typo here. The 1397 should be 1.97 in that confidence interval. That's the bottom line of that first row. For the radiofrequency ablation

versus surgery comparison, there is low quality evidence that there is no difference between the interventions for technical failure. This is based on pooled results from 12 studies. The rates appear similar but no P-value is reported. A meta-analysis of technical failure data from five studies of patients with greater saphenous vein varices found no statistical significant difference. For sclerotherapy versus surgery, evidence from quantitative analyses presented in four systematic reviews represents low quality evidence suggesting that there may be no difference between the two treatments. Two of the included systematic reviews found no statistical significant difference. This was based only on two studies and one review and one study in the other. A third review reported a higher rate of failure and pooled results from foam sclerotherapy study arms and surgery study arms, but did not report the statistical test results. A fourth review conducted a meta-analysis of six studies that found better results associated with surgery for anatomical closure.

The next outcome is technical recurrence. This is generally described as clinician-noted recurrence or the presence of reflux, recannulization, or new varicose veins in a treated limb diagnosed by duplex ultrasound scanning and typically, it's in the absence of patient reported symptoms. For the endovenous laser ablation versus surgery comparison, there is moderate quality evidence of no difference between laser ablation and surgery. A network meta-analysis using data from 23 studies was conducted to compare the hazard of having technical recurrence when treated with laser ablation, radiofrequency ablation or foam sclerotherapy compared with surgery at six months, one year, and two years. The analysis indicated that the rate of technical recurrence after endovenous laser ablation may be less than after surgery; however, the effect decreases over time, and the wide credible interval does suggest some uncertainty. The meta-analysis of two studies examining laser ablation compared with surgery for treating small saphenous vein varices found better results with laser ablation after one year. Two other reviews reported no difference between endovenous laser ablation and surgery based on their analyses, and another review found no difference between surgery and endovenous thermal ablation procedures. They combine radiofrequency ablation and endovenous laser ablation to compare it with surgery. Then, five-year results from three randomized control trials suggest a higher rate of recurrence in the laser ablation group than the surgery group. Statistical significance was not reported in one of these studies, and results from another randomized control trial suggests a higher rate of recurrence in the surgery group compared with laser at 12 months, but statistical significance was again not reported.

For the radiofrequency ablation versus surgery comparison for technical recurrence, there is low quality evidence suggesting no difference. This is a meta-analysis of data from four studies that suggested no statistical significance difference between the treatment groups, and a network meta-analysis suggested a small but consistent lower relative likelihood of technical recurrence over time with radiofrequency ablation compared with surgery, but again, wide credible intervals suggest [inaudible]. Sclerotherapy versus surgery, there is low quality evidence suggesting no difference in the short term; however, longer term evidence suggests that rates of recurrence may be similar between the two treatments or better with surgery. A network meta-analysis found that foam sclerotherapy was worse at six months and one year, then slightly better than surgery at two years; however, the credible intervals for each time

period were wide and indicate uncertainty about the results. Two other systematic reviews calculated odds ratios suggesting higher technical recurrence rates for foam sclerotherapy, but results were not significant. In a five-year followup publication, rates of recurrence were statistically significantly higher for the foam sclerotherapy group compared with surgery. An RCT comparing liquid sclerotherapy with surgery found no difference at one, two, or three years.

The next outcome is symptomatic recurrence. This is generally described as patient-noted recurrence that is then confirmed with duplex ultrasound scanning. There is a moderate quality body of evidence that suggests no difference in symptomatic recurrence between laser ablation and conventional surgery. None of the five reviews reported statistically significant differences. A five-year followup publication did not report statistical significance but found a lower rate of visible recurrence in the laser ablation group. Another five-year followup publication reported statistical significantly less recurrence in the surgery group. There was no significant difference at five and six-year followup in two other randomized control trials. For radiofrequency ablation versus surgery, this is low quality evidence of no difference between radiofrequency ablation and surgery. Neither of the two systematic reviews reported statistically significant results. For sclerotherapy versus surgery, there is very low quality evidence that includes few studies and inconsistent results for symptomatic recurrence. Only one of the reviews noted a single study of foam sclerotherapy that specifically reported symptomatic recurrence. This study found no statistically significant difference. Another study favored surgery over liquid sclerotherapy at one year. Three-followup data from one study suggests no difference in medium-term recurrence.

Slide 25 shows the results for change in disease or symptom severity. The clinical outcome measurement instruments used to obtain these results were the venous clinical severity score, the VCSS, which combines patient responses to questions with clinical items to calculate the 30-point score based on ten items. The CEAP was described previously, and among the studies that reported changes in disease severity by CEAP, most of them reported only changes in the clinical, or C-, category. The Homborn varicose vein severity score is an instrument that combines subjective symptoms, clinical findings, and functional data of venous insufficiency. I only saw this used in one study. The AVSS is usually used as a quality of life measure, and it is sometimes referred as the AVVQ, the Aberdeen Varicose Vein Questionnaire; however, the Mozafar study listed here described these results in terms of change in symptom severity. For endovenous laser ablation versus surgery, the overall quality of the evidence was low, suggesting no difference. Results of network meta-analysis of VCSS at one year from six studies found lower postintervention VCSS scores for laser than surgery, but the credible interval, again, crosses zero. A network meta-analysis results represent the mean difference relative to surgery. Three randomized control trials reporting three-year and five-year followup found no significant difference between the treatments. One randomized control trial reported lower, indicating better AVSS scores in the endovenous laser ablation group at one year and 18 months. For radiofrequency ablation versus surgery, there is, again, low quality evidence and no difference. In a network meta-analysis of venous clinical severity score at one year from six studies found slightly higher postintervention VCSS in radiofrequency ablation

than surgery, but the credible interval crosses zero. Based on a qualitative summary in another systematic review are results from three studies. Investigators concluded that disease severity scores generally improved over the length of the followup for both treatment groups with most studies reporting no overall differences between the groups. In one followup publication, three-year results, there was no difference between radiofrequency ablation and surgery with respect to VCSS scores and both groups showed statistically significant improvement from baseline. For the sclerotherapy versus surgery comparison for change in symptom severity, there is very low quality evidence suggesting either no difference between foam sclerotherapy and surgery or better results with foam sclerotherapy. A network meta-analysis, again at one year, found significantly lower VCSS for foam sclerotherapy than for surgery. Two studies summarized in another review found no difference between foam and surgery. Of the three randomized control trials providing primary data, one did not report statistical significance. Another found no difference, and a third reported statistically significantly better results for foam sclerotherapy at 12 months but not at six months.

The next outcome that was extracted is postoperative pain. This is in key question one instead of key question two, categorized it as a patient-centered outcome. Endovenous laser ablation versus surgery comparison, the quality of evidence for pain was determined to be very low due to inconsistencies across the body of evidence for this outcome. Results from a network meta-analysis do suggest that endovenous laser ablation may be associated with a slightly higher median pain score than stripping, but results were inconclusive. Three other systematic reviews reported that individual studies provided mixed results and none of these reviews conducted quantitative analyses. For the radiofrequency ablation versus surgery comparison, there is moderate quality of evidence that radiofrequency ablation is associated with less postprocedural pain than conventional surgery. The qualitative assessment of findings gleaned from data of pain outcomes from studies of patients with greater saphenous vein varices suggested that there may be less pain associated with radiofrequency ablation than surgery, and the network meta-analysis used data from nine studies and results suggest that radiofrequency ablation is associated with less pain than stripping in the first two weeks after the procedure. For sclerotherapy versus surgery, a very low quality body of evidence suggests that sclerotherapy may be no different in terms of postoperative pain than surgery. With respect to pain and network meta-analysis of nine studies found slightly less postoperative pain associated with foam than surgery, but results were not significant. Another review found conflicting results from two studies.

Chris Standaert: So, I'm gonna stop you for a second. I think a number of us are struggling with your methodology and how it translates into something meaningful for us here. So, the committee has some comments, but we have this idea of... we have a review of systematic reviews, right? So, we're missing a number of pieces of information that would be helpful for us, I think. And you correctly pointed out that the systematic reviews are all somewhat different. They have totally different numbers of studies, different distributions of studies. Some are two different Cochran reviews on totally different topics, but you're making, they're not the same, and if none of them address the questions we should have been after, you shouldn't have done that. You should have done a review to address the questions we were after.

Candy Wines: Mm-hmm.

Chris Standaert: So, other people had some comments.

Joann Elmore: Yeah, we were all kind of sitting here kibitzing in the back. I take my responsibility as a member of this committee very seriously, and I rely upon our vendors to help me collect the evidence and to hear your summary, but it's also important for me to understand individual articles, sort of a certain depth of it, and when I saw your search strategy was a review of review articles and just, like, what's the quality of all the other review articles, that doesn't give me the insight that I need as a committee member on our specific questions. I also have questions, you know, you're going on about statistical significance, but I care about clinical significance and quality of the underlying data that goes into this, not quality of the review. So, I'm wondering, this is a really hard topic, because there are so many articles. I don't know if the committee members have a better suggestion going forward for how we can deal with these topics. It's a monumental task that we set out for our vendors, but having... we've all read through your slides, which I think is why we asked you to stop, because I'm just wondering, both how to make certain I understand the data today but also if any committee members have advice for the vendors going forward.

Chris Standaert: Let's leave the going forward discussion for a bit. We're in the middle of a presentation. So, we should really... so if there are questions about sort of how to ...

Gregory Brown: I guess my... the hardest thing about any systematic review is heterogeneity between studies. And if you now add an additional layer of heterogeneity between systematic reviews of heterogeneous studies, I have no... I don't understand what any of the numbers mean clinically. I agree. So, I'm not sure finishing the slides in that section are gonna help us move forward at this point. I guess the other concern I have is that there were handouts. So, I don't know which studies were referred to, but there were RCTs not included in certain reviews. So, we have no idea if they are or not, because we have the reviews not the source clinical trials. So, I'm also understanding how to move forward here.

Chris Standaert: I mean, systematic reviews are limited by the PICO, right, the questions and rules of the review will directly influence the outcome of their review, right? And if you are so inclined, you can set up a systematic review to find just about whatever you want to find, if you set it up right, if you set your rules to determine that. I totally agree with Dr. Brown, this is... we have heterogeneity within a systematic review, but now we have multiple reviews that are totally heterogeneous, and then you're comparing them to one another, and we're getting comparisons of not clinical significance but statistical significance, and our job is to get at in whom might various procedures actually be useful and under what circumstances, and that's a certain degree of granularity that requires a greater degree of depth than we're getting at the moment. So, I think we should go through what you're... your presentation, but somehow in here from you, I don't know if you all can do it, this issue of granularity. We need to understand more about what's happening in these studies, and these reviews aren't the same, right? They're different topics, different groups, different people, and that difference is relevant, and that needs to be called out a bit, so we understand sort of

what they're talking about and where we have data and where we don't have data is useful.

Mark Meissner: You could offer maybe a little bit of advice on it, and I think Dr. Transue pointed out really nicely that this is a very hard area, and it's not the least of which is there are multiple outcome measures that really makes this not very amenable to meta-analysis. There are so many quality of life scores, so many clinical outcomes, that it isn't really... the individual high... I won't even say high quality studies, but what we would consider a good surgical study are probably much more valuable than the meta-analysis is, and I think you're probably just going to focus on something just as an expert, there... so many of these studies that include not important surrogate outcomes, like occlusion of the greater saphenous vein doesn't correlate with quality of life. It's a good technical outcome for looking at the feasibility of the trial, but in the end, it doesn't correlate with patient improvement. So, I think all of those surrogate outcomes, which are commonly referred to as, like, closure rates or saphenous occlusion rates ought to be discarded, elimination of reflux ought to be discarded, any technical recurrence that's based on ultrasound ought to be discarded, and really it needs to be focused on patient improvement and quality of life first and foremost, clinically relevant recurrence requiring reintervention, second most really the important outcomes amongst this myriad of outcomes that are commonly used in trials that really... quality of life and clinically relevant, not ultrasound recurrence are the important outcomes in this.

Chris Standaert: I think that's what our committee, I think that's what people are asking me. I mean, that's the point of the comments here, and even on pain, postoperative pain is a complication not an outcome, I don't think. Pain six months out, pain three months out, pain six weeks out I would think of as an outcome. Pain two days out from surgery sounds like more of a complication than outcome.

Gregory Brown: The other part that I'm still missing, and maybe you can help me, Dr. Meissner, is if I heard right, zero is no problem on the... what is it CEAS?

Mark Meissner: Correct.

Gregory Brown: Two is varicose veins and six is ulcerations, and I don't have any idea where three, four, and five went and how treating to prevent six and maybe it's... and it's not in the study. I mean, that causation is not going to be in an RCT. Can you just help me understand a little better of where treatment intervenes and prevents these further stages?

Mark Meissner: Sure. And that's a little bit of the problem is the CEAP instrument, which I was involved in developing, was never meant to be an outcome instrument. It's a descriptive instrument for putting patients in bins and varies from C0 with no problems to C2, which is varicose veins. C3 is leg swelling and edema. C4 is hyperpigmentation and skin changes, lipodermatosclerosis. C5 is a healed ulceration. C6 is an active ulceration. So, obviously, if you've never had an ulcer... if you've had an ulcer, you're never gonna be better than C5. It doesn't change, and it's not a linear scale either, where C2 is meant to be worse than C6. It should not be used as an outcome measure in these. Now, regarding the second question, do patients progress from C2 to C6.

They do, but it's a minority of patients. It's, less than 5% of patients will progress from C2 disease to C5 disease, and it's just beginning to be understood. Probably the biggest indicator is a family history of having advanced venous disease. If your family has a history of ulceration, you are at much higher risk, and just now there was a great article in Nature in March, we're just starting to identify another source of cost in all of this, or genetic markers of who is going to progress that probably are never going to be worthwhile, because only 5% of patients are going to progress. So, I don't think you can really make a valid argument to treat patients based upon progression from C2 to C5 or C6. It is a very slow process. Most patients are going to progress, and patients ought to be treated on their own symptoms, as they present at the time rather than a goal of preventing progression in the future, if that makes sense.

Gregory Brown: That helps a lot. Thank you. Maybe a different question is, if they've had... so, one of the indications that we're looking at is ulceration. So, if you've had an ulceration, is there any evidence that doing any of these treatments reduces your risk of another ulceration.

Mark Meissner: There is one, only one relatively robust, given the limitations of surgical trials, looking at high ligation and stripping versus compression for A) ulcer healing and 2) recurrent ulceration, which is really probably the more important outcome. All of these interventions probably do not speed ulcer healing, although there are a few problems with that. I think that you can take that away, plus or minus, but it clearly does prevent recurrent ulceration, and over time, if you've had an ulcer and you're compulsive with compression, at two years your recurrence rate is going to be about 18%. With these interventions, it reduces the recurrence rate to about 9% in this trial. So, it's about a 50% risk reduction in recurrent ulceration with these interventions, and I think, unfortunately, that's, as has been mentioned several time, that sort of information is missed in meta-analysis.

Gregory Brown: I think being consistent with compression for two years is almost impossible, but yeah. OK.

Chris Standaert: Then, we're limited by the PICO we have, which didn't look at any RCTs before 2011, I believe, was the cutoff date. So, I assume that's an older study than 2011. So, we would never even see that, and we didn't... their PICO also, it excluded sham and other conservative comparators. Dr. Rege, do you have a comment?

Sheila Rege: A question and continuing with Dr. Brown's questions, um, so C1 through C6 and C1 is just cosmetic. C2 then is that the time when you add that score the VCSS score or something, and you kind of then decide on compression stockings? I mean, how do you clinically... and that's what I didn't get in any of the studies. How do you clinically pathway?

Mark Meissner: So, you know, the CEAP and VCSS really were designed for two separate purposes, one as purely a descriptive instrument to put patients in bins with no real linear progression, although I think most people would consider an ulcer much worse than varicose veins. It's not meant... and a lot of these studies will report mean CEAP

category, which is completely wrong. It was never the way... it's a categorical instrument. It's not a linear instrument.

Chris Standaert: It's not a scale.

Mark Meissner: And in contrast, VCSS was meant to be a scale that changes over time with dynamic features of the disease that change over time. So, it can be applied across the whole range from C1 to C6. Clearly, the VCSS is a very ulcerative skin changes heavy scale. So, it gives... there are three of the ten components, and three of them are based on having an ulcer. So, it is going to be much weighted towards patients with what we would consider more severe venous disease. It can be used in C1 disease, but the scores are going to be very low.

Chris Standaert: So, you have a... that has a floor effect in terms of sort of a symptomatic varicosity.

Mark Meissner: Right.

Chris Standaert: Because it starts fairly impaired if you're... gotcha.

Mark Meissner: And just for some perspective, it's a 30-point scale. Most patients with varicosities will lie somewhere in the five to ten range if you do it, and most patients with ulcers will be in the 18 to 25 range, and most patients with C1 disease, spider veins, will be close to zero, because most of them don't have pain or symptoms at all.

Sheila Rege: So, clinically, you use both?

Mark Meissner: Yes. Right.

Sheila Rege: And is it, I mean, in oncology when you use two things, you kind of, do you go, OK. If it's C2, then the VCSS score has to be six and over or five and over or something like that? I mean, do you... does that?

Mark Meissner: Realistically, I think the C-scores, the CEAP score and particularly the C- classification... the CEAP score has four components, etiology, anatomy, and physiology. Most people just use the clinical classification, zero through six. That's used every day. I think by practitioners. I think the VCSS score is used more often as a research instrument as an outcome measure. I think a lot of practitioners don't use it day to day and don't make decisions based upon it.

Seth Schwartz: I think this is a great discussion to have a better understanding of what these studies are saying, but I think what I'm struggling with the same issue that Joann brought up was the lack of granularity in what we're hearing about, and I think one of the things that I struggle with particularly in surgical trials or when you're comparing different interventions where there may be different indications. So, I think one of the things that we saw...

Gregory Brown: Can I interrupt?

Seth Schwartz: Please.

Gregory Brown: Can we let our speaker sit down?

Chris Standaert: No. She's going to finish her report. No. We need to finish our questions so we can let her go through her report. We have to hear what she has to say.

Seth Schwartz: So, I think one of the things I haven't heard a lot about or at least don't... I haven't really understood very well are what are the entry criteria for the individual RCTs, and are there differences in who we're actually looking at. So, for people that have... you know, some of the interventions, like the laser, it sounds like you have to have fairly small varicosities, whereas if you have large varicosities, 10 mm varicosities, you can't use those interventions. So, I don't know if there's a gradation. So, is laser more effective in smaller varicosities than large ones? I haven't heard any of that and don't really know who is being excluded from these trials and who is being included. So, I don't know if... that's kind of a big question, but it's a big problem, because we're also trying to identify who we're talking about. So, I guess I would ask our speaker if there's any... if she can kind of comment on whether there's any granularity in terms of who is actually in these trials and who is being excluded.

Chris Standaert: Let's go back to Ms. Wine, so you can finish, but yeah. These are the questions, right, this issue of granularity and the problem with systematic reviews and missing inclusion/exclusion criteria, missing applicability, missing all sorts of stuff that we would really like to have to help us think about this, because that's the level we have to work at. So, if you could, I don't know. I don't know how you can incorporate that into your comments, but if you could, it would be appreciated, and if... otherwise, so keep going.

Candy Wines: Just to respond to a couple of things, back to the literature search method, the search for primary data picked up where systematic reviews left off. So, the systematic reviews that were included and then built upon with newer evidence did not have cutoff dates for their searches. So, those reviews should include studies prior to 2011, certainly, and they do. They do include those. The inclusion and exclusion criteria, I did review that for the majority of the individual studies, and no very explicit. Not a lot of detail there. I looked for things, like, vein diameter. It was not often reported. When I get back to my seat and have my binder, I can look up some of the ranges where it was reported to provide that to you. Generally, the inclusion and exclusion criteria that I went over previously applies to these randomized control trials, not just the newer ones that we identified. The level of granularity does get tricky, because as you say, there is some consideration of is there a difference between who is considered for laser ablation or who is considered for radiofrequency ablation. I think Dr. Meissner talked about that earlier and the earlier presentation also discussed the decision making based on patient presentation and things like that. So, the reviews that are presented here are... were selected because they were from our assessment, the highest quality and most directly relevant to the key questions. So, they do cover, as I mentioned, different inclusion/exclusion criteria between them, but they do address the key questions. So, the two that specifically look at greater saphenous vein and small saphenous vein, they looked specifically at those patient populations and

addressed those similar key questions for those patient populations. The Carroll review is much more broad, including patients with any type of varices. So, their network meta-analysis included studies of other comparisons in order to make that network and bring in more data to presumably create a stronger conclusion. So, that was the reasoning for selecting numerous systematic reviews. They all brought something to the evidence.

We were, I believe, at the radiofrequency ablation versus surgery comparison for pain, and the low quality evidence suggests that patients who receive radiofrequency ablation for treatment they experience less postprocedural pain than conventional surgery, and for sclerotherapy, a very low quality body of evidence suggests that foam sclerotherapy may be no different in terms of postoperative pain than surgery. Network meta-analysis found slightly less postoperative pain associated with foam, but the results were not significant.

The next outcome is time to return to work or normal activity. This is one of those outcomes that didn't lend itself very well to meta-analysis so the reviews didn't tend to conduct meta-analysis for this outcome. They summarized it qualitatively instead and I can provide some more granular detail for this outcome if needed. Generally, the summary appears here on the slides. So, there is low quality evidence the time to return to work for normal activities is shorter following treatment of varicose veins with laser ablation than with surgery, but as with the pain outcomes, the metrics to measure this were varied and none of the reviews conducted the analyses of this data. There was one recent publication from a randomized control trial that reported about time to return to 15 different types of behaviors, and for 13 out of those 15 behaviors, sort of activities of daily living or work, 13 of them were less time for the laser ablation group than the surgery group. There is low quality evidence for radiofrequency ablation versus surgery that patients who receive radiofrequency ablation may take less time to return to work for normal activities, but no quantitative analyses were conducted.

For sclerotherapy versus surgery, again, low quality evidence consisting of a few studies suggesting patients who receive foam sclerotherapy may return to work or normal activities faster than those who receive surgery. Three studies across two systematic reviews reported on this outcome. One of these studies did not report statistical tests, and the other two suggest that foam sclerotherapy patients return to work or normal activities significantly faster than the surgery patients. Two recent publications support this. They also suggest that foam sclerotherapy patients resume activities significantly faster than surgery patients.

Now we come to quality of life results. This slide shows the results for the quality of life assessments that were available, and the instruments used to obtain these were general quality of life tool, such as the SF36 and the EQ5D. Both are widely used and validated. The SF36 consists of eight multi-item scales and two summary scales. Scoring is based on a zero to 100 scale where zero equals extreme symptoms or poor health, and 100 equals no symptoms or perfect health. An EQ5D is a two-part utility or preference-based measure of perceived health state. The first part is a descriptive section and it accesses five dimensions using a three-point scale of no problem, some

problems, or extreme problems, and a newer version of this tool uses a five-point scale. Scoring of the descriptive part is based on a zero to one scale where zero equals death and one equals optimal health. The second part is a visual analog scale scored on a zero to 100 basis where 100 is the best imaginable health, and zero is the worst imaginable health. The disease specific tools used were the Aberdeen Varicose Vein questionnaire and the Chronic Venous Insufficiency Questionnaire, CIVQ. The AVVQ is an internationally validated change response tool and the commonly used version includes 13 questions, a combination of multiple choice and a drawing task. Scoring is based on a zero to 100 scale where a higher score indicates worsening quality of life. The CIVQ is designed for C0 to C4 category patients. It uses 20 questions divided in four areas. Responses are based on a one to five scale where one is a minimum effect on daily activities, and five is the maximum negative effect. Then a global index score is calculated using a formula.

So, information about what constitutes a clinically-meaningful change using these instruments to assess treatment of varicose veins is lacking and very few studies identified or discussed findings in terms of clinical significance, and among those that did, both mentioned that they did not find any clinically-significant between group changes.

Statistically significant improvements in quality of life measures from baseline were noted for all treatments in several studies. In between group differences were either not reported or were not statistically significant for most comparisons. The exception to this includes one study of radiofrequency ablation versus surgery. They reported either CIVQ scores for radiofrequency ablation patients at one and two years, reported better CIVQ scores for radiofrequency ablation patients, and one study of liquid sclerotherapy versus surgery that reported some favorable results for liquid sclerotherapy.

The final outcome for key question one is reintervention. There is low quality evidence of no difference with respect to proportion of patients requiring reintervention either because of technical failure or because of recurrence after successful initial treatment.

For radiofrequency ablation versus surgery and sclerotherapy versus surgery, there is very low quality inclusive evidence for reintervention after varicose vein treatment.

The next few slides provide an overview of results for key question two. To summarize, the overall quality body of the evidence for adverse events was considered moderate. Complication rates were generally low and few statistically significant differences were reported for any of the interventions compared with surgery. Serious complications, such as deep vein thrombosis and pulmonary embolism and sural nerve damage were rare with no significant differences between treatments noted in the systematic reviews of the randomized control trials. Two large observational studies reported higher rates of deep vein thrombosis than those that had been reported in RCTs and some pooled analysis. Adverse events, such as bruising, paresthesia, hematoma, phlebitis, and infection were more common but generally self-limiting or resolved with conservative management.

Results for deep vein thrombosis and pulmonary embolism from studies comparing endovenous laser ablation with surgery are shown on this slide. Regarding two observational studies, one of these combined endovenous laser ablation and radiofrequency ablation and compared the combined group with surgery. The other observational study calculated rates of deep vein thrombosis or pulmonary embolism for four different treatment types but did not conduct tests to determine significant differences.

Regarding findings for the sclerotherapy versus surgery group, one systematic review reported 13 deep vein thrombosis after foam sclerotherapy and one after surgery across three studies, 11 of the 13 DVTs were in one study, and these occurred prior to a dose reduction. After the dose reduction, no DVTs occurred among the foam sclerotherapy patients.

With respect to nerve damage and comparison between endovenous laser ablation versus surgery, across the included systematic reviews, analyses generally showed statistically significantly lower rates of paresthesia and nerve damage among laser ablation patients than surgery patients. For radiofrequency ablation versus surgery, two systematic reviews suggest no statistically significant differences between radiofrequency ablation and surgery with respect to paresthesia. For sclerotherapy versus surgery, in one review, two studies reported on this outcome, but only one reported a difference between foam sclerotherapy and surgery. This study found better results for foam than surgery and pooled incidences reported in another review suggests a higher rate of nerve damage among those who receive surgery than among those who receive foam sclerotherapy, but statistical significance is not reported here. In one recent RCT reported paresthesia in nine surgery patients compared with zero foam sclerotherapy patients.

The data shown on this slide suggests lower rates of infection following endovenous laser ablation and radiofrequency ablation than surgery, and two studies reported conflicting results for foam sclerotherapy compared with surgery.

The final slide for key question two summarizes information for adverse events, such as bruising, hematoma, phlebitis, and skin discoloration. Generally, there were no differences reported between the groups.

For key question three in subgroup analysis, four of the systematic reviews described previously focused specifically on varicosities of either greater saphenous vein or small saphenous vein, and one recent RCT enrolled only patients with severe lower extremity varicosis. No studies were identified that reported on subgroup analyses by previous treatment, ethnicity, comorbidities, or other clinical history or patient characteristics.

Information about comparative costs was identified in three systematic reviews and two U.S.-based cost studies. Three systematic reviews suggested available economic data and analyses are limited by variations reporting lack of applicability to settings outside of the U.K. or Europe. They are marked by poor methodologic quality and inadequate reporting or out of date information. Four economic studies were

identified by the Carroll et al group. Two of these were conducted, along with randomized control trials, and two of them were modeling studies. From these, the authors of the review conclude that the available economic analyses of endovenous treatments in comparison with conventional treatment for varicose veins were limited scope and quality, and differences in costs and benefits between treatments are small and sensitive to assumptions. Cost-effectiveness of the different procedures in relation to each other is likely to be uncertain and varied by local costs. Nesbitt et al found six studies, shared one in common with the Carroll et al review just discussed that presented cost analyses. Two studies reported costs for foam sclerotherapy compared with surgery, and both found decreased cost with foam sclerotherapy. Two other studies provided cost comparisons for laser ablation and surgery. Both found slightly higher costs associated with laser ablation. Three studies reported cost information for radiofrequency ablation compared with surgery, while procedural costs were similar for both treatment groups. One study reported slightly higher costs in the radiofrequency ablation group and two reported slightly higher costs in the surgical groups. Overall, the authors concluded that the costs in each of the studies varied. No study reported estimation of costs associated with additional procedures or residual/recurrent varices. This may be of some significance. The Rigby et al review noted that costs were analyzed in some of the studies they identified, but the data on cost-effectiveness was not adequately reported or was outdated. Based on the cost outcomes, sclerotherapy was cheaper, in terms of costs to the hospital, and to the patient measured in terms of money or time missed from work. Two retrospective cohort analyses that presented relative cost information from the U.S. perspective were identified. Both of them looked at radiofrequency ablation, endovenous laser ablation, phlebectomy, and surgery. One study compared average direct costs of radiofrequency ablation with those of surgery, and the other calculated costs per case and net profit or loss. Both studies concluded that the minimally invasive varicose veins were associated with lower costs than surgery in most settings.

Moving on to summaries of the practice guidelines and the payer policies. I'll briefly summarize the practice guidelines, and then move to the payer policies. Publication dates of the eight practice guidelines ranged from 2011 to 2016. Generally, the guidelines recommend endovenous laser ablation or radiofrequency ablation over surgery, unless endovenous thermal ablation is not appropriate for the patient. Sclerotherapy and phlebectomy are also recommended in some clinical situations, but not always as a first choice. Endovenous treatments are not recommended during pregnancy and phlebectomy is often considered as a concomitant treatment along with other techniques. The next three slides in your packet provide details for each guideline, but I'm going to go forward to the payer policies, which are on slide 46.

The information about coverage policies was sought from AETNA, Centers for Medicare and Medicaid Services, Group Health Cooperative, the Oregon Health Evidence Review Commission, and the Regence Group. Only the Oregon HERC did not have a published coverage policy available for review. CMS did not have a national policy; however, a local coverage determination was identified. The remaining organizations have coverage policies for varicose vein treatment, including endovenous laser ablation, radiofrequency ablation, sclerotherapy, and/or phlebectomy, and each policy describes specific diagnostic symptom and/or prior

treatment criteria that must be met. Some details vary, but common elements of the coverage policies include documentation of venous incompetence, minimum size requirements for varicose veins, presence of one or more symptom, some circumstances may require a minimum time period for a trial of conservative therapies, or sclerotherapy and phlebectomy as adjunct treatments.

Slide 48, this is just a reminder of what the different overall body of evidence ratings mean. The evidence presented in this Health Technology Assessment was assessed as moderate or low for each key question.

Based on the information reviewed for key question one, conclusions were as follows: Moderate quality of evidence suggests that endovenous laser ablation is similar to or better than surgery for many clinical and patient-centered outcomes. Evidence for some outcomes, such a pain and time to return to activities is mixed or inconclusive. Radiofrequency ablation is similar to or better than surgery for many outcomes, maybe associated with less postoperative pain than surgery. Low quality of evidence suggests similarities in some clinical and patient centered outcomes between sclerotherapy and surgery; however, it is difficult to draw conclusions about several outcomes because of lack of sufficient or consistent data. No eligible studies comparing phlebectomy alone with surgery were identified. Phlebectomy may have been an adjunct treatment in the studies of the other interventions.

Key question two, moderate quality of evidence suggests that laser ablation, radiofrequency ablation, and sclerotherapy are relatively safe compared with surgery with few significant differences reported. Rates of serious complications are low and similar when compared with surgery in randomized control trials; however, results from two large observational studies suggest that the risk of deep vein thrombosis after procedures may need further investigation. More common complications, such as bruising, phlebitis, hematoma, and infection do occur similarly in both groups.

Key question three and key question four, publications studying specific patient publications are discussed in key questions one and two, but no other subgroup analyses were identified. Regarding the cost outcomes, conclusions from systematic reviews evaluating economic outcomes suggest that available economic data and analyses are limited and lack applicability to settings outside of the U.K. or Europe, but two U.S.-based cost analyses identified found minimally invasive varicose veins treatments to be associated with lower costs than surgery.

To sum it up, there are some limitations to the evidence reviewed. These include lack of reporting, of statistical significance and clinical significance, and methodological limitations of individual studies in a few studies for some comparisons and some outcomes. There is also a lack of sufficient or consistent data in some outcomes, and obvious for potential heterogeneity within the body of evidence. Regarding gaps, future studies are needed to address the methodological limitations of the individual studies, such as variation and outcome definitions and metrics, small sample sizes, more consistent performance, and reporting of statistical analyses, and better reporting or conduct of randomization procedures. Additionally, head to head studies of newer devices compared with conventional surgery are needed. There is also a

need for additional economic analyses that take into account U.S. settings. That's the end. Thank you.

Josh Morse: Thanks, Candy.

Chris Standaert: Usually, we would have more questions now, but I think we have to figure out a few things here. So, our charge is going to be this issue of, when we're done, we have three choices. We have cover unconditionally. I mean, we put any conditions at all when this is done and paid for. We have don't cover, meaning, you know, you can't do this, and we have cover with conditions, and how from what we saw, we ferret out conditions, I think, is going to be our challenge there. The population... so saying it's equal to surgery when I don't know in whom surgery works, is tricky for me, for example, but we have to think about these things. So, we're going to take a 15-minute break, let you guys look at your data, because you're going to get questions about granularity, I have a feeling, inclusions and exclusions, and primary studies, and how... what do we know about the populations that we're treating here so we know who we're talking about. That's going to help us. We'll come back at 10:30, OK?

So, we have time now, as a committee, to go through our view of the evidence and what there is here. Ultimately, we have to get down to a decision in the end, right? So, we can say we wish we had this and we wish we had that, and the truth is if there were an obvious answer, it would never come before us, right? We have never... we just do not get obvious problems. Again, if that were there, they wouldn't need us. So, we have to...

Gregory Brown: Actually, I move that we take the original maybe miswording that was presented and that we cover it all and that there was no reason to bring it to us, and we agree.

Chris Standaert: This is, I hope... one, you just made a motion, so I'm a little hamstrung here. So, if you're serious...

Gregory Brown: I'll withdraw the motion.

Chris Standaert: Thank you. That helps me. Yeah. So, we have to figure out where we can go with this, and does it help us get down to this issue of cover, cover with conditions, or not, and what do we know, what do we not know. What do we think we can get or glean in some other way if we have to, but we have to go through what was given to us. That's our charge, and see where it takes us and what we can, as a group, use our collective wisdom to sort of sort through it a bit. So, it's usually helpful if somebody gives a perspective on what they think we sort of can see and not see, and not so much in just... I've heard comments on the limitations of the report, and we'll get to that, but where are people sort of sitting on this at the moment in terms of what they know and don't know and how they view this data?

Chris Hearne: I'll start with my initial thoughts. I don't see a lot of safety concerns. I don't see that that was presented to us. So, I think that's something we can kind of table, at least for now. Just to kind of give you my gestalt of the evidence, as it's been presented, I see some moderate to low-quality evidence that endovenous laser ablation is comparable

in terms of efficacy to surgery, some low quality evidence for radiofrequency ablation and some very low quality evidence for sclerotherapy. I guess my question to help me understand this a little bit better is, are all of these technologies comparable for... are they appropriate comparisons to surgery, and this is a question you can help us with, Dr. Meissner. Are there patients that, when you're making a decision about which of these technologies to use on any given patient, is it very obvious to you, oh, this is a patient that would be appropriate for sclerotherapy. This is a patient that would be appropriate for radiofrequency ablation, etc.? Or is there some fuzzy boundaries here?

Mark Meissner: I think for 90%+ of patients, as far as who would be a candidate for these therapies would be equivalent. You know, they're all more or less designed to remove a saphenous trunk from the circulation and they all do it reasonably well. So, I would say there may be a few patients that may do better with one than the other, but it's not the population of patients. It's a few individual therapies. So, I think for the purposes of coverage, they, within the limits of the data, they should be regarded as functionally accomplishing the same thing, one versus the other.

Chris Hearne: You mentioned this a little bit earlier, but I wonder if you could just talk a little bit about the thought process that goes into then deciding which one, if it's not sort of a specifics of a population.

Mark Meissner: Well, I think most clinicians who do this probably have their workhorse day-to-day thing that they fall back to, and probably that has a lot to do with training and what they're comfortable with, and that may vary a little bit from clinician to clinician, but I would suggest for almost all clinicians, it's some type of thermal ablation, whether that be laser, radiofrequency, functionally they accomplish the same thing, which is ablation of the vein through heat. I would say most patients would choose, or most clinicians that is their workhorse. Then, there may be a few specialized circumstances that you would choose a different technology, and probably the most common one I already cited, which is an inability to get a straight catheter up a very tortuous vein. There, you would probably choose foam sclerotherapy. There also is one of the things that appropriately is not covered in this review is that all the thermal techniques require tumescent anesthetic, which involves injection of dilute lidocaine through eight or nine needle punctures along the course of the vein, and that serves both to make it so you can do it under local anesthesia. It collapses the vein around the catheter, but it also serves as, in some ways, a heat sink to protect the saphenous nerve and the skin and other structures for injury, and it's very effective for that. It is a little uncomfortable, though, and I think most people do this with at least a little bit of sedation. So, I may choose a non-thermal technology in a patient who, I think, is at mild risk for sedation. Those are the two sort of things in my practice I would consider, and I think other people may have other reasons, but 90%+ of patients, you're going to use the technology you're comfortable with, and in that respect, all of these are more or less equivalent.

Chris Standaert: Are a decent number of people under IV sedation? Are they under conscious sedation of some sort?

Mark Meissner: There's a wide spectrum of practice. Some people use just oral valium, just to take the edge off. Some use nurse administered sedation. I think for rare patients, general anesthesia is not warranted anymore. It's a little bit of the problem with all of the costing data is a lot of these studies have done thermal ablation procedures under general anesthesia. So, I think with very few exceptions, that's not needed with these things, and the sedation can vary on your practice. I don't think there really is a standard of care.

Carson Odegard: Yeah, I have a question of Dr. Meissner. When some of these guidelines say, well, don't recommend as a first line course of treatment is for sclerotherapy for certain things, it seems to me that that is a first line for certain conditions, right, for certain types of veins. Why would they, unless I didn't read the rest of it, but.

Mark Meissner: I think that's true. I think, you know, if we just, sclerotherapy is first line of treatment for C1 disease, for telangiectasias and spider veins which are outside of the scope of this review. Most of those are not symptomatic. It is a choice of treatment, and that's mostly, sclerotherapy is a liquid. When you, most... the commonly used sclerosants are all detergents. So, you can use it either as a liquid or you can make it into a soap, and soaps are more effective, but it prolongs contact with the vein wall, it displaces the blood. It's just more effective. So, for most C2 disease, it is mostly foam sclerotherapy. Most of the data from foam sclerotherapy is, as was nicely covered, comes from physician compounded foam. You aspirate the liquid through a three-way stopcock with air, and it makes soap bubbles. There is a commercial product, as well, but most of the experience is with physician-made foam. Clearly, that's equally effective early on in reducing symptoms. It does have a higher recurrence rate, but one of the advantages of foam sclerosant, physician-made foam sclerosant is, it's very cheap. It requires no sedation or anything. It's a needle puncture and a vial of sclerosant is \$30 to \$40 versus \$1000 for a catheter. So, if it's cheap and it really doesn't pose a danger to patients, you can tolerate that recurrence rate, but I think most of the guidelines, because of the higher recurrence rate, recommend thermal ablation over sclerotherapy based on a higher recurrence rate with physician-compounded foam.

Carson Odegard: Great. Thank you.

Chris Standaert: Laurie, what do you think?

Laurie Mischley: Well, I second Chris's comments that I don't have a lot of safety concerns. I think, in general, as I read this, I was saying earlier, your expert testimony has been fabulous. I actually... the more I participate in this panel, the more I value the evidence that the expert witness brings to the table here. I just see more and more limitations in the ways that RCTs and meta-analyses are not serving the pragmatic questions patients are asking and how we are trying to, in a cost-effective way tend to patient's needs. So, I actually liked... I saw evidence that we were moving in a good direction, both with cost-effectiveness, fewer side effects, and overall general safety. So, while I agree that the evidence is not as strong and consistent and cohesive as I would like, I was leaning towards covering these conditions.

Chris Standaert: Greg, how about you?

Gregory Brown: I'm always impressed with the pragmatism of the British and the NICE guidelines, but if you look at the other guidelines that are in the presentation from the vendor, none of them have any exclusions except pregnancy. They don't seem to have specific safety concerns. I mean, some of them try to rank order, preference of treatment in certain scenarios. I don't think we have the granularity here for us to do that, and I like the comment that you made at the beginning about, there seems to be with increasing surgery increasing safety issues and lower invasiveness and lower complication rates. So, it's really a patient choice or shared decision-making process there, as to where you fall in that spectrum. So, other than the exclusions that I think that the Health Care Authority brought up of the infection, pregnancy, am I missing... I would think this sounds like something we need to cover. The one area this impacts me is doing joint replacements, I can tell you that every patient almost that comes into my postop after a hip or knee replacement wearing compression stockings is, when can I get these things off. So, the bit about telling someone with a hernia to wear a truss. It's like, it's just not practical. They're hard to get on. They're hard to use. Use it for two years straight, and it reduces your risk of recurrence, I mean, like, come on. I can't do anything consistently for two years, I think, as an individual behavior. So, it sounds to me like something that is cost-effective, pretty low risk profile, and benefits patients.

Chris Standaert: I guess one of my questions is, is the issue of in whom. I saw all this data in comparing surgery to these procedures, which seem, given the quantity of data, relatively equivalent, some low data some poor data, but what I'm really struggling with is, in whom, right? So, this issue of who gets better? Who doesn't get better? Who actually needs it, right? So, equivalent doesn't help if it's equivalently ineffective, right, or equivalently done but not necessary. So, I struggle with that, trying to figure out just having a varicosity and one symptom? Is that pain, fatigue, like, what is that? It seems like there is a significant lack of uniformity and there is a lack of credentialing and a lack of sort of who is making that determination, and I see lots of patients having a varicosity who are saying my leg hurts, but there are lots of reasons their leg could hurt. It could be their bad knee. It could be their back. It could be all sorts of things, and the varicosity is obvious, because it sits there, but when their toe is numb, it's probably not the varicosity. So, it's tricky to me in that sense, and I didn't see that.

Gregory Brown: Well, I, again, that's the pragmatism of the British. If it wasn't effective, I don't think they would have that guideline. It seems to be all-comers. Now, you can always say there is multiple causes for leg pain or whatever, and I think the issue is a patient with one symptom and occasional bothering isn't going to go in to be evaluated. I mean, the fact that they're in the clinic and being evaluated. I completely agree about the credentialing part so that... but I don't know that we have that authority. We can ask how the Health Care Authority deals with that, but is it only people that are fellowship trained or credentialed in certain procedures, because you're right. If all you can do is sclerotherapy, and you don't have... and you're a dermatologist and wanting to do cosmetic things, then that's the only thing you're going to offer patients and do, and that's not really the group that we think needs it. So, is there a way on the credentialing side, but I think that's out of our prevue.

- Laurie Mischley: Well, I was just going to add to that. I don't think that, I do see the spectrum between cosmetic and need, and just having one symptom, if I had ugly varicose veins and all I had to do is say it hurts, I do think that it's not true that patients wouldn't be being evaluated if they didn't need the therapy, and I think that some sort of safeguard against preventing people who desire cosmetic intervention from saying it hurts and getting that covered is prudent.
- Chris Standaert: You can create a need, right, in a marketing strategy. You can create a need, right, that wasn't there before. You can say, yeah, so six billboards, right? You can say, ooh, that thing, I don't know. I remember those ads for when they started treating toenail fungus, all these pictures of people hiding their feet, right? I had patients who never thought twice about that in their entire life until they saw feet being hidden on TV. It was a wildly effective ad that created a market, I think, in a way. So, you can do that, and I think it's almost when you get to these... the outcome issues, like somebody wants this varicosity treated, and there really is a difference between somebody with extensive venostasis disease and ulceration and skin changes and the whole thing and somebody with an isolated varicosity without that. Their primary goal actually may be to get rid of the varicosity for purely cosmetic reason or whatever. Or they don't really have pain. They don't really care if their pain is better or not, because that's not why they did it. They don't expect that. They just want the thing gone. It all gets very muddy in there and by blanket coverage, that is essentially any varicosity that exists, right?
- Kevin Walsh: But if we come up with conditions that are different than the agencies and the payers, we're asked to generate a reason why, and as you've stated, there's no... we have nothing within the literature review to allow us to do this, but to fall back on the existing... I think the existing restrictions of the payers.
- Chris Standaert: Well, our mandate isn't that we have to do what the agency is saying. It isn't that we have to do what the guidelines say.
- Kevin Walsh: That's not what I said.
- Chris Standaert: That's not at all what our mandate is.
- Kevin Walsh: We had to offer a reason why we're offering a different...
- Chris Standaert: We can say there's no data to support the, so three months of compression... if we have no data to support that, we can say there's no data to support that. Therefore, we don't agree with it. If we don't think there's data to support anything anybody gave as an inclusion/exclusion, we could say that too, just the absence of data.
- Kevin Walsh: You're looking back and forth across the fence here on me.
- Chris Standaert: Well, I'm not trying to.
- Kevin Walsh: You're saying we should just... how can we come up with any exclusions besides blank, you know, cart blanche.

- Chris Standaert: No. I didn't say that. I'm pondering what they might be. I'm not saying we can't come up with anything. I'm curious how people view this and whether there are things, and I think we have to get back to those inclusion/ exclusion criteria. Yes. I am.
- Kevin Walsh: I wanted to ask Dr. Transue...
- Chris Standaert: I mean, I think we have to go back to them at some point and see if they can help us. Go ahead.
- Kevin Walsh: ...I wanted to ask Dr. Transue how she proposed the three months of conservative therapy?
- Emily Transue: Does this just turn on automatically? Because it was, I think it is a difficult one. I think it was because it was a fairly standard inclusion in sort of people who were referred to surgery. So, I think it was relevant to a lot of people that we were looking at and relevant to a lot of the other guidelines, but I do think it's a very relevant question.
- Kevin Walsh: I know Group Health doesn't have that in their guideline, and I... can you speak to the origin of this... of conservative therapy?
- Mark Meissner: I think this is of historical interest, because the data does exist from the 80s that's included in very few systematic reviews, but in the 80s, the original trials of compression versus surgery were done, and the surgery uniformly was more effective than compression. So, all recent trials have used, as was appropriate and in this case, surgery is the comparator not compression with that, and prior to increased utilization with the minimally invasive technologies, compression in general wasn't included in it, and I think it was largely included as a barrier to jump over to get coverage for it, and you were commenting on the British, and I'm sure it was... I didn't see it specifically but probably the... at least to my mind, the best trial that was done to look at this data was done by the British Health Technology Assessment for the NICE guidelines, and they actually did a clinical trial looking at this. It was relatively small, but it was appropriately powered. It had 247 patients who were randomized to surgery or compression, and using the EQ5D, the overall improvement in quality of life over a two-year time horizon was modest, it was 0.1, but it ended up coming out at about, I believe, it was about 9000 pounds per quality adjusted life year. So, clearly, it was more cost-effective than compression on a quality adjusted life year basis.
- Gregory Brown: A 0.1 in an AQ5D is a 10% improvement in quality of life. That's pretty dramatic.
- Chris Standaert: I want to go back to our vendor. We asked you guys some questions. So, these issues in primary studies, like inclusion and exclusion. So, if we look for... if we're gonna start trying to say in whom might we do this if we're gonna draw up... to agree with somebody or disagree with somebody, a guideline on who they put in and who they put out, we have to go to our data. That's where we should be going. So, if we have the data that sort of talks about specific populations or inclusion/exclusion criteria on a consistent basis, that helps us. Can you help us with that from the primary studies that we have?

Candy Wines: Well, I had time to review... a few of the inclusion/exclusion criteria are from the studies that were represented by the systematic reviews, along with...

Chris Standaert: Wait, from the study... what do you mean by the studies that were represented by the...

Candy Wines: The individual studies the systematic review...

Chris Standaert: ...in the systematic review. Thank you.

Candy Wines: ...in addition to the newer publications and studies that you saw. And I didn't find anything that really set outside the inclusion/exclusion criteria and patient characteristics that I described earlier. Generally, from the ones I've looked at, there's limited information about inclusion/exclusion criteria. It ranges from everything to patients referred for treatment to a little more detail about whether it's specifically in the greater saphenous vein or small saphenous vein and reflux of a certain measurement, but there's not much in terms of what I think could help you answer this question in this literature. One thing to note is, these are randomized control trials, so anyone willing to enroll in them should be eligible or appropriate for either treatment that they could receive and willing to accept the treatment that they'd receive. So, there is some, I guess, equivalence there in terms of if they're going to get laser ablation or surgery if they're enrolled in this study.

Chris Standaert: But my question regards... so, the equivalence thing is frustrating me, right? So, what I'm frustrated with is, it could be equivalently ineffective, right? That means it shouldn't be done in anybody. They shouldn't be getting the surgery or any of these, right? That's what I'm having trouble with that... I don't know who that is. I'm trying to see if you can help me with who that might be and where these boundaries are. You said, well they're appropriate for the procedure. How? Who? What? How is that determined? What is the metric if we're not standardly using clinical measures of function, if we're not, you know, and if you say, well you have to have ultrasounds, then the cost is going to go up, right? So, now we're going to ultrasound everybody, which is another \$1000. Then, we're going to do pictures, which is another \$1000. Then, we're going to do, you know? So, it's... it all goes, but how, that... this issue of they're equivalent, kind of, I'm missing something, right? I'm missing the people in whom they are equivalently effective.

Candy Wines: Mm-hmm.

Chris Standaert: Right? Not just they come out the same, good or bad.

Candy Wines: Right. Yeah, I wasn't necessarily talking about how they came out. I was saying for entering the study, you know, they would need to be considered appropriate for either treatment that is being offered in this study.

Chris Standaert: Yeah. So, what determines that?

Candy Wines: That is an excellent question. It's hard to glean from the literature. I would defer, again, to Dr. Meissner, maybe if there's a clinical picture that they consider. It's unclear to me from what I have in front of me.

Mark Meissner: I think that's true. I think the general inclusion criteria of these have been symptomatic C2 disease, and there is a range of symptoms that I think is really difficult to quantify in an individual patient. I think that's part of what you're talking about of equivalence is, is again, it goes back to the same thing. There really are no comparisons of surgery to nothing. It all goes back to surgery... comparison to surgery versus compression stockings that are all quite old trials that we've sort of jumped ahead from those trials to comparing surgery as the comparator versus these new technologies, and I think looking back a little further, surgery is judged to be superior to compression based on... with some limitations, reasonable randomized clinical trials in the 80s and 90s. I think Michael's Trial, which is the one the NICE guidelines is based on is from 2004, somewhere around in there, 2003.

Chris Standaert: Joann, what do you think?

Joann Elmore: Let me make certain this is on. I don't know what to think at this point. I have a couple of concerns, some that I've already raised, some that are statistical in that there may be no statistically significant difference, but I suspect some of these studies were underpowered. So, I'm not certain what to make of that. Then, I have clinical concerns, and it gets at this tight boundary between cosmetic versus pain and function and ulcers. You know, we want to help patients, but yet, we want to be careful and I don't think the State wants us to support cosmetic treatment. I don't know if anyone noticed that these scales that are literally throughout all of these slides, the Aberdeen Varicose Vein Questionnaire, and then this Validated CIVIQ Scale, these are built upon 10, 13 individual questions. Some of them are on pain, but some of the individual constructs within these scales ask about cosmetic issues. For example, the, let's see, the CIVIQ Scale, one of the survey questions that is a part of this validated scale is, I feel embarrassed to show my legs. Another one is, it limits me going to discos and wedding parties and cocktails. Another one on that CIVIQ is, I feel on edge, and then I feel a burden to people. Now, these aren't specifically related to the pain, per se. It could be the overall, I mean, I'm a primary care doc. I know how to deal with patients feeling on edge and feeling a burden. There's other constructs in there. Then, the Aberdeen Varicose Vein Questionnaire, at least the one that I pulled up here, because it was not available, I don't think, in our evidence vendor report. There are 13 questions, and let me just read two or three of them to you. One of them has to do with, do you have purple discoloration on your legs? Another one is, does the appearance cause you concern? And then finally, does this influence your choice of clothing? So, now that I've dug a little deeper, I realized that maybe, maybe not, there's no statistically significant difference, but I think that maybe we're underpowered, and maybe they're comparable on these indices, but the indices are built with some cosmetic components in them.

Chris Standaert: The indices aren't even used clinically, really?

Joann Elmore: Yeah. So, let me get back to, again, and I appreciate, so much, our clinical expert here. Tell me about the pain. Tell me about kind of how hard this is on patients, and clinical significance of this. That would really help me.

Mark Meissner: I think that's a really important question, because, you know, typically varicose vein pain, it's usually aching and heaviness, worsens throughout the course of the day, usually worse in the evening, usually worse when you stand up. If you, like some of the carriers require you to document all of these activities in detail, and if you ever ask a patient, tell me what it is you can't do because of your pain, it's never anything. I mean, the patients can do their daily activities because of this pain, but it is the sort of pain that they'll say, yes. I can get home in the evening and I'm... it's really hard to take care of my kids and do the housework without sitting down and elevating my legs in the evening. So, this is not disabling pain, but it is this sort of discomfort that does interfere with the usual activities of daily living, mostly in the evening, and largely outside of work. Some of them, if you're a cashier who is standing all day, there are people who stand all day who will complain of limitations, that they need to stop, get their legs up for 20 or 30 minutes and then go on again. Does that help?

Chris Standaert: But as an outcome measure, we had postoperative pain, which I don't really consider an outcome. I didn't see pain. I didn't see pain at six months, pain at three months. Was that an outcome measure for anybody in any of these... so again, and whether... this is the problem with the systematic review issue, right? So, those 30 articles in there, did some of them look at pain? That's what I would love to know, because we're talking about, why do you do this, right? My suspicion is that the vast majority of people, or a lot of them, their primary concern is cosmetic. Maybe they're functioning is limited a bit, but they don't like the vein. So, it's, but I'm not sure that's an invalid reason to do it, but it's tricky how you sort that out from...

Gregory Brown: I don't think that's a fair assumption.

Kevin Walsh: I don't agree either.

Gregory Brown: You know, I, I, that...

Chris Standaert: I mean, that's what I don't know. I don't know. I don't know.

Gregory Brown: There's...

Chris Standaert: I don't know the indication...

Gregory Brown: ...I mean, I actually like the wording that was presented from the agency, you know, symptoms of pain and/or swelling sufficient to interfere with instrumental ADLs or presence of complications, ulceration, recurrent thrombophlebitis, very direct.

Chris Standaert: Mm-hmm.

Gregory Brown: Does that mean that someone who just wanted it for a cosmetic reason couldn't figure out how to gain the system, absolutely not. We can't come up with a coverage decision

that's going to preventing gaming on any level, but that's not the point here. We're here to say, people that have real varicose veins and have real symptoms, they should be covered. I think that's the question we're being asked.

Sheila Rege: So, this is Sheila, and it's my first time. So, I'm just looking at safety, efficacy, and cost. I think all of us agree safety not a question. It's safe. Efficacy is low to moderate. I actually pulled a retired Medicaid Florida LCD. It's retired, so it's not valid, but [inaudible]...

Chris Standaert: And it's in Florida.

Sheila Rege: And it's in Florida, you know, but they were not, and I would like our expert to give an opinion on this. What they required, they said C1, which is just telangiectasia, a little bit of cosmetic, is not covered. If it's C5 or C6, which is ulcers, it's covered. The physician has to document what they're going to do for the next 90 days and do it. When it got to C2, which is this, you know, varicose veins, well is that really cosmetic, is it symptomatic? Then they had to sit down and do that funky VCSS score with which pain, none, mild, moderate, severe. On the varicose veins, no varicose veins a few scattered, moderate is it's only on the calf or the thigh, and severe is on both the calf and thigh. Edema, they again went to is it limited to the foot and ankle, above the ankle, and that's the one that you said researchers use. They went into pigmentation. They went into inflammation. Again, it was just where is it and, you know, how much of your body it covers. This retired LCD said anything C3 and over, meaning edema, start of edema, venous edema, stasis edema, and over should be covered. C1 is cosmetic, and with C2, they recommended a 90-day course of something else unless there was significant symptoms, and that, there's no data that I heard, but as physicians that made sense when I see patients. So, I wanted to get... but it sounds like it's not documented clinically in real practice.

Mark Meissner: It should be. It definitely should be. It is not often used, and that's... in an effort to raise the bar, I think that's where the attempts to accredit vein centers have come into existence. Then, so if you're an accredited vein center, it's actually required that you document that.

Sheila Rege: Both the CEAP and the VCSS?

Mark Meissner: And the VCSS. So, there are mechanisms to make compliance with it, and I think there are also a couple of registries that I think if you participate you have to document that, as well, and I don't think that's unreasonable, the VCSS being what it is. Part of the issue with the VCSS is due disclosure, there's only ever been one validation study of it and that was by myself. So, it... I can tell you it's a little bit weak on the validation part of it.

Chris Standaert: So, my comment before got cut off a little bit. So, the cosmesis issue, what I was trying to say is that I think that's an important part of why people seek treatment for these, but essentially, I don't know that that's totally inappropriate either. I think if you give somebody a below-knee prosthesis and they want it to cosmetically match their other leg and look as natural as possible, I think it's a very reasonable medical expense.

Somebody has facial trauma, and they want a facial reconstruction, or they get burns and they want facial reconstruction for cosmesis, I think that's medically appropriate. So, I don't think that's necessarily a problem. So, in this case, it's tricky, because it's tangled into these other things. Yes, people can game it and they can say, yeah, my leg hurts. Again, they may be very happy with the procedure, because they no longer have the visible on their leg, but we don't know if their leg still hurts, because nobody asks them if their leg still hurts six months later, and that's probably why those symptoms are in these scales, because they are an important part of clinical decision-making for patients as an informed consent procedure, right? So, I don't think, I'm just trying to say, it's there. Really, I'm not certain it's an invalid concern on the patient's part or nonreasonable medical procedure for that.

Joann Elmore: Can I ask the vendors, pain is obviously something I'm hearing from our expert. It's very important, and it's poorly covered in the scales, the varicose veins scales, and in your report, you have table five, which is the outcome of pain, but that's actually a risk, sort of pain short postop. Do we have any data on pain alone, you know, three months, six months, for these procedures, because I'm hearing from our expert that that's what's important? Is there someplace in the document I should be looking?

Candy Wines: There we go. There isn't a particular place to look in the document. The pain measure or outcome that you're talking about is one of the elements covered in the clinical and quality of life tools and it's usually summarized in those more global scores. So, that's where that is.

Mark Meissner: And I think that's another thing that's a little bit hard, because the comparator, again, is surgery, and after the initial postoperative period, like I said, all of these are equivalent. There is no benefit, and it's the same as laparoscopic cholecystectomy or endovascular aneurysm repair or any minimally-invasive technology. The benefit is up front in six, I mean, pretty much after six weeks, there is no difference between these. They are equivalent when the comparator is surgery.

Carson Odegard: I have a question of Dr. Meissner. We talk about these outcome measurements and scores and things, but practically, from a clinical practical standpoint, when a patient comes in, like what I do with treating spines, I really don't have to ask all these questions. I can find the pain and whether they tell me on some sort of scoring device or not, you know if they're a candidate. You know if they're telling the truth, and so when these patients come in and they, I could see for documentation purposes of filing these outcome measurement surveys out, but you can tell. I mean, you know where the pain is. You can palpate it, right, and you can kind of know what category they're in. I'm excluding ulcerations, C6 and that type of thing. You kind of know what category they're in, excluding ulcerations, C6 and that type of thing.

Mark Meissner: Clinically, certainly you do, and I think that gets back to why maybe this VCSS score isn't standardly used is, it's a very useful instrument in research and tracking change in populations over time, probably less useful for the individual patients. You're making a clinical decision on the individual patient, not so much for the population of patients.

- Carson Odegard: I mean, if you have a robust data set and pain is in there, you can start looking at it, but we don't have evidence.
- Joann Elmore: In other words, I'd like to see the individual single question that says, are you still in pain, yes, no, and to see whether it improves.
- Chris Standaert: Seth, what do you think?
- Seth Schwartz: Pain is reported in a lot of these. If you go back to page 150 of the report where the individual reviews are...
- Joann Elmore: But that's what I was asking about.
- Seth Schwartz: ...parsed out. In several of them, pain is listed in the results.
- Joann Elmore: Page 150?
- Seth Schwartz: I think it's, sorry 130 maybe.
- Gregory Brown: While you're looking, I also failed to mention the first sentence in there, eligibility or indications, and that is, is varicose veins greater than 3 mm. So, people with spider veins are not going to be eligible under this. Grade 1 or whatever is not going to be eligible.
- Chris Standaert: But this isn't the treatment for that either. This isn't what you do for spider veins. Certainly not the... you have to get a catheter in there. You wouldn't do it for spider veins, I wouldn't think.
- Gregory Brown: Well, you could do sclerotherapy or something.
- Chris Standaert: Sclerotherapy, yes. That's what you said you do, but not, yeah.
- Seth Schwartz: Page 113, I'm sorry. I think we have a general sense of the patients that we're talking about treating, which is people with symptomatic varicose veins. Now, how we define symptomatic we can nitpick that, because it's probably slightly different in the different studies what entry criteria they use, but for the most part, we have a sense of what the symptoms look like. We've looked at a number of different technologies, which for the most part seem fairly equivalent in terms of their safety profile and their effectiveness. Maybe there's some subtle differences, but nothing compelling. We have limited cost data, as we always do. I think... so, I'm struggling to try to differentiate the technologies. I think the only piece I'm hearing is probably surgery under general anesthesia is going to be more expensive than all the other things. So, to cover them all equally I have a little trouble with that, because I'm thinking, why should anybody have surgery if we have these other effective means of treatment, but I think we can at least loosely define and maybe it's just as simple as saying, people with symptomatic varicosities should get coverage for treatment, and I don't see any reason to limit... to do the conservative therapy trials first. I think that's probably the greatest frustration for patients and doesn't seem... while it may be equally equivalent,

as Greg said, if you wear it for two years every single day, at the end of two years, you're in the same spot, but then you take them off and then suddenly you're symptomatic again. So, it's not really meaningful to me to try and limit patients based on any conservative treatments first. So, I'm feeling pretty comfortable right here with saying cover this for patients with symptomatic varicose veins and let the clinicians decide what treatment is the most effective or the best for any individual patient.

Chris Standaert: Question for the vendor. I saw another one in your report. You guys... did I read it wrong? If you go... you excluded studies that were comparative to some sort of sham or... I don't know if you had any, but you put an exclusion in there. You compared things to surgery rather than going back to say, does this work. That's my fundamental problem, even here, that it works as well as surgery. Does that work, right? That's what I struggle with.

Mark Meissner: If the panel wanted more information, and it also has many flaws in it, but the MedCat did the comparison for CMS against compression rather than surgery. So, there is another whole document done by Duke that does that comparison. Surprisingly, the conclusions aren't much different, that the quality of the evidence is very low with it.

Gregory Brown: The fact that surgery is better than compression says surgery is better at something and doing something, correct?

Mark Meissner: At a very low quality of evidence.

Chris Standaert: But our vendor didn't give us that, even, right? So, our vendor didn't give us the evidence that surgery is better than compression. They didn't give us that, because they didn't do it. They didn't go look at that.

Josh Morse: We didn't ask that question, right?

Chris Standaert: No, I know, but that's a boundary. So, some of this gets down to the, do we use the evidence, which is that, so theoretically what we're given. Where do you sort of apply clinical perspectives, you know, but that's, you know, clinical perspectives are level five from all of us? I appreciate what you're saying. Expert opinion is expert opinion, right, and we always struggle when people bring in data that isn't included in what we were given, because then it hasn't really been publically vetted in any way or compared or stratified with the other things we see. So, we don't know how to rank that. Even things about two studies showed this and one study showed that really don't help. You don't know what the studies were, right? So, it's tricky. How do we use our data the best we have to do that, and I'm struggling with that still, personally. I hear what you all are saying.

Gregory Brown: I think there's, to me, there's an unasked question and that is, if we said we don't have the evidence to make a decision today, we need a different report. Come back in three months and reassess it. Do we think that report is going to be any better? What I just heard Dr. Meissner say is the answer is no, because Duke did it comparing it to compression versus surgery and the results are kind of the same and the evidence quality is poor. So, I don't think that that's a viable option. I think then the second

question is, and we've struggled this the two years I've now been on the committee is how do we improve the PICO question process that we give to the contracts and unfortunately, that's not going to be resolved today, but may be a great agenda item for next September meeting, is there...

Kevin Walsh: It's every year.

Gregory Brown: ...well, no, but I mean, I guess the short answer to me is, I'm trying to think, how do we make the process better and that is, is the PICO questions are open for public comment, and we're all busy and we all, yeah, OK. You know? And then we'll say, we'll look at the evidence when we get here. Well, we maybe need to say, no. We need to have it in our agenda that these are the topics that are going out, and these are the PICO questions, and this is what we want to know as a group, as opposed to leaving Josh to try to do it and say, well we put it out for public comment and nobody gave me, and now you're criticizing what we have. That's not fair to him. So, we need to have some formal input.

Chris Standaert: I'm going to back in caution. I've said this over and over for a long time. It is my perspective, and I understand what you're saying. If we get involved in the PICO table, we own the report, right? We can't judge, we can't say this is good or bad. We can't say this helped us, this didn't. Most of us from the start wouldn't have known enough about this topic to come up with an appropriate PICO table. We had known the boundaries of the literature. That's why they talk to people like Dr. Meissner when they set these up, right? I don't know the boundaries until I see them, right? And the... we have to be someone independent arbiters of the data and independent of the process that got it to us in a way so that we can be independent. We can say, this is what we have, and I think there really is an issue that if you put ownership in the process that got you the data, you are wed to the process and that makes it hard at the end of the day. So, it's...

Kevin Walsh: But having...

Chris Standaert: ...there's a line there.

Kevin Walsh: ...I agree, but having input into the process the way anybody else in the State of Washington can who chooses to go to the website is not ownership.

Chris Standaert: No. We have that now.

Seth Schwartz: I think we're off topic. This is considerably off topic.

Chris Standaert: Yeah. This is a September discussion.

Seth Schwartz: This isn't what we came here to discuss here. I think the point is that there was an assumption made in this assessment, which was surgery is effective, because surgery was considered the comparator, and I think that's the way we need to start, right? Maybe that's not the case, but that was the assumption was made when this report was put together, and that's the baseline that we're working from, and we're

effectively comparing all the other technologies to surgery, right? That's really the... where we're starting from. So, our question is, we're not really asked to say should we cover surgery, because we weren't really given surgery versus nothing, right?

Chris Standaert: No.

Seth Schwartz: So, we're looking at the other comparators effectively, and what we're seeing is, there really is not a whole lot of difference, right? Maybe the heat treatments are a little bit marginally more effective, maybe they aren't. Maybe sclerotherapy has higher recurrence rates for reasons that have been well explained to us. That makes a lot of sense, but effectively, we're not seeing any meaningful difference between these technologies. So, if we follow the baseline assumption here, which is that surgery is effective, whether that's really truly significant or not, follow that basic assumption, these other treatments seem to be effective. That's the question that we're going to answer. So, are we going to cover them or not. We've not seen evidence that they are any less effective than surgery. There is some... we can argue about whether they're cheaper, whether they're safer, whatever, but they seem to be equally effective, equally or more safe, and probably equally or less costly than surgery, which is where I'm stuck. So, what I'm thinking, if we're going to look for granularity, should we be saying that you should cover a heat treatment first before you cover surgery, as opposed to should you be covering everything, but I don't know if we have the level of granularity to answer that question. So, we come back to the situation of, if we don't have granularity to say that, then we can't differentiate between them.

Male: I agree with that.

Chris Standaert: Let's go to our decision tool. This is page five in your decision thing. We'll see if this helps us get there. So, however people feel about things, we are obligated to go through these issues, in terms of safety, efficacy, cost, and clarify our thinking, as we go through the process so it's clear we [inaudible] this, because that is our charge. So, wherever your head is, we still have to go back and do this somewhat systematically so that we can make sure we have dotted our I's and crossed our T's. So, I guess one issue is, as we go through this, are we considering all the technologies equivalent, and if so, which technologies are we considering equivalent. So, are we talking laser, radiofrequency ablation, sclerotherapy of some sort. There's phlebectomy that is in our list. So, we have to... we're going to have to figure out which ones we're talking about, which ones we're covering unless we say every treatment, everybody, anywhere wants to do for this is the same. That's a different statement, too. So, we have to make a conscious decision on that, at some point. So, safety wise, they gave us various outcomes they think are safety outcomes. I don't know if safety outcomes is quite the right word, but I would pain as another complication, myself, but they have nerve damage, PE, DVT, I'm not sure what adverse events means. It seems like that's a something. Are there other safety outcomes people saw in here somewhere? I didn't see death appear anywhere, but I assume if you have PE on the list, that would be one.

Seth Schwartz: Skin burning.

- Chris Standaert: Skin burn, so thermal injury of some sort from a thermal device. So, other than... so, PE, obviously, is a major one if that were to occur. I didn't see a lot of reports of PE and death.
- Mark Meissner: PE is reported. It's very rare. It's, like, 0.1%.
- Chris Standaert: So, it's an important outcome, but it doesn't really play out as a relevant factor here. Short-term pain two days versus one day, I don't know what that, I don't know what to make of that. Other ones of DVT, it was variable, yeah? DVT, nerve injury, they are somewhat variable.
- Seth Schwartz: By a few percentage points, but there were no statistical differences. The same was true with some of the other things, infection and that sort of thing, not surprisingly higher with surgery, but you were talking about 1% versus 3%, and it wasn't statistically significant in any of those trials.
- Chris Hearne: I think the studies that showed differences in DVT, were observational, if I'm recalling that correctly.
- Chris Standaert: Sclerotherapy had a very high rate of skin pigmentation, 67% compared to some of the others.
- Mark Meissner: I would say that's a recognized complication of sclerotherapy. It's common.
- Kevin Walsh: Plus, the length of the studies determines whether there's time enough for these things to resolve, as they would if you waited longer, nerve injury, for instance. A lot of that will resolve with time. So, to say at 32 weeks, it's the same situation you will have in three years is not true, necessarily.
- Chris Standaert: No. These are safety issues, though, yeah. Then, paresthesia is, I assume, representative of nerve injury, which is down to 2 or 3%, 1, 2, and 3%. I didn't see anybody saying you take out the tibial nerve and cause a paralysis.
- Mark Meissner: Most of these are probably saphenous neuralgia along the saphenous nerve.
- Chris Standaert: Yeah, which is problematic, but it's problematic with everything whether you operate or you cook it or you heat it or you whatever. OK. So, people see a lot of equivalency in terms of safety other than the skin changes with sclerotherapy is the one I saw? Yes? OK. So, efficacy.
- Chris Hearne: I agree with what Seth said before. There's not enough granularity to identify significant differences between them.
- Chris Standaert: Well, we do have some different levels of confidence, though, in terms of quality of life and other things. Again, sclerotherapy comes out much lower in the data pool, is worse for reinterventions. Phlebectomy has no data whatsoever, and that's in our list.

Mark Meissner: You know, phlebectomy is almost never done as a stand-alone procedure. It's usually done with these others.

Chris Standaert: What happens if you don't cover phlebectomy if it's part of another procedure, because we have no data on phlebectomy? They found no data comparing it to anything. It's not compared... it's not a... I assume a phlebectomy is not necessarily... the comparator would not be taking down a saphenous vein, right? That's a different thing.

Mark Meissner: Oh, and of course a problem with all of this data in that a lot of these trials, it was ablation plus phlebectomy. Phlebectomy is not done alone, but neither was thermal ablation or anything else. A lot of them include phlebectomy in the technique.

Sheila Rege: Is the failure right higher with the sclerotherapy or is that just old data?

Mark Meissner: You know, it's for the data for physician-made foam, and I think unfortunately there's not enough time out from the approval of the commercial foam to know, but with physician-made foam, there was a higher recurrence rate, which if you're a practitioner who likes to use that, you accept that higher recurrence rate by the fact that retreating is very cheap at low risk, but the recurrence is higher.

Chris Standaert: And what do people think were important, or would be important outcomes for this population, outcomes of particular importance? So, technical failure could be important, but if it doesn't bother the patient, it's probably not I wouldn't think. So, it's a questionable, it's an outcome, but it's questionable as to how significant that is. The same with technical recurrence. If there is some flowback through the vein, but again, it doesn't bother the patient and doesn't cause any problems with healing or other things, I don't know how big an issue that is.

Sheila Rege: Well, they have to come back and have it done again.

Chris Standaert: If it's symptomatic, but not if it's an asymptomatic... I'm just saying, as a standalone outcome.

Mark Meissner: And I think, just from the literature, most technical recurrences are asymptomatic. You can always find something by ultrasound, but it doesn't need to be treated.

Chris Standaert: Right. So, if you go back and ultrasound everybody, you'll find a number who are still not... they still have some flow through the vein, but it's not a problem for anybody, so you don't do anything about it, but as an outcome... but again, it's questionable in terms of significance to the patient, I would suspect, and less it results in symptoms and symptom recurrence or alteration in quality of life in some other way. Pain, we thought was an important outcome, but we don't have data, or not great data. You saw some data, Kevin?

Kevin Walsh: Yeah, there's data.

Chris Standaert: What's it say? Not much?

- Kevin Walsh: I don't think there's a significant difference.
- Laurie Mischley: We might want to differentiate between the postop pain and ongoing pain.
- Chris Standaert: Postop pain we put under complications.
- Laurie Mischley: I think also the data is around postoperative pain rather than continued pain.
- Chris Standaert: Even quality of life is difficult, because their scales are floored, meaning they don't... they're not... these people are not wildly, most of the varicosities we're talking about are not the people with ulcers and stuff typically. So, they're in there, but for a lot of people getting this done, this scale does not really reflect... it isn't very sensitive to change for them over time, I would suspect, because of a bit of a floor effect.
- Joann Elmore: And in addition to that, the scales, both on symptom recurrence, quality of life, and symptom severity, they include cosmetic and other aspects...
- Chris Standaert: The disco...
- Joann Elmore: ...that are potentially...
- Chris Standaert: ...scene.
- Joann Elmore: ...beneficial, but that we are not wanting to evaluate or not... I mean, we realize they're importance, but we wanted to evaluate the pain and other things. In regards to the actual pain data, on page 113 there is one study of 77 patients that shows that it's equivalent, but it uses a VAS scale, which I was not familiar with, and it is not in the list of abbreviations. Then, on page 118, there is a second study of 65 that showed a real nice drop in both arms, from 50% supposedly having pain, I don't know what the scale was, down to 3 to 6% in both arms. So, if it...
- Gregory Brown: Visual Analog Scale.
- Joann Elmore: ...oh, OK. Thank you.
- Kevin Walsh: Page 147, the review of Pan et al, they discuss pain.
- Chris Standaert: Does it say what Joann just said or do they say something different? Are you reading it now?
- Joann Elmore: I mean, from the scattering of areas in which it's mentioned, it looks like it is helpful.
- Chris Standaert: In both arms, dropped, yeah? Surgical and other arms dropped. Not surgical arms?
- Candy Wines: Excuse me. I have a slight correction for the outcome that is labeled pain on Page 113 in the evidence table, that... in that study, the VAS was described as a quality of life measure. So, it's mislabeled in the evidence table, but I think it's correctly represented in the report above. I'll confirm that.

- Gregory Brown: So, the EQ5D has five questions. It also has the visual... the patient weighted quality of life, which is zero to 100. So, that's the VAS part of the EQ5D. So, that... so, usually it's reported as Health State Score, HSS, which is the zero to 1, and then the VAS and the part of the EQ5D if that's what it's part of, would be zero to 100, and that's the patient weighting of their own quality of life.
- Chris Standaert: So, our most important outcomes, we think from the patient perspective here that we have, quality of life measures, pain, return to activities and work. We don't really have ulcers. We don't have skin changes. We don't have these things I think would be important, but we don't seem to have them in the stuff we have. If anything, return to work was better in the less invasive approaches than surgery, but whether that's a complication or outcome, a problem or outcome.
- Gregory Brown: I heard correctly earlier, didn't you say only about 5% of patients' progress to ulceration. So, you're going to have a hard time powering a study if only 5% are...
- Chris Standaert: Oh, I know. I know.
- Gregory Brown: ...going to go to that. OK.
- Chris Standaert: I'm pointing out some important outcomes to the patient.
- Gregory Brown: OK.
- Chris Standaert: Yes. Pointing out where we think things would be important. We don't have them, it's still a useful callout in our report. Cost? It's usually a short discussion, unfortunately.
- Kevin Walsh: If the ablation is done outpatient, the cost is a lot less than if it's done inpatient, and they're both probably less than surgery.
- Chris Standaert: Yeah. Surgery is clearly more expensive, it looks like, yeah. Do we know anything about special populations? Initially, when they talked about different types of venous structures, but I didn't hear her talk about age, gender...
- Joann Elmore: Pregnancy.
- Chris Standaert: ...ethnicity other than... well pregnancy is an exclusion factor.
- Joann Elmore: Yeah. Right.
- Chris Standaert: Right? So, that's not a... that's an exclusion not a yeah, but I didn't... so and people would say arterial disease, is this a problem in people with... you know, a lot of these studies I'm looking at now, they exclude, you know, deep venous thrombo... deep vein incompetency. So, and the other issue, that sort of comorbidity stuff in there. You think someone, like COPD, you might be better off doing this than operating on them. This might be better in them, but I don't know. I don't know if that's in there anywhere. Anybody see data on special populations that's relevant to us? No. So,

we're interested in it, but we don't have it. OK. So, we're going to move onto our evidence vote. So, for those not familiar with it, we have two levels of voting here. This is a nonbinding vote on what we think the state of our evidence is, and there are specific questions here we're going to vote on. This is really meant to reflect our collective thinking on sort of how we view the data on these three elements of safety, efficacy, and cost. It may or may not relate directly to our second vote, but theoretically should help inform our second vote, because we would like to think that there is some consistency between how we view the data and what we wind up doing. I don't mean to beat a dead horse. So, my first question, so there is sufficient evidence technology is safe for the indications considered. I don't know that, but indications are tricky, because they're not spelled out very well in the studies that are done, and we're doing a comparative thing on one versus the other assuming equivalent indications. Anyway, to the best you can answer this, is there sufficient evidence this technology is safe for the indications considered? Unproven, less, equivalent, more in some, or more in all are your choices. These are your yellow cards.

Gregory Brown: So, it goes back to Seth's earlier comment about if our task it so leave us assumptions that surgery is effective, it's...

Chris Standaert: Well, I don't know. Where, so... where... no. We're not... so, did we get that... that assumption is plainly stated somewhere? It's not. So, that's not in our... unless these guys told us that was their assumption from the beginning, which I didn't see anywhere.

Seth Schwartz: Let me rephrase, the assumption that surgery is effective.

Chris Standaert: Right. We're not asked to consider that, and that's not part of our scope. Yeah. So, we're just talking comparators assuming, I assume at this point equivalent indications for the two, because that seems to be what was done in the studies, or in the multiple... so surgery versus a nonsurgical approaches.

Joann Elmore: Any of the ones we looked at.

Chris Standaert: Any, unless people want to split them, we're going to lump them all. Lump? OK. That's what I was assuming. OK. So, safety?

Josh Morse: Nine equivalent.

Chris Standaert: So, efficacy and effectiveness. Is there sufficient evidence this technology has a meaningful impact on patients and patient care? So, this would be... in this setting, again, we're a bit stuck. You'd like to say, compared to natural history or nothing, but in this case, we're... I assume we're answering this question in comparison to surgery, right? So, compared to surgery, is there evidence the technology has a meaningful impact on patients and patient care? That's how I would phrase that question.

Josh Morse: Eight equivalent, one some, more and some.

Chris Standaert: So, is there sufficient evidence the technology is cost-effective for the indications considered again, on a comparative basis. That's what we're being asked to do.

Josh Morse: OK, I see three unproven and six some.

Chris Standaert: OK. So, my clear sense is that the people, the bulk of people are not thinking of not covering this. We just said it's equivalent in many ways. So, the questions will come down to cover unconditionally versus cover with conditions. If we cover with conditions, we have to define those. Cover unconditionally means we don't put any conditions on whatsoever. So, if there are... I've heard some voices on both sides of that coin.

Kevin Walsh: Help me with the procedure. If we vote cover with no conditions, it's still up to the agencies to pose some conditions?

Chris Standaert: No. If you vote cover with no conditions, anybody who does it will bill and they will have to pay for it, yes, for any reason whatsoever. There's no, you put no condition on the use of that technology, yes.

Seth Schwartz: Then, I would propose that it would be simple like we talked about before, just in patients with symptomatic varicose veins, these technologies are covered.

Chris Standaert: So, that's a condition.

Seth Schwartz: Yeah. It is a condition, but I think the condition is simple, symptomatic varicosities, and we don't have to define it any more than that.

Chris Standaert: So...

Mark Meissner: Let me...

Chris Standaert: ...wait, wait, wait. Oh, go ahead. Yes.

Mark Meissner: I don't know whether it's appropriate for me to make a comment, which is much more as a practitioner than as the expert. My concern on conditions is not so much, I think everything that's been discussed sounds appropriate. What I, both as a taxpayer and as a practitioner don't want, I want to see every appropriate patient have access to this. I don't want to see the numbers skyrocket off the chart, and to me the bigger concern, rather than covering the individual patient is all of these patients have at least three, sometimes four veins, and there are... the way you milk the overutilization is by seeing a patient with varicose veins and saying, oh, I'm going to take care of your saphenous vein this time, and I'm going to see you two weeks from now, and then we're going to take care of your short saphenous vein, and then we're going to do your anterior accessory saphenous vein. I think that's where, if you're going to be unscrupulous and utilize the system, it's not so much differentiating the cosmetic versus the noncosmetic, it's doing these three or four veins per patient. There's no... I mean, it's a thing that people are starting to look at for appropriateness is, in an individual patient, how many axial saphenous veins for a patient are you taking care

of, and if it's 1 to 1.3 per patient that's fine. If it's 3.7 per patient, that's probably inappropriate. So, if I, just as a member of the public and as a practitioner, I would want some condition that if you're going to do more than one vein, there has to be some reasonable reassessment of have you improved the patient's symptoms with one intervention? Do you really need to do a second or third one, because in the long run, I think that's what's going to hurt everybody, both as a taxpayer and a practitioner and as a patient if this explodes with patients doing three or four veins per patient?

Kevin Walsh: That's an excellent point, but that goes to the economic basis of how medicine is paid for. It's beyond our prevue.

Chris Standaert: No, it's not. So, if the studies that were done were a single treatment, then we can say it's a single treatment, right? If the studies done were sequential treatments, treating four veins over a month in their control. If it was a single treatment, if they did one single intervention versus surgery, we can say that, if that's what we have our data of equivalency on. If the studies looked at people who had sequential interventions, we did one ...

Kevin Walsh: I can't remember answers to any of the ifs that you've just generated.

Chris Standaert: That's why I'm, so...

Kevin Walsh: Well, I looked, I mean, we all looked at the evidence.

Chris Standaert: ...right. No, I'm going to ask the vendor so we put it on the table, right? So, in the studies that are in here, and if you can't state it from the systematic reviews, you have 15 individual RCTs, were they a single intervention, like a single point of time where they did the intervention or they did a surgery or were the interventions done sequentially where they went a vein this week, another vein next week, another vein, and did they set that up on their protocol? Do you know how that was done in these studies?

Candy Wines: I don't recall reading about sequential laser ablation or radiofrequency ablation, but there was some information about sequential followup phlebectomies or, in some cases, maybe followup sclerotherapy after an intervention. So, some sequential treatments after the initial main treatment, and they varied between the studies.

Carson Odegard: The problem that we're going to run into here is that even if it is just one procedure, you can have the same appropriateness criteria for the next procedure, right? So, we're talking about utilization data, and we don't have that, as far as sequential procedures. So, how do we make a decision on something that...

Sheila Rege: So, in cancer's equivalent, we have a patient who comes in with bone mets and three bone mets, and if you want to milk the system, you treat one and then you treat another one, and that's unfair to the patient. So, what we kind of finally came up with is, you only get... you can only get paid once for a certain period of time, and I would ask the expert what that period of time is. So, that is an incentive to the physician to

do all of this in one setting if they can, if the patient can tolerate it. That's from cancer extrapolating.

Mark Meissner: It's slightly different in that nobody's going to die from their varicose veins like they might from cancer, but I do think there are certainly, unlike having three bone mets, there are patients who may have more than one abnormal vein who will get better with just treating the first vein. I think there should be some reasonable period of time that may be six weeks, twelve weeks, that the patient has to be reassessed before approving another intervention for them. I think what bothers us all is when you see a patient record that walks into the physician's office, and they assess them and say, well my plan is going to be... I'm going to do the greater saphenous vein and then ten days later I'm going to do the small saphenous vein and ten days later I'm going to do the anterior accessory saphenous vein where this plan to do multiple veins is reached up front with no interval to assess whether the patient did better after one procedure. So, I'm not sure I would limit multiple interventions, but it has to be some reasonable amount of time with reassessment before they're reintervened on.

Chris Standaert: So, if you do... and we've done this before. To say we haven't would be unfair where we've restricted things saying you can't repeat this within six months or a year. We have put caps on how many you can do in a year. We do this... we've done this frequently on this committee. I know, for example, if you were to do, say a radiofrequency ablation of a facet joint and lumbar spine, it hurts for, like, three weeks. So, you don't even think about doing anything else for six weeks or so, 'cuz you don't even know what's going to happen. If you go... there are lots of other... if you, you know, even when we looked at Synvisc, the little bit of data you had, nothing really happened until six weeks, right? So, there are... so, as a clinical thing, what is the... if you do a laser or a radiofrequency ablation, what is the time course of healing, or resolution, of sort of recovery from that procedure where somebody feels like I'm good, where you would actually know the outcome? Is that two weeks or is that really like it takes a couple months for that to happen?

Mark Meissner: I think reasonably, it's particularly if you're doing phlebectomies on the patients, it's four to six weeks, and four to six weeks until you're back to baseline, and then whether you need some additional time to make sure you're still symptomatic is debatable, but it ought to not be... I don't even think it ought to be at monthly intervals. It ought to be at least six weeks or some weeks beyond that.

Chris Standaert: Because I would think you'd want it not so long that if the patient really was still wildly symptomatic you couldn't treat them, but not so short that... but you want it long enough where the clinician really is incentivized to help the patient that time. So, if the patient comes back saying, you know, what you did didn't work. Well, I didn't do enough. I could do more, but I can't do it for three more months because of whatever. That's... they're going to have an unhappy interaction with their patient and they're incentivized to do the procedure to make the patient well the first time.

Kevin Walsh: My memory may be faulty, but my recollection is that when we impose time limits or time restrictions, there was some evidence, or it was a standard that we were agreeing to. We weren't developing it de novo, and there is nothing in these reviews that

discuss what you're considering. So, on what basis are we going to come up with this recommendation?

Chris Standaert: So, I'm going on the basis that if our studies were largely a single intervention, it's largely a single intervention, right? We're not viewing this as a sequential procedure. We don't have data on it as a sequential procedure.

Gregory Brown: So, is there a reason you can't do two veins on the first setting?

Mark Meissner: No, and in fact, yeah. I think in... you can argue whether it's appropriate for C2 varicose veins. It probably is appropriate for patients with ulcers who, you know, you would like to get the maximal benefit, because every patient is going to recur eventually. I think it's appropriate for that. I think there are certain anatomic patterns that might be appropriate to do two veins at once, probably never one where it's appropriate to do four veins at once.

Gregory Brown: Right. Well, if you're... well, we don't have the evidence so I won't go there.

Kevin Walsh: I think we have to wait for value-based payment to answer this question. I'm sorry.

Chris Standaert: Can you just put something up on the board. So, we're going to get back, so one quick thing. Anybody who wants to just cover unconditionally? So, if the majority say we're going to cover unconditionally, then we don't have to do this. Nobody said that. OK. So, we need conditions. This certainly is one of them. So, is there a frequency? Is there a limit? Is there a... and do we have anything to go on to do that?

Joann Elmore: Should we start with the agency medical directors' recommendations that listed the size of the varicose veins and three months of conservative therapy without improvement and some specific symptoms and then the usual exclusion? No.

Chris Standaert: Sure. We can start there.

Kevin Walsh: I disagree. I don't think the conservative care thing doesn't seem to be based on anything. I mean...

Joann Elmore: The only thing it gets us is...

Kevin Walsh: Group Health...

Joann Elmore: ...you won't do a repeat every two weeks, more surgeries.

Kevin Walsh: ...you're proposing that if somebody has persistent symptoms after three months postsurgery, they would then be... they would have the option to have the subsequent surgery?

Joann Elmore: That's correct, according to the agency medical directors' recommendations, that's how people could get repeat multiple veins, although I guess they could do multiple veins the first time, too. I'm assuming they charge each vein, and this doesn't get...

are we going to specify both legs? I don't think we need to get into those details. I think we're safer without.

Chris Standaert: I don't think it's unreasonable to say it's an invasive procedure, and it takes time to get over it and determine what the clinical outcome from the procedure was before you do it again, right? I don't think if somebody were to say, you can't do an epidural steroid injection every other day for a week, I don't think that would be an unreasonable statement. There's no data to say don't do that, except that that doesn't fit at all with the biology of what you just did. So, we follow the biology of what you're doing in the healing time. I don't think that's an inappropriate way to start putting a time limit on something.

Gregory Brown: Could we do each segment at a time, and is ...

Chris Standaert: Can you put up the agency directors' ... just start there?

Joann Elmore: Just start typing what was on the slide.

Chris Standaert: Just copy and paste the agency directors' recommendation, and we will [inaudible].

Gregory Brown: Is 3 mm the standard definition of a varicose vein?

Mark Meissner: Yes.

Gregory Brown: So, I would propose we have the 3 mm in there just so that someone's not injecting 1 mm vein, well, you know, because that... so we have a definition.

Chris Standaert: That's a small vein, isn't it, 3 mm?

Mark Meissner: 3 mm is a small vein.

Chris Standaert: That's a small varicosity.

Mark Meissner: You know, at 3 mm, you're really talking about the tributaries rather than the main saphenous...

Chris Standaert: I mean, the saphenous is bigger than that to begin with, that's an occluded saphenous.

Mark Meissner: Right. A normal saphenous vein is about 4 mm.

Chris Standaert: Yeah.

Sheila Rege: So, what would you recommend as an expert?

Mark Meissner: I think really this really only applies to phlebectomy or sclerotherapy if you're going to treat tributaries with phlebectomy or sclerotherapy, and that ought to be 3 mm. for phlebectomy and sclerotherapy, because it's tributaries, it's not the main saphenous trunk.

- Kevin Walsh: Can I ask people to look at page 152 of the report, which is the NICE guideline, which I think kind of comes at what you're talking about but from a different angle. They're saying to offer endothermal ablation, and if that's unsuitable, then to offer sclerotherapy, and if that's unsuitable, then to offer surgery. I think that comes at the size issue without getting into mm cutoffs.
- Chris Standaert: They also talk about truncal reflux. They talk about incompetent veins, as an inclusion criteria. Doesn't it seem that's what truncal reflux means, yeah?
- Kevin Walsh: And it also says...
- Mark Meissner: Truncal reflux is the main saphenous trunks, greater saphenous, shorter saphenous, anterior.
- Chris Standaert: So, it means they're...
- Mark Meissner: Not the tributaries.
- Chris Standaert: ...but they're incompetent or they're... so, it's not just a big vein, but it's one where the valves aren't working.
- Mark Meissner: Correct.
- Chris Standaert: Right.
- Mark Meissner: Reverse flow.
- Chris Standaert: Right.
- Mark Meissner: Not to want to complicate things, but that is sort of a standard inclusion criteria for ablation procedures in most carriers' policies. You have to have incompetent veins that are defined by more than half the second of retrograde flow on an ultrasound scan, which you don't want to make it more complicated, but that's really the point to start is having more than a 0.5-cm of retrograde flow on an ultrasound scan or reflux.
- Chris Standaert: I don't know if our data lets us say that, so much as lets us say incompetent veins or truncal reflux or some other slightly more vague term.
- Mark Meissner: And in reality that's sort of the standard. I think everybody accepts that as an evidence-based definition of incompetence, more than a half a second of reflux. Was there a common inclusion criteria in our study regarding incompetence of veins?
- Candy Wines: It's [inaudible] by the duplex ultrasound per the measurement that indicates reflux, as you mentioned.
- Chris Standaert: So, people use that measure frequently in these studies?
- Candy Wines: It wasn't always specifically mentioned, but when they did mention it, yes. It was the...

- Chris Standaert: They mentioned the... which criteria, what he just said?
- Candy Wines: Yes.
- Chris Standaert: Can you state what he just said so that I have...
- Candy Wines: Sorry.
- Chris Standaert: ...no. If you can't state the number, then that's, then we need to be more vague. That's all.
- Candy Wines: Yeah, I'm just trying to find it in writing to repeat it back to you, but I can't right now.
- Mark Meissner: In general, you can confirm it. It's just reflux more than a half of a second in duration or 0.5 seconds.
- Chris Standaert: OK. I think we should definitely have something about reflux. So, varicose veins greater than 3 mm and a line. So, truncal reflux, yeah. So, reflux in the main veins, in the main saphenous vein. Then, if it's in our data, we can define it.
- Mark Meissner: I'd probably say reflux in the treated vein, proposed treated vein, greater than 0.5 seconds.
- Chris Standaert: In the post-treated vein?
- Mark Meissner: No, in the treated, in the proposed... in the vein you're going to treat.
- Joann Elmore: So, reflux in the vein that you're going to propose treating. OK.
- Chris Standaert: So, not truncal reflux.
- Sheila Rege: Chris, I actually found a Medicaid, from Noridian, which is our jurisdiction LCD on varicose veins.
- Chris Standaert: Mm-hmm, what do they say?
- Sheila Rege: They have indication for surgical treatment. They have indications for laser, which is all of the above, meaning it's symptomatic and has to have one of the following, pain or burning severe enough to impair mobility, recurrent episodes of superficial phlebitis, nonhealing ulcer, bleeding from a varicosity, stasis dermatitis, refractor dependent edema, and absence of aneurysm of the target segment, maximum vein diameter of 12 mm for radiofrequency ablation or 20 mm for laser. I mean, they get very, very technical.
- Chris Standaert: That's getting way more granular, and I don't think we can be...
- Sheila Rege: I don't think that we can... we can't do that.

Joann Elmore: Not based upon our evidence vendor, no.

Mark Meissner: They do have a statement on reflux somewhere in there.

Sheila Rege: They do.

Chris Standaert: What's their statement on reflux?

Sheila Rege: Caused by reflux, do they require reflux. No, they don't require reflux.

Chris Standaert: Caused by reflux.

Sheila Rege: They just varicose veins caused by reflux, but they don't require...

Chris Standaert: Right. Well, that means that it has to be there. They just don't define what it is.

Joann Elmore: Demonstrated reflux in the affected vein.

Chris Standaert: Yeah.

Joann Elmore: How about just keep it vague? Demonstrated reflux in the affected vein.

Chris Standaert: Yeah. Are people largely OK with that?

Gregory Brown: I would actually... from what Dr. Meissner said, I would withdraw the 3 mm apparently, because...

Joann Elmore: Because it's so small?

Gregory Brown: Because it's so small.

Joann Elmore: But that was the indications in some of the surgeries, the RCTs.

Sheila Rege: And that makes it C2, correct, the 3 mm?

Mark Meissner: And really, it should be tributary varicose veins greater than 3 mm. It's not the saphenous trunk itself.

Joann Elmore: Actually, the definition of a varicose vein is greater than or equal to 3 mm. So, we don't even need it, because this is varicose veins.

Chris Standaert: Well, that's a reflux that defines the problem.

Gregory Brown: But you say... but you said the average varicose veins is 4 mm.

Mark Meissner: Well, the average saphenous trunk...

Gregory Brown: Or I mean saphenous vein.

- Mark Meissner: I think it's important to differentiate the visible varicosities, which are the tributaries, versus the main saphenous trunk. So, do you want to have... I think you sort of want a tributary criteria in there to keep people from wanting to treat 1 and 2 mm tributary veins, even though their saphenous is incompetent? So, I think tributary varicose veins greater than 3 mm is pretty reasonable in C2 disease.
- Chris Standaert: So, add the word tributary. Now, we do have a fairly large study from [inaudible] from 2016 from the class trial, 800 patients, and they said reflux exceeding one second on duplex ultrasound, which is what you were talking about.
- Mark Meissner: And then people debate that. I think 0.5 is the more standard. Some people do use one second, not unreasonable either.
- Sheila Rege: I find it interesting that the intraoperative ultrasound guidance is not separately payable with ERFA, laser ablation, or sclerotherapy for Medicaid.
- Chris Standaert: Yeah. OK. And we have conservative therapy.
- Seth Schwartz: I think we should get rid of it.
- Joann Elmore: Why?
- Seth Schwartz: The conservative therapy before? I don't think we've shown... I don't think we've seen that it's effective, or more effective than any of these other treatments.
- Joann Elmore: But all of us are clinicians, and all of us have seen patients that come in reporting pain and then they go away, and it's two days later. It goes away. I mean, I want to make certain that we're treating something that's really there.
- Seth Schwartz: We could talk about symptom duration...
- Joann Elmore: This seems reasonable.
- Seth Schwartz: ...then, rather than conservative treatment first. That's one way to handle that.
- Joann Elmore: OK.
- Seth Schwartz: Or if they come in and say I've been dealing, I've got that pain in this area for six months, you don't have to make them go away for three more months. I mean, by the time they get to you, they're not going to see you the day after it happened and you do this treatment.
- Gregory Brown: That's not what the billboard says.
- Chris Standaert: See, that's the problem, right. Yeah. You've got to have something in there that makes this a problem that people are trying to deal with in some way. It sounds like compression and elevation...

Joann Elmore: Well, there is no data on compression that you guys are saying. So, I can see...

Chris Standaert: Again, we have no data. The only data...

Joann Elmore: ...so, I like the comment...

Chris Standaert: ...we have is...

Joann Elmore: ...of a duration...

Chris Standaert: ...from them.

Joann Elmore: ...of.

Chris Standaert: I mean, you have to have a duration of symptom and a degree of functional impairment that is real in some way, so at least you're not sort of, you know, hey, you guys said you can, you know, fix this sort of thing off the billboard and they drive in and go. So, I'm OK with getting rid of three months conservative therapy if we talk about duration and severity of symptoms...

Joann Elmore: Yeah, just put it...

Chris Standaert: ...in some way...

Joann Elmore: ...in the next symptom.

Chris Standaert: ...so that we have a bar.

Joann Elmore: Symptoms greater than three months of symptoms.

Chris Standaert: Sheila, you had a bunch of things in that statement from was it NICE or was it, which one of those were you reading that had the big long list of criteria? Not the retired Florida thing? So, what are we looking for for symptoms? Is it... I mean, Seth, you did say just symptomatic?

Sheila Rege: Pain or burning? I would defer to the expert, recurrent episodes of phlebitis, nonhealing skin ulceration, bleeding from a varicosity, stasis dermatitis, refractory dependent edema.

Gregory Brown: Well, what I heard is clinical stage 3 to 6.

Sheila Rege: Yeah. That seems easiest, stages 3 to 6.

Mark Meissner: I think the instrumental ADLs is more accurate than impaired mobility. The only complication I would add is bleeding.

- Chris Standaert: So, what they have is reasonable? So, we just put a duration on it, minimum of three months of symptoms of pain and swelling.
- Joann Elmore: And he said adding bleeding.
- Chris Standaert: Yeah. They had, I assume that's a complication as an example. So, we can add...
- Seth Schwartz: Three months, not six months.
- Chris Standaert: Three months.
- Joann Elmore: Three months.
- Chris Standaert: You can throw bleeding in as a complication, so ulceration, bleeding, recurrent, yeah. Sure. Those are examples. I would put, like, e.g. or something at the beginning so these are examples, not a decisive list. So, e.g. ulceration, bleeding, they're examples.
- Gregory Brown: You've got it. You've got swelling, you know, yeah, ulceration healed or not.
- Chris Standaert: So, again, so if we stay there. Yeah, swelling is edema, yeah. So, exclusions? Clearly those are fit. A lot of these things said deep vein thrombosis. I mean, do you do, I mean, if you're doing this and you have deep veins that are incompetent, as well, do you still do this procedure?
- Mark Meissner: In very few of these trials was deep vein reflux an exclusion criteria.
- Chris Standaert: An exclusion criteria. It was in some.
- Mark Meissner: Well, deep vein thrombosis was. Most trials haven't excluded concurrent deep venous reflux with it.
- Sheila Rege: We could put as an exclusion, spider veins or superficial telangiectasia, but I think we've got it.
- Joann Elmore: We're good to go.
- Chris Standaert: Well, those aren't varicose veins. So, they wouldn't have a grade 3 mm reach, I would assume.
- Gregory Brown: Do we want to take out the last sentence?
- Chris Standaert: Yeah, leave that. You're fine there. Don't take that sentence out. OK. Get rid of the last sentence. Yeah. Do we have to spell that out, all modalities or are we just saying, we're not parsing. So, we're just saying the...
- Joann Elmore: All modalities. It's covered. We don't...

Chris Standaert: Let's put all modalities within the scope of this report, yeah. There might be other things that appear that we don't know about, and we don't want to cover them. We can't. They may want to cover them, but we can't. Does the report list somewhere in the key questions? What does the phrase say?

Josh Morse: Endovenous laser ablation, radiofrequency ablation, sclerotherapy, ambulatory phlebectomy.

Chris Standaert: So, we probably should spell them out so we are clear. Dr. Meissner, is this opening up the barn door?

Mark Meissner: I think the modalities is a little bit of a concern, just because all of these are reasonable, well-accepted, reasonably cheap modalities. There are some others that weren't included in here, like, mechanical chemical ablation that does have a CPT code now. There are others like cyanoacrylate glue, which is quite expensive that don't have CPT codes and are those going to be covered going forward or?

Chris Standaert: No. We're going to specify these four. That's what we're going to do.

Sheila Rege: There are new codes are being...

Chris Standaert: Huh?

Sheila Rege: ...there are new codes being proposed now.

Chris Standaert: Yeah, but we can't talk about anything that we didn't talk about, right, so. There are a lot of those words. Alright, do people have other conditions while they edit this for us? Alright. We have our final language up there so we know what we're voting on. So, are we talking about, does this report cover indications for surgical ligation, or are we just talking about the other ones? Agency people? This is just the other ones, right? This isn't surgery. Yeah. So, take out surgical ligation and stripping. We didn't talk about it. This is our whole problem. We didn't talk about any indications for that. Yeah. That was a comparator not the...

Mark Meissner: I would favor leaving surgical ligation and stripping in there, just because it was the comparator. These were equivalent, and it's rare patients, because no patient is going to sign up for that and nobody is going to do it unless there's a specific reason to do it. There are occasional specific reasons. I probably do two a year.

Gregory Brown: If we don't mention it, then Health Care Authority can do what they want, correct?

Chris Standaert: Right. Exactly.

Gregory Brown: Yeah. So, we can take it out.

Chris Standaert: So, so the question isn't so much reasonable or unreasonable in certain circumstances. The question is, what is within the scope of what we are trying to address, and if they already have a policy or they want their own policy, or they want to do something else

with surgery ligation, they can certainly do that. It just doesn't fall under the scope of what we just said, and by saying a minimum of three months of symptoms, that means that repeat surgery would have to be a minimum of three months, because they still have to be symptomatic.

Joann Elmore: Exactly. That was my point.

Sheila Rege: No. They're going to use the fact that they were symptomatic before the first procedure was done, if...

Chris Standaert: They can clarify how they would like to interpret the language. That's not our intent. Our intent is not that, I don't think. OK. So, our final vote. Any more comments or questions? So, based on the evidence about the technology safety, efficacy, and cost-effectiveness, these four technologies in the setting of varicose veins are either not covered, covered unconditionally, or covered under certain conditions, which are these. That's exactly... specifically what you're voting on.

Josh Morse: Nine cover with conditions.

Chris Standaert: So, now we have to determine whether we're consistent with Medicare and expert guidelines, and I think to the best we can be, we are. They're a little all over the place, and they're a little vague, and some... there are certainly no Medicare NCD to help us. OK. Alright. So, that's it.

Joann Elmore: We should, again, thank our clinical expert. It was really very helpful to us getting your input.

Mark Meissner: Thank you. I enjoyed being here. It's nice to see my tax dollars are being well spent.

Joann Elmore: I think it's time for lunch.

Chris Standaert: Well, we have to start at 1:00.

Gregory Brown: How about 12:45.

Josh Morse: Hey, Chris?

Joann Elmore: Yeah, let's go 12:45.

Josh Morse: Do we want to reconvene a tiny bit early and take care of some of that end of day stuff before the 1:00, so we can get out of here earlier.

Chris Standaert: 12:50?

Josh Morse: 12:45.

Chris Standaert: OK. We're going to get started. Hello? So, before we get going on our afternoon, there was a comment made to me about the morning thing. We added the word

tributary, and it looks like we just restricted ourselves to treating tributary varicosities. That's how that reads if I read that. I think the public comment was accurate myself, and I think we need to include, I don't know what the word is, saphenous varicosities or varicosities, including tributary varicosities greater than 3 mm.

Joann Elmore: Why do we need the word tributary?

Chris Standaert: Because the... well, the problem you have is, the saphenous vein normally is four. So, saying it has to be more than three to treat it means you can treat every saphenous vein in everybody, right?

Seth Schwartz: I'm still not totally clear why we have a mm requirement anyway. Why can't we just say varicose veins? If that's the definition, why not just say varicose veins?

Gregory Brown: Well, because varicose veins are from the regurgitation or the valve, you know retrograde flow. So, he was saying you can have 2 mm varicose veins that you can see. So, that prevents you from treating that.

Joann Elmore: It is not a varicose vein by the CEAP definition unless it is greater than or equal to 3 mm. Wasn't that what they taught us?

Chris Standaert: So...

Gregory Brown: That's right.

Joann Elmore: So...

Gregory Brown: Just varicose veins.

Joann Elmore: ...we can take out that first tributary varicose veins greater than or equal to 3 mm.

Chris Standaert: I think the word tributary is tricky. Either we have to say, you know, varicose veins, you know, for tributary varicosities, they must be greater than or equal to 3 mm and then demonstrate reflux in the affected vein so we can clarify that we're looking for bigger tributary varicosities.

Sheila Rege: Greater saphenous or small saphenous vein or tributary greater than 3 mm.

Joann Elmore: But if the definition of varicose vein requires the 3 mm...

Sheila Rege: No, it doesn't. I don't think so.

Chris Standaert: Well, it has to be specified somewhere.

Joann Elmore: We have to look it up in their...

Chris Standaert: So, I don't have an issue with specifying that tributary veins have to be greater than 3 mm, but we need some way of calling that out as that's what we're talking about, not...

- Sheila Rege: We can say greater and lesser saphenous vein, or tributaries greater than 3 mm.
- Chris Standaert: We only greater and lesser saphenous veins [crosstalk].
- Gregory Brown: No. He said four, at least, to treat.
- Chris Standaert: Right.
- Joann Elmore: Varicose veins are in the C2 category. That is defined by greater than or equal to 3 mm.
- Chris Standaert: Yeah. I guess you just take out the word tributary and assume people aren't going to be treating normal saphenous veins that just have reflux but aren't really enlarged or symptomatic, because even by saying that, we didn't really restrict anything about the saphenous.
- Sheila Rege: Another policy says greater... all of them say great or small saphenous veins, and they then say the accessory, which I assume is what he's talking about, tributary, greater than a certain dimension.
- Chris Standaert: So, if we just say varicose veins greater than 3 mm, then they can treat whatever other varicosity they want, but the tributaries have to be at least 3 mm.
- Sheila Rege: And that's what...
- Chris Standaert: Right.
- Sheila Rege: ...that's what the medical director had also recommended, so.
- Chris Standaert: Right. So, just go back to varicose veins greater than or equal to 3 mm. Oh, just before, we just need a quick, we have to vote. We just changed that. So, now that we've done all that, we can revote our vote to cover with conditions. We should have some sort of...
- Sheila Rege: And did somebody [crosstalk]?
- Chris Standaert: Huh?
- Sheila Rege: Somebody [crosstalk]?
- Chris Standaert: We should have some sort of vote that we agree with this change, because we already amended our thing. So, we will have to revote again.
- Josh Morse: Mm-hmm.
- Chris Standaert: So, can somebody give me a motion to approve this change to our conditions?
- Gregory Brown: New vote.

Chris Standaert: Second?

Joann Elmore: Second.

Chris Standaert: OK. All in favor approving this change to our conditions?

Chris Hearne: What did we change?

Chris Standaert: We changed from tributary varicosities to just varicose veins.

Chris Hearne: Oh.

Chris Standaert: So, we didn't restrict ourselves to only treating tributary varicosities.

Chris Hearne: OK.

Chris Standaert: You gotta raise your hand.

Josh Morse: It looks like everybody approves. Thank you.

Chris Standaert: Thank you.

Josh Morse: So, we'll publish this as the draft and not the previous version, thanks.

Chris Standaert: Thanks. Moving on to our afternoon topic. We don't have our clinical expert here yet. Dr. Johnson is ready to go, it looks like. So, we're going to start with chronic migraine and chronic tension type headache. Dr. Johnson is here to speak for the state of representatives.

Shana Johnson: Alright. We're ready and everyone can hear me OK? Alright. So, I'll be presenting the agency medical directors' presentation on chronic migraines and chronic tension type headaches.

Headache disorders are a leading cause of disability and diminished quality of life. They are a common reason for patient visits and primary care, neurology, and emergency departments. There are a variety of interventions that may be used to manage chronic type headaches, and the purpose of this technology assessment is to take a closer look at the evidence supporting these interventions.

The interventions selected following the scope of the topic included onabotulinumtoxinA injections, trigger point injections, transcranial magnetic stimulation, manipulation, acupuncture, and massage.

When reviewing these studies, there is a focus on the clinical significance of the change in pain measure outcomes. Having done chronic pain for many years, I also took a particularly close look at the functional outcomes of these studies, long-term followup and sustainability of effects, and when considering medical policy, the impact of social and psychological stress, and the approach and management to chronic pain.

The agency medical directors' concerns regarding this topic regarding safety, efficacy, and cost were rated as medium to high.

Taking a look at the State's data, so the first slide shows cost in paid dollars for care. You can see PEBB in green. The cost has gone from about the 200's to about the 600,000 mark from 2012 through 2016. Medicaid has also increased from the 40,000 to about 600 mark.

Taking a look at how many people are receiving interventions for headache treatment per 1000, you see PEBB has increased from about four to seven over the last four years, and Medicaid has increased roughly from about one to about two.

To give you an idea of the modalities and the interventions being used, you can see the majority is onabotulinumtoxinA treatment, which with a much smaller amount going to manipulation, acupuncture, and massage. When we look at the Medicaid data, there is a limited Medicaid benefit when it comes to massage therapy, acupuncture and chiropractic, and that's reflected in that most of the utilization you see is just onabotulinumtoxinA injection.

Next, I'm going to just review our current State agency policy. There is a fair amount of variation across the agencies presently. When we look at PEBB compared to Medicaid, both cover onabotulinumtoxinA injections for chronic migraine covered with conditions. Trigger point injections are covered in PEBB, as well as Medicaid. Transcranial magnetic stimulation is considered investigational in PEBB, but it is covered with limitations in Medicaid. Manipulation, massage, and acupuncture are covered with limits in PEBB.

When we switch over to Medicaid, Health Care Authority Medicaid does not have an adult chiropractic benefit, and in regards to massage therapists and acupuncturists, they are a noncovered provider, which is in Rule WAC0150.

When we go to Labor and Industry, onabotulinumtoxinA injections and trigger points are covered with limits, transcranial magnetic stimulation is determined on a case by case basis. Manipulation, massage are covered. Acupuncture is not covered.

Department of Corrections, most of these procedures are on prior authorization for review with the exception of acupuncture, which is not covered.

Pertinent national coverage determination from the evidence vendor report did note that acupuncture was considered not medically necessary. The other interventions did not have national coverage determinations.

There are a couple of key studies I wanted to pull out and just make a few notes on, as part of the pathway to explaining our medical policy recommendation. For chronic migraine and onabotulinumtoxinA injections, the Preempt1 and Preempt2 studies were moderate quality trials. They did exclude patients with significant psychiatric overlay and those with primary secondary headache disorders. In the discussion

section of the studies noted the clients had been inadequately treated by available medical Therapies. In their outcomes, their pain measures, there was a decrease in mean headache days per month at -1.4 Preempt1 and -2.3 in Preempt 2. In Preempt1, there was a baseline difference in migraine severity that was thought may have contributed to the smaller effect size in Preempt1 compared to Preempt2. The clinical significance of decrease in number of days per month I think is of note. They also looked at functional measures, including the headache impact test. For those of you not familiar with it, this questionnaire has six key questions that ask things like how often is the pain severe? Does the headache limit ADLs? How often have you felt too tired due to your headache? How often have you felt irritated due to your headache? How was your ability to concentrate and ADLs effected by your headache, just to give you a sense of how many functional measures are included. In that, the headache impact test scores decreased by -2.3 and -2.5, that of which is considered to be clinically significant change of score. The percent with severe decrease in score reduced by -2 and -11%. There was no change in acute medication use, although a post-hoc analysis did identify a decrease in triptan intake. There were more serious adverse events in the onabotulinumtoxinA group compared to placebo, and the evidence vendor will go through that in more detail.

There was a transcranial magnetic stimulation that found interesting results. Overall, the study quality was graded at low, and the study was short term. They did find a moderate effect size of improvement in headache frequency and severity of greater than 50%, but the functional measures that they used were not prespecified or validated measures. They also noted that there was no difference in analgesic use between groups. There was another study that showed a promising effect that looked at chronic tension type headaches and manual therapy. Digging into the actual intervention, the intervention included manual therapy, but it also included what would traditionally be considered more physical therapy. In that, it included muscle exercises and posture correction. So, it was hard to sort out how much of the effect was from manipulation, more the rehabilitative exercise, or a combination of the two.

The other interventions tended to have low quality data with small effect sizes or very low quality data or no effect.

So, based on the technology assessment, the agencies' recommendation was, for chronic migraines to cover with conditions onabotulinumtoxinA injections. Those conditions would be following treatment of comorbid psychiatric conditions and other primary or secondary headache disorders in patients that have been inadequately treated by available prophylactic medical therapies. The other interventions were not felt to have adequate evidence to support coverage.

For chronic tension type headaches, the recommendation was noncoverage to the below interventions due to insufficient evidence supporting their efficacy. Ready for questions.

Chris Standaert: Do people have questions for Dr. Johnson?

- Chris Hearne: Slide six shows the number of dollars paid between Medicaid and PEBB for chronic migraine and chronic headache treatment, and I see that the Medicaid numbers, in particular, go up pretty steeply from...
- Shana Johnson: Yeah.
- Chris Hearne: ...2012 to 2016 but on slide seven, it looks like the number of people actually getting these treatments haven't increased as dramatically. I'm just wondering if you can shed some light on why that is?
- Shana Johnson: If I were to hypothesize, it would be because pharmaceutical treatment with onabotulinumtoxinA injection...
- Chris Hearne: Is driving high costs.
- Shana Johnson: ...tends to be spendy. Whenever there is increased use of a high-priced pharmaceutical, there tend to be seen exponential curves in spend and pricing when... I mean, that's just what I've seen by patterns of data I've seen over the last six months. You know, my other caveat, which... if our data person could comment on this as well... is our Medicaid data can be a little difficult between the 2012, 2006 periods, because sometimes they have to use shadow data based on whether it's managed care or regular Medicaid, and there has been a lot of mixing of the populations. Chris, do you feel like that makes the data messier at all, by chance? In other words, can be confident in these numbers based on his question, or some of the factors I just mentioned could affect their validity.
- Chris Sullivan: There's two things in the Medicaid data. One is that we have encounter data from the managed care. Encounter data is always kind of messy. What we get is what's called the shadow amount. Many times it's not the true amount of what was spent, but what would have been recorded as being spent, so we use that. The other is, Medicaid had a huge jump in population when ACA came in. So, your most... the adult population 18 to over 65, I'd have to go look at it, but it was a huge, huge jump from about 480,000 to almost 960. So, that accounts a lot for sort of the jiggly numbers that occur in that period. There was a huge shift also from fee-for-service over to the managed care. So, it's a little strange, but we do the best we can with the claims numbers, and everything is just taken straight off the claims for utilization and paid dollars.
- Shana Johnson: Thank you.
- Chris Sullivan: Does that help?
- Shana Johnson: That's great. Thank you.
- Chris Standaert: Can you guys distinguish between headache and tension headache, migraine and tension headache in this data? Are then encoded differently? Are they somehow screened to require differently?

- Shana Johnson: Now, in this, correct me if I'm wrong, but in this data all interventions for all headaches were included in the pot so to speak. So, this data includes massage therapy, trigger point, manipulation, and onabotulinumtoxinA for no matter which headache type you got it or why.
- Chris Sullivan: But Medicaid, chronic tension headaches are CPT coded separately.
- Chris Standaert: They are coded separately.
- Chris Sullivan: They are coded separately, yes.
- Chris Standaert: But they'd be included ... they're included here. So, you could...
- Chris Sullivan: Yes.
- Chris Standaert: ...you could separate them if you wanted?
- Chris Sullivan: Yes.
- Chris Standaert: OK, but we don't know that? We don't have them separate? We just have them together?
- Chris Sullivan: I don't believe we reported them separately here, but I have them separately.
- Chris Standaert: That would be useful to see. Yeah, do you have them separately?
- Chris Sullivan: I will try to get that right up.
- Chris Standaert: That would be totally cool to see. Yeah. And the Medicaid data here, that's all botox basically, because they don't pay for anything else.
- Shana Johnson: I think that's a fair assumption.
- Chris Standaert: Yeah.
- Kevin Walsh: So, when I looked at this data, I'm never very impressed when somebody compares themselves to placebo. I'm never very impressed when somebody compares themselves to placebo. That seems like the softest target one could identify in the study. When I look at the botox versus topiramate data and I look at the acupuncture versus topiramate data, acupuncture seems to fare a whole lot better in my mind against topiramate than botox does. So, I'm interested in why your recommendation...
- Shana Johnson: Well, I guess I started with... before you can compare something to see which works better, you have to know that it works period, right? Well, I wasn't convinced, on my review of the data, that acupuncture was effective period. So, I don't know what to make of acupuncture compared to Topamax. So, that was my thought process when I was thinking through it.

- Kevin Walsh: So, you thought botox... you thought the evidence stated or identified that botox was more effective, period, than acupuncture was, period?
- Shana Johnson: No. I think you're saying something different. So, botox had at least moderate quality trial data supporting that it works compared to placebo. Acupuncture did not have good quality data compared to anything that it worked period. So, if I don't even know if it works against placebo, I don't know what I'm looking at when I'm comparing it against another medication. That's just the way I think through it. Like, or that's the way I thought through it. Maybe it's incorrect.
- Kevin Walsh: So, I'm not disagreeing with you. I'm just trying to clarify a bit. In my mind, when I look at the decrease in headache frequency and the headache severity of a treatment, that, to me, is part of what I would use in the definition of whether it works.
- Shana Johnson: Yes.
- Kevin Walsh: So, when I looked at those criteria for botox versus topiramate and those criteria for acupuncture versus topiramate, acupuncture decreased frequency of headaches and decreased severity of headaches versus topiramate much more than botox did versus topiramate.
- Shana Johnson: Well, I believe the two trials you're citing are both not very good quality. So, I guess I don't necessarily believe the data. I feel like the strongest data doesn't necessarily support those conclusions, and...
- Kevin Walsh: And I...
- Shana Johnson: ...over the year, I guess, I've really understood and seen how you show an effect with a bad study, and as soon as you tighten up that study, the effect goes away. So, I think I was less impressed. So, again, I didn't think those trials were good enough to hold a lot of weight with me when I look at it.
- Kevin Walsh: So, hearing that, I mean, I've often felt that the quality of the data that we get is poor.
- Shana Johnson: Mm-hmm.
- Kevin Walsh: But yet, we're left to make a decision based on poor data. So, it would be interesting for the agency to come up with some threshold mark for quality that says...
- Shana Johnson: I know.
- Kevin Walsh: ...below this mark of quality, we're not even going to let you look at the data, because we don't think it's sufficient for you to make a decision. That would be one approach, but when I get all the data, I feel like it's all kind of in the same pot, and I'm left to parse it out. I'm not disagreeing with your point. I'm just saying if that's so, maybe there should be a threshold for quality in order to get into these reviews.

Chris Standaert: I mean, I think that's part of our job. So, I mean, we bitch both ways about this, and... with the vendors, you know? So, there are some where we say, oh they got to be more liberal, some they're too tight, you know? Our job is to... we're the ones that are supposed to be the evidence experts here and sort of evidence-based medicine in how we rank and stratify data. So, granted much of the time we don't get the clinical studies and the granularity we need to do that, but when we get them, we should be able to do that and Dr. Johnson is making a judgment of the relative merits of the different studies and the strength of evidence implied by them, but that's sort of our job, I think, once we get them.

Joann Elmore: And I'll just add one comment about the acupuncture versus topiramate in that you would need to have a placebo acupuncture, because otherwise this is acupuncture versus taking a pill, and there was no placebo arm in that, that was added.

Chris Standaert: So, we can get to some of that when we get to the evidence side and Dr. Skelly and her colleagues, and they will tell us some things. Dr. Murinova just came in.

Natalia Murinova: Hi.

Chris Standaert: You were walking in cold. So, we're going to try and help you.

Natalia Murinova: OK.

Chris Standaert: OK.

Natalia Murinova: Thank you.

Chris Standaert: Dr. Murinova is our clinical expert. She's a neurologist at the University of Washington, headache specialist. You can introduce yourself a bit more. We don't have, let us know if there's a conflict of interest. We'll talk about all this, but...

Natalia Murinova: OK. Yeah, so...

Chris Standaert: ...just introduce yourself briefly, and then we'll get into some other issues here.

Natalia Murinova: Yeah. So, hi. So, my name is Natalia Murinova. I am one of the few headache experts for our six states. I am board certified in headache, neurology, and I used to be an internist before I became a neurologist and headache expert, and what I do predominantly is clinical work and clinical research.

Chris Standaert: Thank you. So, in terms of conflict of interest, do you have any conflicts that you can disclose for us that would...

Natalia Murinova: Zero.

Chris Standaert: ...be related to any industry or funding...

Natalia Murinova: None.

Chris Standaert: ...of research or any of that sort of stuff from the industry.

Natalia Murinova: No conflict of interest.

Chris Standaert: OK. So, to explain, normally I would talk to you about this before you got here. So, we're going to...

Natalia Murinova: Mm-hmm. OK.

Chris Standaert: ...talk about it now, because you're here. So, the very... this is an evidence-based process. You weren't here in the beginning. The committee has been around for ten years or so, since Dr. Odegard was a child, apparently, and we are an evidence-driven committee. We have an evidence vendor who prepares a report, which you have seen. That is the basis of the evidence from which we have to make a decision, and we are by statute, we have to decide based on three factors. We have efficacy, safety, and cost. Those are our drivers. Again, from evidence, and particularly evidence we are given. So, our clinical expert, which is you, we like to have, because it really helps us with clinical context of things, how to do things, when they might be thought of or not thought of. Clinical perspective matters. We are all clinicians at the table. That's why we're all here, and that's why this process runs this way, because we are clinicians here making the decisions. In the end, we decide to cover various things. We have three choices when we're done. We decide to cover them, to cover them with various conditions that we can specify, or not to cover at all, and we can go lump sum with everything that was brought before us or we can parse out the individual technologies that are here. We could parse out acupuncture from botox, for example, or we could lump them together, depending on what we feel like doing at that point, but that's our charge. In the end, we have to do that. So, we use the data to help get ourselves there. We like your help to understand, again, some of the clinical context of these things and how they are used. Data and interpretation and perspective, that is helpful. We are bound by the data from the vendor, because that really is the data that is prospectively obtained with a whole public process of sort of setting up key questions and PICO tables and sorting through and public input along the way, and that is what's available and accessible to us, as data. So, outside data beyond that is helpful in terms of perspective, but we're a little hamstring in terms of using it, because it... we didn't get it from them. So, is that helpful?

Natalia Murinova: Yeah. I understand.

Chris Standaert: So, we appreciate your time. I know it's a lot of time to actually get down here and take a half a day out of your life and your clinic and all that, and we really appreciate the time. It's useful for us. Now, you're walking right in the middle of our discussion. So, we just had our agency vendor... agency representative speak, Dr. Johnson gave their perspective on what they think of the data. Now, we have time for public comment, and we're in our window on the phone. We had nobody in the audience signed up to speak. So, the four of you back there aren't raising your hands jumping up and down. So, we have nobody in the audience signed up to speak. We can go to the phones. We're still in our window on our schedule for the phones. So, people on the phones, if you are out there, you are unmuted on the phone now and we can hear

you. This is the Washington State Health Technology Clinical Committee. It's the afternoon session of our meeting today discussing nonpharmacologic treatment of chronic migraine and tension type headaches. This is your chance to address the committee in terms of open public comment. So, if there's anybody on the phone who wants to address the committee or make a public statement, this is your chance to do so. So, if so, please identify yourself and we'll hear what you have to say. Nope. Nobody. Hearing none, we'll move on. Alright. Who is presenting? Spectrum, who is presenting, Andrea? So, Dr. Skelly will be presenting for us their perspective on the evidence they were able to obtain regarding our topics.

Andrea Skelly: Alrighty. I would like to first take an opportunity to thank the individuals who helped contribute to this report who are listed and for the opportunity to share our findings with you. As you have already heard, let's see, there we go. As you already heard, headache has a high disease burden and also a high cost burden in terms of care. It affects a large number of individuals. Usual care across both chronic tension headache and chronic migraine include a variety of pharmacological and nonpharmacological treatments, including many of the ones that are listed here. One thing to notice for pharmacological treatment, some of the same pharmacological treatments that are used for acute episodes of care are also used for preventative aspects, and many of these are used off-label, so, antidepressants and anticonvulsants, as well.

The focus for our report is on chronic headache and the preventative aspects for chronic headache. In terms of some classification issues related to headache, our focus, again, is on primary headaches. Those are headaches which do not have an underlying other cause, such as mechanical headaches or other headaches. We were also interested in chronic headache and the classification that we've attempted to use is the chronic headache is there. If it's 15 days per month or over 180 days per year with regard to chronic migraine, eight of those 15 days should be spent with migraine type features. So, again, for this report, we have included primary headaches, chronic tension headache, and chronic migraine, or a combination of these.

Moving on, characteristic features of chronic migraine include recurrent unilateral pulsatile pain lasting 4 to 72 hours, may be accompanied by nausea, vomiting, light/sound sensitivity. Common migraine without an aura, or classic migraine, are both included in this report. Chronic tension headache by contrast is a little bit different pain characteristics in terms of it being more of a dull nonpulsatile and diffuse bandlike pain. The intensity is mild to moderate and can also impact the scalp, head, or neck. There is no clear cause for chronic tension headaches. Stress and muscle contraction are often attributed to that. In terms of classification, there have been a lot of change in classification over the last 20 years in terms of how headaches are characterized. The terminology has changed. So, some of the things in the literature in terms of how they characterize it have changed, as well. For the purposes of our report, chronic daily headache, again, if you look in the literature and if you look in the patient related information available, chronic daily headache has been defined as a variety of different things that it's been taken to mean, mixed headache, which would be a tension headache and mixed migraine headache, it's been taken to mean a variety of different things in the lay literature, including transformed migraine and other things. For the purposes of this report, those studies that classified chronic daily

headache were those that had coexistent chronic migraine and chronic tension headache. This may not be the best classification, but again, we're sort of stuck with what we have in the literature. More recently, chronic daily headache has come to be used to discuss chronic migraine headache more specifically. One of the things to think about in terms of the characteristics of headaches is that they may change daily or within any given day. So, there are a variety of things to consider there. In terms of symptoms, they may subside just spontaneously or with medication. With regard to studies there may be regression to the mean or maybe some cointerventions and possibly placebo effect. Again, coexistent migraine and chronic tension headache may have characteristics of both. One may predominate at any given time. One thing that one of our clinical reviewers brought up is that medication overuse headache was probably common in most of the studies that were reported, although some trials did try to exclude patients with medication overuse headache. It wasn't well defined in the earlier literature and may be persistent, and in the report, we have attempted to identify studies and the extent to which they may have included patients with medication overuse headache recognizing that there would be some misclassification in that.

Kevin Walsh: Can I ask for a clarification?

Andrea Skelly: Yes.

Kevin Walsh: Which medications are considered in that term?

Andrea Skelly: I think...

Natalia Murinova: I can answer that. It's all acute medications that are short-acting. So, the biggest epidemic here actually is over-the-counter, so acetaminophen, Motrin, ibuprofen, Excedrin, all the prescription triptans, and the biggest problem that Washington State has is opioids and barbiturates. So, all of them, all of the acute medications. So...

Kevin Walsh: They're all being considered in this term?

Natalia Murinova: Yeah. So, any, any medication they take acutely, it's over a certain amount per month. So, most medications if you take them simple, like acetaminophen more than 15 days per month, and that's the biggest epidemic we're dealing with, are very likely to cause chronic migraine or chronification of migraine.

Kevin Walsh: And am I wrong that criteria was not a metric that was evaluated in any of these studies?

Natalia Murinova: No. It wouldn't... I don't think it will be, because the majority of what we're finding is the majority of the physicians do not have the capability of diagnosing it, so...

Kevin Walsh: No. I meant, I meant...

Natalia Murinova: Some...

Kevin Walsh: ...when we're looking at performance.

Natalia Murinova: ...right.

Kevin Walsh: When we're looking at whether something works or not, we're looking at headache frequency. We're looking at headache severity change. We're not looking at whether patients continue to overuse the over-the-counter or prescription other medications, as a metric for improvement.

Natalia Murinova: So, and some studies actually do that. They do look at decreased medication. There are studies that look at that.

Andrea Skelly: It's included as a secondary outcome. So, I will not be presenting that information, but we do have it available in the report and are happy to discuss it, you know, to the extent that it's available. In most of the studies, they did not quantify or clarify what exact agents were used that would make them think that they had medication overuse. Some of them didn't define it other than saying that they used over 15 medications per month. Some didn't define it at all. So, it's very mushy.

Natalia Murinova: It's not clear right now if things can work if you do not address medication use and/or not. So, that's the biggest... you know, studies that are moving in that direction, you know? It's, like, to decide whether if you start a preventive medication, will it be effective and/or not if you don't address the underlying medication use. A lot of them seem to be effected in spite of that. So, I mean, it's not a black and white kind of deal.

Andrea Skelly: Alright. Thank you. So, in terms of treatments, one of the treatments selected for evaluation is the use of botulinum toxins. While there are seven different botulinum toxins potentially available, only the onabotulinumtoxinA, botox, has been approved for treatment of headache disorder and is exclusively approved for chronic migraine headache, as defined up here, and you can see the indications and contraindications for that.

In terms of dosing from the FDA available patient information, you can see that the doses are around 155 units injected into 31 sites. You can see that the sites are distributed across the head, the neck, and the scalp. The FDA does have some information that says that one should not exceed a total dose of 360 units administered every 12 to 16 weeks or at longer intervals. It does have a black box warning associated with the patient information indicating that there are symptoms that may be reported hours to weeks after injection, and that can include swallowing and breathing issues, as well as other life-threatening issues. So, we can go into more information on that, as you see fit.

If we go onto the next slide, there are a number of other treatments that were part of the scope for this particular report, and in terms of other treatments, acupuncture briefly can be defined as a solid filiform needle that is inserted into specific energetic areas. Sometimes, they are inserted into trigger points. There are manual therapies, which broadly defined include passive movement of joints and soft tissues by hands or equipment. Massage is more distinct from the standpoint that it involves soft body

tissue manipulation. Then transcranial magnetic stimulation is something that has been more recently evaluated, and it consists of a copper wire that... a coil that's attached to an electrical source. The current is run through the coil, and it generates a magnetic field then sends pulses in through the scalp and the idea is that the extracorporeal magnetic pulses produced penetrate into the brain, the neurologic tissue, and stimulate the nerve cells and alter the firing of the neuronal cells. That's the primary mechanism, by which it supposedly works. In terms of indications, it is indicated for acute treatment of pain associated with migraine with aura. No contraindications were listed. It was a bit of a challenge to find a lot of information on this particular technology. We also looked at trigger point injections, which are different from nerve blocks, in that they focus on muscle knots, and they be associated around nerves, but this was separate from nerve block, in terms of the type of intervention.

So, if we move onto the key questions, the key questions basically ask whether or not any of these treatments are... when compared to placebo, sham, waitlist, no treatment, or other usual treatment options, whether there's evidence for efficacy, safety, differential efficacy, or safety, and about cost-effectiveness.

The PICO is in your report. Basically, we're again looking at patients with chronic migraine or chronic tension headache and again included the category of chronic daily headache. We have discussed the different interventions and comparators. We focused on RCTs. We did consider observational studies if they met our inclusion criteria for safety, and we looked for full economic studies and full-length publications published in English.

In terms of the inclusion criteria for outcomes, our focus was on treatment responders, or those who had success with treatment, in other words, the portion of individuals who have achieved a specific threshold for improvement in a given measure. Most commonly reported, though, were reduction in numbers of episodes or reduction in numbers of headache days or headache free days. Those were the most common reported outcomes. We did look at validated measures for function and other disability measures, and of course adverse outcomes, as well. One thing to note here is that the timeframes for all studies were very short compared to some of the technologies you've reviewed. So, for the purposes of this report, eight weeks was short-term, intermediate was eight to twelve weeks, and anything over twelve weeks was longer-term. I didn't want to call it long-term, but it's longer-term, and as you'll see, we don't have a lot of data on longer-term use. Strength of evidence, as you know, is something that considers each primary or critical outcome separately and looks across the literature for that outcome. Looking at the risk of bias, which we separate out in terms of [inaudible] for each included study, and also it looks at consistency, directness, precision, and reporting or publication bias. All of those go into the sausage making for strength of evidence determination.

So, looking at this slide, we see that the outcomes, each individual outcome across studies is then given a high, moderate, or low, or insufficient strength of evidence based on our confidence in the quality of the evidence and the findings and their stability.

A large number of full texts were reviewed. We have over 2900 studies, abstracts, to look at, and in the end, we included 35 studies. The majority of the evidence is for botulinum toxin for all of the different headache types. So, that would be the primary focus for our discussion at this point. You can see that for other treatments, there is much more sparse data.

The Preempt trials are the primary trials that discuss the use of botulinum toxin A with placebo, and the Preempt1 and Preempt2 trials were done almost simultaneously. The Preempt1 trial was primarily North America. The Preempt2 trial also included other areas of the world, especially Europe. The primary outcomes are listed here. Where possible, we attempted to look at each of the trials individually to make sure there was consistency or not consistency; however, a lot of outcomes only pooled data across the two trials were available, and you can see then the other citations and the number of patients in each group were somewhat different, based on the outcome that was looked at, and the type of information that was available for that outcome. One thing to point out is that there was a 24-week double-blind placebo-controlled phase to these trials, after which there was a 32-week open label phase where people from both placebo group and the botox group would be allowed to have botox open label. So, most of the data we will show you, except for a little bit of the safety data, will focus only on the randomized trial portion of these trials.

Chris Standaert: Dr. Skelly? So, just one quick question on these studies, maybe you know the answer. It seemed odd they... I tried... I read these studies and they seemed like, essentially identical study protocols at the exact same time...

Andrea Skelly: Mm-hmm.

Chris Standaert: ...in two different studies...

Andrea Skelly: Mm-hmm.

Chris Standaert: ...with the same people and the same funding.

Andrea Skelly: Mm-hmm.

Chris Standaert: That then came out as another publication of pooled analyses that actually changed the statistical significance of the individual studies. So, I didn't understand why they did that. Why didn't they just run... it's weird... run one study.

Joann Elmore: I can tell you why?

Chris Standaert: Oh, why? Yeah.

Joann Elmore: The first one was not significant, their primary outcome.

Chris Standaert: Yeah. Oh, no...

- Joann Elmore: And so, they... because of that, their primary outcome in Preempt1 was frequency of headache episodes, something like that, and it wasn't statistically significant, and some of their secondary outcomes were statistically significant. So, in Preempt2, they changed their primary outcome.
- Chris Standaert: But they, but they were...
- Joann Elmore: And in the pooled, they used the... this new changed Preempt2.
- Chris Standaert: Because their recruitment overlaps. So, they must have known, yeah. It's weird. It's odd. And like I say...
- Joann Elmore: And what you're saying the pooled is, you're not going to spend as much time...
- Chris Standaert: Yeah.
- Joann Elmore: ...on, because that was open label. People knew what they were getting, and there was a very strong placebo effect.
- Chris Standaert: No. Well, they pooled this 24-week data and ...
- Andrea Skelly: Yeah. Some of the pooled data were for the 24-week randomized, and we will report that, because that's all we have. We weren't able to separate the data. We will only look at the open label piece for some of the safety outcomes.
- Chris Standaert: I mean, it has a little bit of, like, look that they went fishing. Like, they had one that was mean change in baseline headache episodes and one in days, and they figured, you know, two different studies, we'll find something. It's, like, it's like you created two studies to have two primary outcomes and hope you got one.
- Andrea Skelly: The rationale that they provided in the study says they had the availability of a Preempt1 data and then guidance provided by newly-issued International Headache Society trial guidelines reevaluating headache prophylaxis and earlier expressed preference by the U.S. Food and Drug Administration supported using headache day frequency as a primary outcome measure. So, that was their rationale for changing.
- Natalia Murinova: So, that's an ongoing... a very good pickup. So, that's an ongoing issue with trying to compare a lot of the data that there is no current consensus what is the best outcome. So, currently, the feeling is that headache days along with the disability... the problem is that a lot of the disability measures were not developed for chronic. They were developed for acute. So, that's what we struggle with is that it's difficult to compare exactly what you figured out. That's what you'll see when I'm going through usually comparison. So, a very good pickup, you know, on that, but currently it's probably the mean consensus would be that they should be using headache days, but some people use headache... so, some people go further and would argue that you should use headache hours.

Gregory Brown: I was going to say, a headache day is any 24-hour period where you have headache symptoms?

Natalia Murinova: Right.

Chris Standaert: It says more than four hours.

Natalia Murinova: Yeah.

Chris Standaert: Is how they define... like, so you're... if you have 15 in 30 days, it has to be more than four hours on that day. That's a headache day.

Andrea Skelly: Though some people would argue that it really should be headache hours.

Chris Standaert: It's hard to count.

Andrea Skelly: OK. So, moving on. In terms of chronic migraine, so, the way I've divided our presentation this afternoon is to look at chronic migraine first and because of the potential close association between chronic daily headache and chronic migraine, it'll be presented second, and then we'll do chronic tension headache.

So, in terms of chronic migraine, here are the outcomes reported. Table one on page 68 has the list of the various outcomes measures and what we could find with respect to minimum clinically-important difference and validation. As already mentioned, studies reported things in days or in episodes. So, within each of those, we could look at responders, those that achieved some threshold of success for treatment, or look at the mean change in days. Headache intensity or pain usually on a ten-point or zero to ten VAS was also reported in many of these studies. In terms of function and disability, there wasn't a lot of information for some of the measures with regard to minimum clinically important differences, but the HIT score, which was mentioned by Dr. Johnson, was... the minimum important difference was considered to be 2.3 points. The Preempt studies also looked at whether or not the HIT score, if you had a severe HIT score at baseline, how many of those had HIT scores over 60, indicating severe headache at the end of the study. The Migraine Intensity Disability Score was also one. There was one reported in one of the studies that they called functional disability. It appears to be an author-defined and not a validated measure. We'll get to that in a moment, yeah.

Kevin Walsh: Can you explain... so the... for the HIT-6, the scale is 36 to 78?

Andrea Skelly: Yes. That is what we found in the literature.

Kevin Walsh: OK. So, Chris, remind me... we have a lot of orthopedic studies that we've been looking at in the MCID had to be, like, 30%, didn't it?

Chris Standaert: Yeah, but they've...

- Andrea Skelly: A couple of things about MCID is that it's patient population dependent how they... how it's defined. And what may apply to one type of study and one population may not necessarily be applicable across other populations.
- Seth Schwartz: Well, I know it's difficult to compare a headache to back pain. So, what's your appreciation of the...
- Gregory Brown: Well, like, the Oxford... I mean, I don't know this one, but for the Oxford Knee Score, some people rate it 12 to 48. If you say your lowest is 1 to 5 and others rate zero to 4...
- Kevin Walsh: Isn't there a...
- Gregory Brown: Well, the MCID for the Oxford Knee Score is 5. So, it's, you know, 10% of the scale, 10% of the scale.
- Kevin Walsh: This is 2.3 points of a scale of 36 to 78 is, like, less than, like, about...
- Chris Standaert: Yeah.
- Kevin Walsh: ...6%.
- Chris Standaert: And for back pain, it's roughly 13-ish out of 100. So, it's...
- Kevin Walsh: I was just trying to understand if they set themselves a low bar for MCID here?
- Andrea Skelly: That was a number that we found, actually, in a study. We can look up the study if you're interested in the... that tried to validate that 2.3, and yeah.
- Chris Standaert: Because as a percentage of that scale, that's pretty small is what he's saying.
- Andrea Skelly: Yeah.
- Chris Standaert: Yeah. So, like, a pain of 1 out of 10 is 10%, you know?
- Kevin Walsh: You high jump six inches.
- Chris Standaert: Huh?
- Kevin Walsh: Like, I can high jump six inches.
- Andrea Skelly: I can't.
- Gregory Brown: I know.
- Andrea Skelly: So, moving onto the results for efficacy, looking at responders. When we take a look at the 50% threshold for reduction in migraine episodes over 12 weeks, again, that's our "longer-term." It's not super long-term. There was moderate evidence from one

very small poor-quality study that over a 16-week period of time that botox was associated was not statistically significantly associated with a change in the percentage of patients meeting that threshold, and the same held true for the pooled data from the Preempt1 and Preempt2 trials. Again, we only had pooled data available from the trials for that particular outcome. If we then change our view to looking at migraine days and headache days, we see that there were statistically more individuals receiving botox versus placebo who had a 50% or greater reduction in the number of migraine days or headache days, again at 12 weeks or greater. Again, only pooled data were available. We considered this to be moderate evidence.

If we take a look now at the means and the differences in the means across studies, we can see that for botox versus placebo, in terms of migraine episodes, again, there were no statistical differences between the two treatment groups, but if we take... and if we take a look at mean headache episodes, as well. So, again, we're seeing a pattern of difference between episodes and migraine days in this next slide where there was a statistically significant difference favoring botox in terms of the mean reduction in migraine days and headache days; however, in both instances, the pooled difference was less than two days, and it is unclear whether that would meet a clinically significant threshold. We considered that there was moderate evidence for those particular outcomes. If we take a look at the proportion of patients who by 12 weeks had severe headaches still, significantly fewer botox patients had severe headache based on HIT scores by 24 weeks, and in terms of the reduction in the mean HIT scores, again, it favored botox, and we felt that there was moderate evidence to suggest that for these outcomes, botox was favored.

Looking again... now most of the studies, again, looked at botox versus placebo. This is one study that did look at botox versus Topamax, topiramate. In terms of 50% reduction in headache days, there were no statistically significant differences. In one very small study at very high risk of bias, the evidence was considered to be insufficient at 24 to 36 weeks, because the loss to followup was over 60% in that time period.

Again, looking at the same study, botox versus topiramate, there were no statistical differences for any of the functional measures at any time point. The evidence was considered low at 12 weeks, but at the later time periods, was considered to be insufficient.

Another study looked at botox versus amitriptyline, and in terms of the longer-term evaluation, they looked at whether or not there was a 50% reduction in the number of pain days and a greater than three-point reduction in pain. Neither were statistically significant, and the quality of evidence was considered to be low.

Looking now and shifting gears now to acupuncture versus usual care. One study in the U.K. reported statistically significant improvement following acupuncture with one moderately high risk of bias trial. One thing to note is that the sample size is... the effect size is relatively small, even though it was statistically significant and because of the high... the risk of bias of this study and imprecision, we downgraded it and considered it to be low quality evidence.

Looking at that same trial and looking at their threshold of 35% reduction or greater in the number of headache days from baseline, again, there was a statistically significant improvement following acupuncture versus usual care, but the confidence in the estimate is low. There were small but statistically significant differences favoring acupuncture with regard to any headache days, mild headache days, or moderate to severe headache days, and again, it's unclear that these would be clinically significant. We did have a study looking at acupuncture versus topiramate, and in terms of 50% reduction in number of headache days, and this is only over four weeks. So, this is very short-term. More acupuncture patients had that 50% reduction or greater and the effect size is actually moderate to large. However, the small numbers of patients in this trial and although it was moderately low risk of bias, we felt that the quality of evidence was low.

Looking at that same trial and looking at reduction in the mean of any headache or moderate to severe headache days, again, there was statistically significant improvement versus topiramate seen in the acupuncture group, and again, our confidence in the estimate is low because of risk of bias and imprecision. Again, this is all short-term. This is only four weeks.

If we look at spinal manipulation, shifting gears once again, versus amitriptyline, one study looked at different thresholds of responders. More patients receiving manipulation therapy achieved 20% or 40% reduction in headache intensity scores compared with amitriptyline; however, the results were not statistically significant for the greater than 60% reduction. Again, we felt that the evidence quality was low. The authors also did report that the percentage of headache days per month tended to favor manipulation but it was not statistically significant and the quality of evidence was low.

Moving now to transcranial magnetic stimulation versus sham, one study using high frequency waves did find that more receiving the transcranial magnetic stimulation did have a 50% or greater reduction in headache intensity scores, but again, the size of the trial and the quality left us to believe that the quality of evidence, overall, was low. At four weeks, the same study did find a statistically significant improvement with regards to reduction in migraine attacks per month, mean migraine attacks per month versus sham. The other study, which was much smaller and used low frequency transcranial magnetic stimulation. There were no statistically significant differences and the small and poor quality of the study led us to believe that the evidence was insufficient. Then, the... going back to the high frequency study, which was the only one that reported functional disability scores, again, they did find a statistically significant improvement with the transcranial magnetic stimulation versus sham, but again, we felt the quality of evidence was low.

We shift now to chronic daily headache and again, most of the evidence relates to looking at onabotulinumtoxinA versus placebo. We do have one that looks at comparing that to topiramate. We also have one massage versus sham trial to look at.

Similar outcomes, headache days, headache episodes. Again, we tried to focus on responders where possible, and identify where measures provided information on a

minimum clinically important difference. For the number of headache days, the only thing that we could find and you may want to take this with a grain of salt, is that one of the trials considered three days change in the mean from baseline to be clinically significant, but does not provide further validation of that. Then, we have the others that we have looked at again.

So, looking at botox versus placebo in terms of that threshold of 50% reduction of headache days, again, more onabotulinumtoxinA recipients had that reduction compared with placebo. The relative effect size is small. The absolute numbers are here. Oh, by the way, I forgot to mention that for those of you who want the pooled strength of evidence tables, they are in section five of the report, and you can find that there is additional information there as well on this, but we considered the strength of evidence low based on this one trial of moderately high risk of bias.

If we take a look at looking at the different trials at four weeks, eight weeks, twelve weeks, and then longer term, there was one trial that looked at four, eight, and twelve weeks, and there were no statistical differences between botox and the placebo at any time point with regard to headache free days. At 24 weeks, we were able to pool some data. The pooled data were not statistically significant, but you can see that there is heterogeneity with one favoring botox one favoring the placebo. It is unclear why that should be, but we felt that the quality of evidence was low for the pooled estimate, and at 32 weeks, the one trial did not find any statistical difference between the two treatments.

Looking then at headache days per month and function, we're looking at botox versus topiramate, again, the only other active treatment that we have for this headache category. Very poor quality study, was downgraded for risk of bias and imprecision. At four weeks and twelve weeks, there were no differences. They don't provide us with any further data to calculate effect size. In terms of function, there were no significant differences just based on looking at the means for either the HIT or the MIDAS. Again, they do not provide sufficient data to calculate an effect size. Quality of evidence was considered low.

Headache attacks, no statistical difference in... we're looking at massage versus sham. Sorry. We should have oriented you. We're looking at massage versus sham, reduction in mean headache attacks per month, and the headache disability index, and there were no statistical differences at either time frame, but again, a very small poor-quality study, and the confidence in the evidence is low.

We shift gears again looking at chronic tension headache. Again, botox is the most commonly studied intervention in this group, although we do have two acupuncture studies versus sham and one versus other active controls and one manual therapy RCT on trigger point.

Again, similar outcomes, episodes, headache days and episodes, headache free days or headache free periods, pain intensity, headache index, and then we have functional measures of HIT score, the headache disability index, and the sickness impact profile. For the HDI for the headache disability index, the authors suggested that a 16-point

change in the 100-point scale would be clinically significant. We were not able to find validation of that other than what the author reported.

Looking at the efficacy results, again, looking at responder categories at four and eight weeks, patients who had... there was no difference between the number of patients who had botox versus placebo with regard to 25% or greater reduction in pain intensity and at... the same was true at twelve weeks, and the evidence was considered to be insufficient from these two trials. One thing to note about the chronic tension headache trials and the botox versus the placebo is, all of them were very small. Most of them were very poorly done, and the data, overall, were considered low quality or insufficient. Case in point, when we look at four weeks and twelve to 24 weeks, there was a difference favoring botox with regard to number of headache days per month in the short-term four weeks, and also across two studies at 12 to 24 weeks, but again, these are very small trials, and there was substantial heterogeneity. Again, there is not enough information to explore that heterogeneity. We consider the results were insufficient quality to make a judgment.

With regard to looking at botox versus placebo and mean pain free days per month, there were no statistical differences in one study at four weeks or across two studies in eight weeks.

Now taking a look at headache days per month and in the headache disability index, we didn't feel that there was sufficient information to draw a meaningful conclusion. The statistical significance wasn't reached, although it would appear that there were more patients in the botox group than the placebo group that experienced headache reduction in days. Again, sample size of 40 is very small. In the other trial looking at the HDI scores, although the scores were significantly lower with botox that suggests improved function, again, a sample size of 28 and the quality of the study did not leave us with very strong evidence for conclusions, and it was considered insufficient.

If we now go to acupuncture versus sham, there were no statistical differences between groups for any of the thresholds, either 33% or 50% improvement in headache index, either long-term or short-term, again, very small study and unclear that this provides us sufficient evidence for a conclusion.

Across two studies, looking at acupuncture versus sham, there were no statistical differences. With regard to mean headache episodes, again, this is short-term only, and because of the quality of the studies, the size of the studies, we felt that there was insufficient evidence to draw from conclusions. The only other active treatment for acupuncture to discuss in this slide was one trial that had three arms and with regard to acupuncture versus physical training and exercise, physiotherapy, relaxation training, there really were no differences between the groups; however, it was unclear in the physiotherapy group what the effect sizes were, because they didn't provide us with adequate data.

Moving to then manipulation versus usual care, looking at headache days, manipulation was associated with greater improvement with regard to more people having reduction in the headache days over a two-week period from baseline. They

also then looked at the number of headache days per two weeks in a continuous mode, and again felt that there was statistically significant improvement. Again, the quality and size of the study did not allow us to give it a grade higher than low.

If we take a look at the headache impact test and headache disability, the headache impact test, the mean difference was five, which would meet the threshold of 2.3 for clinically significant. It was statistically significant, but again, a very small study. We felt the quality of evidence... this was a very poor quality trial. We felt that the evidence and our confidence in it was low. Again, with statistically significant improvement in headache disability inventory was noticed; however, it did not meet the author-defined threshold of 16 point or better reduction.

Trigger point injections, the only trial that we had looking at trigger point injection was very small and very poorly done. It was at moderately high risk of bias. Basically, the only thing that we could give them credit for was blind assessment of outcomes. So, we considered the evidence insufficient.

Moving to complications and harms. So, again, we're going back to chronic migraine. We're looking at botox versus placebo, remembering that placebo may or may not be associated with certain types of adverse events. More adverse events were reported with botox versus placebo. Those were both treatment related adverse events by 24 weeks or serious adverse events long-term by 24 weeks, and that's across the two Preempt trials.

Chris Standaert: Could you specify what you mean by serious versus treatment related?

Andrea Skelly: Yeah. Let me, let me go to my notes here. In general, things were kind of poorly specified in many of the trials with regard to adverse events, and in terms of adverse events, treatment related adverse events were neck pain, muscle weakness, eyelid ptosis, those were reported by a higher number of patients in the botox group than the placebo group. All adverse events were considered treatment related. In terms of serious adverse events, it was not described by the author. So, we don't have good information about what was considered a serious adverse event. Most of the adverse events, the reports indicate the authors felt were to be mild or moderate in severity, and that they resolved without sequelae. That's about all the information they give us about that, unfortunately. If we go onto the next slide, it's even murkier. Treatment-related serious adverse events were only reported in the one trial, the Preempt2, and their definition of a treatment-related serious adverse event, which occurred in only one patient, was one hospitalization for migraine. That might be considered a rare outcome and they may not have had a sufficient power to detect differences, although again, the comparator is placebo.

If you would like to look at the laundry list of adverse outcomes, you can see that those are highlighted were the ones that they highlighted in the report, and give you the sort of absolute risk for the neck pain, the muscle weakness, and the ptosis, as well as the other adverse outcomes. All of the data I have shown you so far for safety have been for the 24-week double-blinded placebo-controlled portion of the study. They also did, in one of the publications, look at all patients who had continued the... in the open

label phase. So, the patients who got placebo during the randomized phase were allowed to have three botox injections. The patients who had botox, randomized botox, had an opportunity to have three more. So, here, we have a comparison of three treatments versus five treatments, and you can see that there are no statistically significant differences between the two with regard to adverse events. Again, these are not well defined. Again, remember that this really constitutes a single-arm case series.

If we then move on to botox versus topiramate, there were no statistically significant differences with regard to adverse events up to 36 weeks. I would add that there was substantial loss to followup, as you see at the bottom. At 24 weeks, there was only about 65% of the patients available for analysis. The timing events was not reported, and this looks at drug-related adverse events probable or possible drug-related adverse events and discontinuation related to adverse events. Again, the quality of the data is very low. The loss to followup is great, and so we do not have a lot of confidence in those results.

Chris Standaert: Does that say that 86% of people had a drug-related adverse event or that 86% of adverse events were drug-related?

Andrea Skelly: It was reported as drug-related adverse events. Did I miss...

Chris Standaert: No. I'm just trying to figure out if those... if that's the portion of people who had an adverse event that was attributed to the drug, or whether they're saying that 86% of the people who got put onto topiramate had an adverse event from the drug?

Andrea Skelly: That would be 86% of the patients who had topiramate had an adverse event from the drug versus 69% of the patients who had botox had an adverse event from botox.

Chris Standaert: Those are really high rates.

Andrea Skelly: Yeah.

Chris Standaert: Yeah. OK.

Andrea Skelly: Yeah.

Chris Standaert: I'm just saying, yeah. Yeah. It doesn't make you too excited about it, but yeah.

Andrea Skelly: This is not a very good quality study. Yeah. And this is not a very good quality study. So, when you've got that large and differential rate of loss to followup, you know, the percentages, you know, how meaningful are they, at least from an evidence standpoint. If we look then at that same trial, they said, basically 100% of the botox patients had some sort of adverse event, again not well defined, and about 96% of the patients had some sort of adverse event. Again, these may not be serious adverse events, and you see that, of those adverse events, there were 93 in the botox group, 133 in the topiramate group, and then this is the breakdown in terms of the percentage

of events for each of those outcomes. So, total events... oh, events over total... total events, outcomes.

Gregory Brown: Just so I am clear. So, if you inject botox into your forehead and your eyebrows and they're weak, that's an adverse event?

Natalia Murinova: Yes. That's considered, you know, even though it's expected, that's.

Chris Standaert: [crosstalk] pick up their eyebrows.

Natalia Murinova: [crosstalk] So, I think it really depends on the injection technique. So, I mean, in our clinical practice, we don't see these kind of numbers.

Seth Schwartz: I'm still not understanding those percentages, because if you look at the botox group, it says only 26 patients had an adverse event.

Andrea Skelly: But patients could have more than one adverse event. So, they took the total number of events.

Seth Schwartz: But if then you look under the individual events, their denominator is 93.

Andrea Skelly: Mm-hmm.

Seth Schwartz: So, they had 26 out of 93 actually had an adverse event.

Chris Standaert: I think those numbers are the percent of adverse events attributed to the medication.

Andrea Skelly: Yes.

Chris Standaert: Not the percent of people in the study who had an adverse event.

Andrea Skelly: Exactly.

Chris Standaert: Right. They're saying it's the drug. It's not just sticking a needle in somebody. It's a drug.

Andrea Skelly: OK. So, looking at botox versus amitriptyline, one poor quality trial gave us some information, but again, it's kind of hard to know because amitriptyline is an oral medication and botox is an injected medication, but here are the adverse events. Again, we didn't feel that there was a lot of confidence in the information to draw strong conclusions. If we take a look then at the other interventions, acupuncture and spinal manipulation, there's very limited data on the adverse events that were reported. When we look at acupuncture, no serious adverse events were reported either versus usual care or versus topiramate, but these are very poorly defined. We considered these findings to be insufficient. When you look at spinal manipulation versus amitriptyline, discontinuation due to adverse events was less common with the spinal manipulation versus the amitriptyline, and they report that 58% of the patients

in the amitriptyline group did experience side effects up to four weeks. That was the length of the followup was the four weeks.

If we take a look at TMS versus sham, basically everybody reported some level of discomfort from the procedure. It's interesting that 15% of the patients who got the sham also reported some level of discomfort. Discontinuation due to adverse events, neither of the trials that were available really described why people discontinued, what kind of adverse event led to that discontinuation, and it was a fairly poor quality set of studies. So, we felt that the evidence was insufficient for safety here, as well.

Going on to chronic daily headache, we have a little bit more information from two trials, Mathew and Silverstone. Significantly more patients receiving botox than placebo had treatment-related adverse events, same as we saw with the chronic migraine. These data do break it out into other specific outcomes. So, dysphagia was more common and pooled across studies was statistically significant, but I would put forth for your consideration that it may not be as stable estimate, because of the width of the confidence intervals, and there was no difference in injection site pain. When we look at headache, there were no differences between groups, but there was a statistically significant difference between botox and placebo, favoring placebo. When we looked at shoulder pain, neck pain, neck rigidity, again, we don't feel that the quality of evidence is very high. It's low. There is a lot of imprecision, and the confidence intervals are very wide. Botox was associated with more muscle weakness and more hyperesthesia, but no difference in hypertonia when pooled across the two studies. Again, very imprecise measurements, very imprecise effect sizes, and the quality of evidence was low across all.

Looking now then at topiramate and adverse events over the longer term up through 24 weeks, nausea and mild fatigue. Nausea was more common with botox versus topiramate, and there was no difference with regard to fatigue. Quality of evidence for both was low.

Massage versus sham, again, there was no statistical difference between groups in terms of adverse events reported, which included mild fever, soreness, and other discomforts.

If we look at botox versus placebo now going to chronic tension headache, we've moved on from migraine, there were no statistically significant differences between groups related to treatment-related or severe adverse events. Again, moderately high risk of bias trial and low quality of evidence.

Again, versus placebo, pain at injection site and vertigo were reported across the smattering of small trials that we had. Vertigo was uncommon. It may be a rare event. We really didn't feel that there was sufficient evidence to draw a conclusion.

Similarly, with acupuncture and manual therapy, it's really unclear what... we cannot draw any conclusions about adverse events and safety for vasovagal reaction or 'any adverse event.'

If we take a look at trigger point injections, the only one we have for trigger point injections, again, a very poor quality study. You can see that those with trigger point injections were lidocaine versus saline as a sham. There were some that were more common with the sham than there were for the trigger point injection with lidocaine. I'm not sure what to make of that, but we did feel that the evidence was low for those.

Transcranial magnetic stimulation versus sham, again, all of them were considered minor adverse events. It was short-term, again, because of the quality of this study, which only had 28 patients, we felt the evidence was insufficient.

Moving to question three, we have a new key question. So, we're looking at differential efficacy or safety. There was one trial that looked at acupuncture versus usual care, and in the longer term, it appeared that patients who had more severe baseline symptoms may have had greater improvement with acupuncture versus usual care. They don't really provide much data. All they provide us with is a P-value for interaction and say that these other factors did not... there was no evidence of interaction for them.

Looking, again, at acupuncture versus topiramate, these authors concluded that patients with more headache days and more moderate to severe headache days may show more improvement following acupuncture. Again, it's very difficult, because the data really does not allow us to explore this, and the sample size is so small that the finding of effect modification is questionable. No interaction was observed for any of the other characteristics.

For manual therapy, they did look at patients who had comorbid migraine and those that didn't have comorbid migraine. Again, there was no differential effect based on that factor for treatment, but again, the data were insufficient to draw any conclusions.

Moving on to economic studies, there was one moderate to poor quality economic study looking at botox versus placebo and one very poor quality study looking at botox versus placebo, both included that botox may be cost-effective at a willingness to pay threshold of 20,000 pounds to 30,000 pounds, and in their modeling, there was uncertainty related to whether or not you could really extrapolate data beyond the 24-week randomized control trial time period. There were a lot of issues with these studies, particularly related to the fact that it's versus placebo, and it is unclear whether placebo and usual care are considered to be reasonable options to compare it to. It is unclear how long the time horizon should be. Again, there are only 24 weeks' worth of data from the randomized control trials, and it is unclear whether or not this is a therapy that would be continued over several years, and what are the ramifications of that. Adverse events and discontinuation in this particular economic study were not well defined.

There was also an economic study looking at acupuncture versus usual care, which, again, concluded that the incremental cost-effectiveness was favorable towards acupuncture at a reasonable willingness to pay threshold. The problem is that, again, usual care was couched as avoid acupuncture. There is no detail about what included

usual care. It was very interesting. Again, it is not compared to a more active treatment. This study... the other study was in Italy. This study is in the U.K. So, generalizability across the pond is unclear. Again, they had a limited time horizon and the need for continued periodic treatment is unclear, and they really did not provide high quality sensitivity analyses for their models. Then, lack of longterm followup data, again, was a limitation.

So, moving, finally, on to the summary. Here we have your Readers Digest condensed version. So, with regard to chronic migraine and looking at botox versus placebo for the primary outcomes, we have the responders looking at greater than 50% decrease in migraine episodes. Again, there was no statistically significant difference, and the strength of evidence was considered to be moderate with regard to that outcome. When we look at the 50% or greater reduction in migraine or headache days, the two RCTs, the two primary RCTs, did indicate that there was a small effect that favored the intervention, in this case botox. Looking at the mean episodes per month, again, no difference, moderate evidence. Looking again at days, it goes the other way where there is maybe a small effect, but it is unclear if it's clinically significant across three RCTs, and that's up to 24 weeks. So, that's longer term. If we look at functional measures, two RCTs suggest that there may be a small benefit to botox versus placebo, but again, it is unclear whether some of this may be clinically significant. One RCT looking at the MIDAS score found no difference between the treatments.

Looking then at more active controls, the trials topiramate and amitriptyline, one randomized control trial for each. There were no statistical differences in either responders or functional scores across either of those trials, up to twelve weeks, again, noting that across all outcomes, data are insufficient for 24 and 36 weeks due to extensive loss to followup.

Acupuncture versus active controls, it appears, again, as we saw in the detailed results, that single RCTs may suggest that acupuncture is better than usual care or topiramate. Again, this is low quality evidence, even though there were statistically significant findings. The evidence quality was considered low.

If we look at manual therapy or manipulation versus amitriptyline, again, one RCT indicates that responders may favor manual therapy over amitriptyline. The other outcome in terms of headache days per month was not different between the treatment groups, and that's only at four weeks, again. So, this is just short-term.

Also, short term, the transcranial magnetic stimulation versus sham. Again, it appears that for the primary outcomes, there was a statistically significant effect. Again, the quality of evidence is low. The quality of the studies is poor, and even though they did show small to moderate effect sizes, the quality of the evidence should be considered.

Looking now at chronic daily headache, we have the one trial looking at responders of botox versus placebo. One indicates that botox would be favored in this case for chronic daily headache versus topiramate. There were no statistical differences between treatment groups across one trial, and that included headache free days, headache days, and functional scores.

Massage versus sham, no difference between treatments. The quality of evidence is low. Looking at manual therapy versus usual care, again, statistically significant. It favors the intervention. Effect size is small, but the quality of evidence is low.

For all of the other comparisons and outcomes that you see listed here, we considered there was insufficient evidence to draw any conclusions. This is summary across the other chronic tension headaches comparators and outcomes.

Looking at safety, botox was associated with more treatment related adverse events and serious adverse events for both chronic migraine and chronic daily headache. There were no statistical differences for chronic tension headache, but again, for chronic tension headache, the trials were small and not well reported. Most of the botox information for chronic migraine comes from Preempt. Then, for chronic daily headache across Silverstein and Mathew trials. We don't really know much about treatment-related severe adverse events across two trials. There was more discontinuation following botox across two trials, again versus placebo. Strength of evidence was considered low when you look at chronic migraine and Botox versus topiramate. Drug-related and possibly drug-related adverse events were lower with botox, but it was not statistically significant. There was less discontinuation due to adverse events with the botox versus topiramate, again very limited information versus amitriptyline, just in terms of injection site pain and edema. Chronic daily headache, more nausea with botox, no difference in fatigue, but the quality of evidence was considered low.

Acupuncture, we had two in chronic migraine, one in chronic tension headache. Again, adverse events, safety information was very poorly reported. There is a low confidence in the estimate of any side effect being less common with acupuncture versus topiramate. No differences in other outcomes, and there was insufficient evidence when we looked at serious adverse events, differences in continuation, or again vasovagal reaction was reported but they said there were a few, and there really isn't much information to go on. So, insufficient evidence for that.

Manipulation versus amitriptyline, discontinuation due to adverse events was lower in the spinal manipulation group. Again, low evidence versus usual care. We really didn't have any information to draw from conclusions.

Transcranial magnetic stimulation versus sham, again, discomfort was common. It was virtually in all the patients who had transcranial magnetic stimulation. There was insufficient evidence, really, for any of the other outcomes.

Gregory Brown: I have a question.

Andrea Skelly: Yeah.

Gregory Brown: How can you have a sham if patients know that they're getting a treatment, 100% of them had discomfort?

Andrea Skelly: Well, it was blinded. So, the way they did the sham was, they had the same equipment hookup. They had the same little skull cap thing, but they...

Gregory Brown: No. I understand.

Andrea Skelly: ...didn't turn the, but they did not turn the juice on.

Gregory Brown: I understand. So, clearly, when you turn the juice on, you hear something, whatever, you know you're being treated.

Andrea Skelly: That I don't know. I don't know that that is the case. It may or may not be, whether there's a sound or not.

Natalia Murinova: I can tell you about, you know, like I don't know what transcranial magnetic stimulation they were doing, because, I mean, the only transcranial magnetic stimulation currently that we're using is the ST, you know, like, the one transcranial magnetic stimulation, and I've tried it and you don't feel anything at all. So, I think you couldn't tell the active from, you know, sham. So, I mean, there is noise, but if you can have the noise in sham, it would be identical. I've tried the transcranial magnetic stimulation. You don't feel there's... there is nothing. So, I was really, really surprised when they have discomfort. I don't know what is causing the discomfort. It doesn't make sense to me.

Andrea Skelly: And it may be the type of device that you're using versus the type of device that they are using, so. Moving on, then, to massage and trigger point injection, again, very limited information on adverse events related to these particular interventions.

Natalia Murinova: And sham acupuncture, you basically break the skin. That's what they're claiming. So, you will feel that someone is poking you, but you're not going in I show they...

Gregory Brown: This one is massage versus sham.

Natalia Murinova: ...oh, massage versus sham, sham massage, you know?

Andrea Skelly: Yeah, the sham here was ultrasound that wasn't turned on if I remember correctly. So, the question is, is that a real active... is that a real sham, you know? What, what do, yeah. Anyway, the quality of evidence was low for any adverse events for both of these treatments and their respective comparators for chronic daily headache and chronic tension headache.

Differential efficacy or harm, again, insufficient evidence, maybe patients who present with more symptoms and more severe headache days may do better with some of these interventions, but again, the evidence was considered insufficient.

Cost-effectiveness for chronic migraine versus placebo and botox, one poor quality study, one really poor quality study. It may be cost-effective, again, but there are a number of limitations to the studies. Same with the acupuncture. There is a suggestion that it may be cost-effective. The quality of the study was moderate to poor, but again, a number of limitations need to be considered.

In putting the summary together for the executive summary, there is some thoughts that I would leave you with that medication overuse at baseline and prior prophylactic medication use really was not well reported in some of the trials, and if so, it's a little unclear what impact they may have had on the outcomes. Data beyond 24 weeks is sparse and limited. The implications and needs for continued treatment for chronic migraine, in particular, and the benefits and harms in the longer term were not clear from the studies that met the inclusion criteria. We have limited data on interventions versus active comparators that you would see in a clinical situation, and the impact of coexistent headache types on the outcomes is not clear. So, if you had chronic migraine and chronic tension headache, both in the same population and in the same patient. It's kind of unclear, at least from the literature, what the impact would be. The Preempt trials did indicate that there may be a large opportunity for place effect in patients with both chronic pain and headache. There is also the possibility for some of these things, regression to the mean. That can always happen for some of the outcomes. Again, the general quality of the studies really is low across the interventions. The botox studies, the Preempt studies, were the best studies that we had. Again, a reminder that the nomenclature related to chronic daily headache and chronic migraine have changed over the last several decades. So, I will leave you with that.

Chris Standaert: So, questions for Dr. Skelly? She will be here as we discuss this afternoon a little further, but if there are questions immediately about her presentation.

Gregory Brown: Yes, more of a clarification of an observation. So, some of the research I've done around hyaluronic acid, using outcomes of responders seems to favor the treatment more than if you do a validated patient reported outcome or some more objective measure. Does that apply in here? Is that real? Is that just?

Andrea Skelly: Can you clarify?

Gregory Brown: Well, what... you know, when they say, so, sorry. So, a responder is, you know, someone that had more than 50% reduction, and looking at the percentage of responders. So, that's... so they, you know, but you define what a responder is. So, it's an artificial construct. There's no MCID. There's nothing there. So, where we could find no effect of hyaluronic acid in objective measures or could find... you know, had a responder technique that seemed to show that HA is effective. So, that's why I'm asking, is that... I don't have enough breadth of area. Is this something that's common where responder measures seem to always do better than some other more objective measures?

Andrea Skelly: I think it may depend on the area and...

Gregory Brown: OK.

Andrea Skelly: ...I'm talking off the top of my head, but I think in some respects, people put more emphasis on being able to define a clinical threshold. Now, granted, you know, for some of the responder categories, it is unclear how did they choose 50% or 25% or 30%, and I think that's something that certainly would be worth looking into, and it

may depend a little bit on the measures that you're using, as well. And MCID for validated measures, like I said, can vary across patient populations, and they can vary across even several studies in the same type of patient population, but I don't know that it's universal. I think that it's a higher bar to say somebody, I mean, from a statistical standpoint, if you're dealing with mean measures, means, continuous data, you have more statistical power to find a difference, but that may or may not be clinically significant, and if you're using a valid measure, then maybe you then have that MCID that you can hang your hat on. So, from a statistical point, you may be right that for some of these things you've got to reach a higher bar, because you're dealing with a dichotomous variable, and you just don't have as much oomph to find a difference between treatment groups.

Gregory Brown: Well, I think it's actually the opposite. That's what I've observed is that it seems to me where... when you, like I say, pick your own criteria for a responder...

Andrea Skelly: Mm-hmm.

Gregory Brown: ...you somehow seem to be able to meet that criteria easier than in a continuous variable of a validated measure.

Andrea Skelly: Yeah, it may be. I, you know, I would have to look into that. I don't have a good answer off the top of my head.

Chris Standaert: Question for you about the Preempt studies. The whole two study thing was really curious to me and switching primary outcomes was really curious to me. There also, I mean, they are funded by Allergan. Three of the authors of all the studies are employed by Allergan. Every single author is wildly conflicted by relationships to... not everyone, but lots of them are. Their conflicts of interest paragraph is fairly lengthy for their whole author pool.

Andrea Skelly: Mm-hmm.

Chris Standaert: You know? And that's what we have, and it's, we got 24 weeks and botox is... every other condition I've ever used botox for, be it dystonia, spasticity, it's... they're ongoing, right? They're...

Andrea Skelly: Mm-hmm.

Chris Standaert: ...the drug doesn't last forever, and your body tends to rebuild your neuromuscular junction connections and tends to sort of evolve around the drug, and there are, there are longterm consequences to the drug. When you give botox to people over years, they atrophy. They do. They... you know, these patients with dystonia, you don't really have a choice, because they've got to find another way to move their head, and they vary, but they atrophy. There is a longterm consequence there. So, it's... but, I don't know. I don't know what your thoughts on that are.

Natalia Murinova: So, my thoughts on it, you know, as a clinician actually using, you know, botox is that, you know, some of the comments that you say, you know, are very valid. The question

is, we don't really have currently any other way to... this is the only data that we're going to use is the problem.

Chris Standaert: Mm-hmm.

Natalia Murinova: You know, for evaluation, but, you know, as a clinician, so these guys were laughing and saying, OK, two-point, three-point is significant, you know, not laughing but, you know, commenting like what is significant, and if you have someone who has chronic migraine who 'tried everything'...

Chris Standaert: Mm-hmm.

Natalia Murinova: And they're disabled, you know, they're someone who is very highly educated, you know, and they have been, let's say three months and, I see them nonstop, but we have here a very educated group in Seattle. Like, the patients that we see at the University of Washington are much more educated than other clinics throughout states, and often that's the only option that you have is botox to give them out of chronic migraine. The comment, and it's a really comment is, what if then no one has established that and we need to kind of move, you know, do you need to continue botox for more than a year to... what, what is the cutoff, and I would tell you clinically, you know, I could tell you all of this, but it has not been studied. So, you need to sustain normal neuronal function for at least two years. If you can do that, then most people, you know, do really well and you don't need it ongoing chronically, but no one has established at the... looked at... and that's what we need to look at is, what is reasonable recommendation. The other, you know, option is, you know, for me it's not difficult to diagnose someone with medication overuse, but often you don't have any other choices to get them out of medication. So, let's say, I would tell you, Chris, you know, you're rational and I would tell you, OK. You know, you absolutely cannot take daily triptans.

Chris Standaert: Right.

Natalia Murinova: You know, and then you would tell me no, but I'm a physician. I absolutely can't do anything else. I have to take them, and that's what I'm dealing with day in and day out. You have to have options. So, that's where you have to be very, very careful is not taking away options, but, you know, being very savvy and kind of redefining and saying let's go to where it's, you know, saying OK, let's approve it for a year and then reevaluate. That's what a lot of... that's what most insurances do. They do not allow you to use botox unlimited. You have to show that you had, you know, significant improvement, you know, and it's currently defined as reduction of migraines more than 50% to continue using botox, and I think that's much more rational as saying... not completely taking it off but going, OK. What is realistic? I mean, how long, you know, is a realistic trial? Is it a year trial? Is it, you know, how long should you, and why should we continue it for years? I mean, if the person is better, shouldn't he then have the interval of taking them off and retrying and doing other things, and if you can address medication... the biggest problem in the state that no one is addressing is the medication overuse and that's what we're dealing with.

Chris Standaert: Right. I mean...

Natalia Murinova: So, currently, we have data on 2400 patients I can show you, because we're collecting it at the University of Washington. No one is paying me to do that. I am doing it kind of on my own, and I can tell you, 80% of patients that we're seeing are newly-diagnosed chronic migraine with medication overuse, but no one has prior to me or our staff diagnosed. That's the epidemic of the state.

Chris Standaert: No. I appreciate that. That's why we're in...

Natalia Murinova: So, we need options to get... so, it's not enough to diagnose people with medication overuse. You need to figure out what are then the options that we can offer to people to get them off medications and turns out botox is a very, very good option...

Chris Standaert: So, I mean, again our...

Natalia Murinova: ...yeah.

Chris Standaert: ...our charge isn't necessarily to deal with the entire spectrum of things. We have the data that we have on one thing. So...

Natalia Murinova: I agree.

Chris Standaert: ...you know, it's not a... there's no active decision to take away options, because that's why you look at things in context.

Natalia Murinova: Agree.

Chris Standaert: No. My question was from a methodologic standpoint how that... for Dr. Skelly from the evidence side how that impacts her view of the data.

Natalia Murinova: I think it's very good. You have an excellent point that the data that we have are very biased data. We need some kind of independent data from researchers that are not being paid by Allergan.

Chris Standaert: No. I was just curious about Dr. Skelly's thoughts on that.

Natalia Murinova: Yeah. So, that's all the drug studies that...

Chris Standaert: So...

Natalia Murinova: ...you see, all of the...

Chris Standaert: ...no, wait. Wait. Can you...

Natalia Murinova: Oh, oh.

Chris Standaert: ...I just want to hear... I'm sorry. I just want to hear what she has to...

Natalia Murinova: I apologize.

Chris Standaert: ...say to answer my question.

Natalia Murinova: Mm-hmm.

Andrea Skelly: So, Chris, your question relates to the impact of funding on study findings or?

Chris Standaert: Well, that seems to be the large population of our data, right, is from, you know, purely industry funded studies with industry funded people largely with industry paid employee authors.

Andrea Skelly: Exactly.

Chris Standaert: Right? Which is problematic.

Andrea Skelly: Mm-hmm. It is.

Chris Standaert: You know? And, and it's not... it doesn't necessarily invalidate data by itself, but I always find it problematic. I was just curious...

Andrea Skelly: Yeah.

Chris Standaert: ...about your perspective on that and how you view it when you look at data and quality of data.

Andrea Skelly: Well, you know, we do try to follow a systematic approach looking at the traditional risks of bias and grade even suggests that you don't knock down for the funding source. With that said, there are plenty of opportunities to also look at what else is wrong with the data without dinging them, if you will, for that potential bias from industry, and sometimes it's hard. You know, there's... this is maybe off topic, but there is a bunch of ... there is a guy named Ben Goldager, find him on YouTube. He's got some great information on how industry... and he looked at, I think, SSRIs and different antidepressants, and what was published data and what was the unpublished data and how the effects were different between the two. So, I think that certainly there is a possibility that the data could be biased, but putting our finger on...

Chris Standaert: Sure. [crosstalk]

Andrea Skelly: ...how that impacted it is a little bit more of a challenge.

Chris Standaert: Dr. Elmore?

Joann Elmore: I have three questions for our evidence vendor. Do we take a break now or should we do them? What would you like, boss?

Chris Standaert: If you have direct questions for her now that she might have to go look up, ask her now.

- Joann Elmore: OK. I think the first two are kind of easy. Question number one, your slide 14 says that there are four RCTs on chronic migraine botox versus placebo.
- Andrea Skelly: But you only see three.
- Joann Elmore: That is correct. Are you counting as the fourth the pooled?
- Andrea Skelly: No. There were four studies. There is another small study by Vo.
- Joann Elmore: OK.
- Andrea Skelly: And it did not... we did not report on the primary outcomes of interest.
- Joann Elmore: Got it. OK.
- Andrea Skelly: But the data are represented in the full report under other outcomes.
- Joann Elmore: Yeah. I had a hard time following that. Sometimes, in the text it would help me if you added the actual references, because I had to keep looking and looking to figure out which is the primary references. So, that would help us in the future.
- Andrea Skelly: Primary references in the slide or in the...
- Joann Elmore: Both.
- Andrea Skelly: OK. So, you want the name of the author?
- Joann Elmore: And in the text, I mean, yeah. Use a referenced bibliography so that as I'm reading your text, there is the... you know, this is reference number 32. Then, I know what article to look up.
- Andrea Skelly: OK.
- Joann Elmore: So, question number two, the clinically significant migraine day change, I want to try and get a grasp on this. I understand how severe migraines can be, and you referenced sort of Mathews 2005 defined an MCID, you know, a clinically significant reduction in three days per, I think this is per month, a 28-day period.
- Andrea Skelly: Correct.
- Joann Elmore: So, if a treatment can cut down by three days, that's clinically significant. Have there been any national groups or anybody else that has defined this? This is real important for us.
- Andrea Skelly: I understand that it's important for you, and we did look, and we did not find anything.
- Joann Elmore: OK.

- Andrea Skelly: All we have is that statement from Mathew that says we considered a three-day change to be clinically significant.
- Joann Elmore: Got it. OK. And then my third and final question is more to see whether I have this correct, my summary, because the most data that I see from your very well put together, you know, your detailed review, has to do with botox and chronic migraine, and there are three RCTs that constitute this evidence for the one clinical area where we have the most data. Of those three RCTs, one is Freitag 2008, total of 41 patients.
- Andrea Skelly: Yep.
- Joann Elmore: 20 got injected, and this was good because they at least excluded patients with medication overuse, but, you know, this very, very small study a lot of people that somehow they just sort of lost them, and it was industry sponsored. So, that's one of the three. The other two are the Preempt1 and Preempt2. They were both industry funded. A lot of patients were not eligible, more than half that they started with. They excluded patients above the age of 65.
- Andrea Skelly: Mm-hmm.
- Joann Elmore: You know, understandable, but 17% of our PEBB patients in our state are above that age; 66% of the patients, or so, in these two trials were overusing medications, which is really problematic and messy, as our expert has explained. Then, I think I read somewhere that there may have been a potential for unblinding, because 70% of them were aware of what arm, they correctly guessed what arm they were in. You know, who knows whether they... 50% by chance would guess it, but, you know, there was a small amount of unblinding. Then, for one of these two studies, the Preempt studies, one of the two, their primary outcome was not statistically significant.
- Andrea Skelly: Correct.
- Joann Elmore: In the Preempt2, they reached statistical significance. A lot of their secondary things reached statistical significance. Then, in the pooled study, I want to make certain I have this big picture. In the pooled when they lump the two studies together...
- Chris Standaert: Mm-hmm.
- Joann Elmore: ...the absolute difference was between the many, many hundreds of patients that got botox versus the sham placebo, the absolute difference was 1.8 days improvement over a 28-day period, and that is not supposedly clinically significant, according to this one 2005 Mathews. Who knows, I mean, if you're that patient it might be. Then, the final piece of evidence that I'm hearing from you is that there are a high percentage, not just 5 to 10%, but is it 30%? Is it 50%? A lot of adverse events are reported. Some of them are expected.
- Andrea Skelly: Mm-hmm.
- Joann Elmore: Do I have the big picture from that?

Andrea Skelly: I would say you've done a very good job, yes.

Joann Elmore: OK.

Chris Standaert: So, let's take a break until 3:00, and then we will talk. Ten minutes.

Alright. We need to get going. So, we have some things to think about here, some data to work through. So, this is now where you have to do what we did this morning. We have to go through our evidence and data and our perspectives and get to some way of deciding what to do. Again, we can be lumpers or splitters. We can... we'll certainly talk more general, I suspect, for impressions at first, but we have, you know, five different technologies up there and have to decide what to do with that. I mean, do we take them all individually? Do we draw a line somewhere? Do we lump them all together? What do we do with that? We have to take them. We have to think about that as we go through this, as well, because we have to address all five, and we have to address all five from these perspectives of efficacy, safety, and cost wherever that data happens to take us. It could be a long conversation or a short conversation depending on what we think about it for each one, but that's where we have to get to eventually. So, we have to comment on it all at the end.

Kevin Walsh: So, could I make... I would like to make a suggestion.

Chris Standaert: OK.

Kevin Walsh: I don't think there's a significant difference between migraine tension and daily in terms of these outcomes. So, I would propose that we just talk about the modalities and not further parse them out into the different headache groups. Part of that is based on the fact that several places in the study they talked about chronic daily headaches, which is a combination of both is the predominance in the population. At least that's what they said.

Chris Standaert: It seemed a bit different to me when they got to chronic tension history, as opposed to migraine and chronic daily headache and calling that out as a specific thing.

Kevin Walsh: Well, there are specific things, but well...

Chris Standaert: I guess it's how you split them all clinically, like, how do you, how do you parse out which one exactly you have?

Kevin Walsh: There is?

Chris Standaert: Yeah. And so if that is really difficult and that becomes then, and people just call it all migraine, then you call it chronic daily headache. They don't even use the term chronic tension headache, even if it's different if you have what you can clearly say is chronic tension, maybe that's a different category of headache, yeah or no?

Natalia Murinova: Yes.

Gary Franklin: Chris, can I ask a question? This is Gary?

Chris Standaert: Yeah.

Gary Franklin: So, the definition of chronic migraine is at least 15 days a month, only eight of which have to be migrainous.

Natalia Murinova: Can I clarify that actually?

Gary Franklin: Well, wait a second. Let me finish my question, OK?

Natalia Murinova: Sure.

Gary Franklin: So, if about half the days aren't migrainous and about half the days are muscle contraction headaches...

Chris Standaert: Mm-hmm.

Gary Franklin: ...then you, then it's even more complicated to me.

Chris Standaert: Right.

Gary Franklin: In terms of this nosology of what it is you're treating.

Kevin Walsh: It makes it almost less relevant what you call it.

Chris Standaert: It makes it almost less relevant what you call it, except that our inclusion criteria for various things count those things. Count migraine days.

Carson Odegard: It's how you measure it, too.

Chris Standaert: Yeah.

Carson Odegard: That's a big.

Chris Standaert: So, we can think about that. Let's think about it, as we go through the data and see what people find when they look at it. Yeah. Clinically, do you find that distinction easy to make, migraine versus tension headache versus daily headache, or are they all kind of very [crosstalk].

Natalia Murinova: So, I was just clarifying that, you know, exactly, you know, as Gary said in chronic migraine current definition is that you have to have preexisting history of migraine and then currently how people think about it is that these people then transformed into chronic migraine. So, they are very different, actually, from the people who have just tension type, but if you said would it be difficult or not, you know, for someone who is not, you know, a headache specialist to know. So, current definition is that you have 15 headache days, but it's an arbitrary decision why it's 15 not 14 or whatever, but half of those then have to have... be defined as migraine, but the migraine definition could

be by the patient using migraine medications or be migraine. So, that makes it a little bit, maybe more, you know, complicated. So, but there were differences in, as you said, let's say botox for tension versus botox for migraines. So, botox clearly I wouldn't use for tension type. I would use it only for chronic migraine.

Chris Standaert: Gotcha. OK.

Female: [inaudible]

Natalia Murinova: No. So, only in 60% of people, migraine is one-sided and 40% it's bilateral. So, location doesn't matter. It's the severity. So, by definition, tension type headaches are not supposed to be debilitating, severe. So, by World Health Organization, basically puts only migraine into the ten most disabling conditions, not tension headaches. So, tension headaches, by definition, are not debilitating. I don't know if that answers your question.

Joann Elmore: Chris, you suggested that we discuss whether we want to split in any way, and I would...

Chris Standaert: At some level, we have to be.

Joann Elmore: ...propose that we do the split and have a discussion of botox and then a discussion of all the other modalities. This is based upon kind of what I've heard of the evidence and also the draft agency recommendations.

Chris Standaert: Mm-hmm. I think that's fair.

Joann Elmore: Which one do you want to do first?

Chris Standaert: Botox. So, we might as well go for it here. That gives us a comparative bar, I think. So, what do we think of the botox data? We have a... these reviews have a lot of patients for some of the things we look at. They were conflicted a bit.

Carson Odegard: Are you saying on botox?

Chris Standaert: No. No. No. What do you think of botox? Just start talking. What do you think? You hit your mic. You hit your mic, Carson. What do you think?

Carson Odegard: Well, just like what was stated, obviously there is some data that shows that botox is effective in chronic migraine, but obviously it doesn't appear to be so in the tension headache. So, I wouldn't even think about talking about the tension headache, maybe just talk about the chronic headache and then we'll sit that out.

Chris Standaert: Chronic migraine.

Carson Odegard: Correct.

Chris Standaert: Or migraine or chronic daily headache, whatever that blurry zone is. OK. And you said you think there's evidence that it's helpful? Effective is what you used.

Joann Elmore: That worries me when you use that word.

Chris Standaert: Sorry. You said effective. Do other people see the same thing? Are they convinced by the data that it seems to work to a degree that's clinically relevant?

Joann Elmore: Plus a few words maybe [crosstalk].

Chris Standaert: Mm, yeah. I thought I'd add them in there, yeah. That's the question though, isn't it?

Joann Elmore: Mm-hmm.

Chris Standaert: Do you see that in there? Is it sort of fuzzy for you?

Laurie Mischley: It's fuzzy. I know that we ask these questions separately, but in the context off the cost and the side effects when you then take the weight of the clinical relevant improvement into consideration, it becomes even fuzzier for me.

Chris Standaert: Right.

Laurie Mischley: If it were side effect free and very inexpensive, I might be more enthusiastic about the tiny improvement...

Chris Standaert: We wouldn't be talking about it.

Laurie Mischley: ...that we see, but I'm not sure that this tiny improvement that we see is justified given some of these other considerations. So, that's where my sticky place comes in. I'm certainly... I have a hard time... I'm all too aware of the industry's role in these research studies, too. I mean, just being a part of that world in my other life as a researcher, I hear how industry's shape the questions that are asked to get the answers that they want, and that doesn't necessarily translate into the data that we are presented.

Chris Standaert: Right.

Laurie Mischley: It's not across the board. I'm not saying all industries who do research is bad either.

Chris Standaert: No.

Laurie Mischley: But, I think that from what we get handed, it's hard to tell where the pollution may have taken place, if there was pollution.

Chris Standaert: That's a great statement. Yeah. I like that. Right.

Chris Hearne: I would almost take the opposite. For people who have really severe migraines, presumably most of these people have gone through several trials of different medications and failed them, and if you have really severe migraines, and if you can

get one to two days of your per month back, that seems like a reasonable benefit to me. I realize that's not based on anything but my own personal judgment, but I think that the thing that we really should talk about is the Preempt1 and Preempt2 trials and this sort of moving of the goalposts that we've already discussed. That is a little bit troubling to me, and I was wondering if Dr. Murinova, if you could speak to... it seems like there has been a shift in how... the outcome that's sort of used across studies and do you feel like... I guess, does that make you feel uncomfortable when you look at that shift in those two studies and do you think that was done for ethical reasons or was that done so that they could make their study look better essentially?

Natalia Murinova: So, I think the... most of the initial outcomes that were developed... I'll answer it kind of circumspectly, and I apologize. I'm not going to go directly, but most of HIT-6, MIDAS were developed for episodic migraine, not for chronic migraine. So, most of the studies in the past were done for, and people didn't even used to differentiate episodic from chronic. So, this is kind of a newer search. We're currently using International Headache Society criteria just to update you. We're currently using 2Beta version. So, it hasn't been existence as long, let's say, as DSM, you know, or any other criteria. So, that attempt to try to put everybody on the same page of, you know, let's call an egg an egg, you know? Let's call a chicken a chicken, you know? We didn't used to have that. So, it's more novel within the last, let's say, ten years.

Chris Hearne: OK.

Natalia Murinova: So, that's where even the decision, even for me, like, what is the best outcome to look at? It's really complicated. So, we currently... most of the headache community feel that there are really not excellent measures in chronic migraine versus episodic. The headache days and headache severity are probably ... or the headache hours some people would push, are probably the easiest things to start looking at, and that's where the move is towards in all the current studies is the headache days, because it's the chronic migraine. It's not the episodic migraine.

Chris Hearne: OK. So, that's sort of what's being used now.

Natalia Murinova: That's a valid, yeah. That is what is being used now in all the studies. We don't know if it's the best measure, but it's trying to... you pointed out having some at least objective way to compare study to study is the headache days or the headache hours. That's where a lot of the newer studies are moving, because they would say well, you know, I have patients who have gone, let's say from everyday headaches that were 24/7 nonstop to one hour per day that went from 10 out of 10 to 3 out of 10. So, it's still the same headache days, but, you know, it's a very dramatic decrease, you know, in the quality of life. I don't think that doesn't reflect, and that's where the studies are very difficult to compare. So, moving forward, it's going to be easier with the newer studies, because it's going to be headache days, headache hours, intensity, uniform, but currently the old studies you don't have it uniform, and it's really difficult to compare the trials. I don't know if I'm answering your question.

Chris Hearne: No. No. That answers. It seems to me that if that's now the sort of becoming the standard for how we measure outcomes in chronic headache studies, then even if the

authors of this Preempt1 and Preempt2 were, perhaps, doing something unethical or fishy with their study that it led some credibility to the Preempt2 if they're using headache days and headache days is now what is accepted in headache research, then it makes me feel a little bit better about accepting those results at face value.

Chris Standaert: You know, it's curious from a methods standpoint, but yeah. I see where you're going. They also did...

Joann Elmore: The enrollment in Preempt1 and Preempt2 time period were the exact same times. Preempt1 was in the U.S. They looked at the data and they could have easily made the change for their analysis of Preempt2 based upon the finding that in all these U.S. folks, Preempt1 what they had hoped would be statistically significant wasn't. So, they changed it.

Chris Standaert: So, they were [crosstalk].

Joann Elmore: I'm suspicious of it. And I'm also hearing that number of days doesn't have the quality of characterizing this sort of terrible pain these patients have as number of hours, and they do not provide that.

Natalia Murinova: No one has that. I think that is what is probably going to... you know, that's the feeling that it should move towards.

Gregory Brown: It sounds to me like you'll move towards a quality adjusted life years, and you'll talk about headache hours, which is severity times the number of hours, because if you have a 24-hour headache of a two, is that the same as a five-hour headache of a ten, but just saying you had a headache for four hours, minimum of a day, is...

Chris Standaert: But it isn't... I mean, that's what they're seeing here isn't, like, night and day. In fact, the placebo response is pretty profound, right? So, that drop was pretty huge, and then the incrementally drop you get for using botox wasn't huge, and then there are people who really didn't... they didn't have any other sort of prophylactic medication. They didn't have prophylactic medications for four weeks before the study. So, yeah, they took them off of that and kept them on all the Tylenol or whatever, or they never... that's where I'm curious. They were never on that. It's, like, that's the setting up of the rules to influence the outcome of it is a bit curious, but anyway, it was a profound placebo response.

Natalia Murinova: Can I...

Chris Standaert: A little more for botox.

Natalia Murinova: ...mm-hmm. Can I comment on the placebo. So, there is only one study, and it's actually from Harvard. It's vitamin D but simvastatin where they were savvy enough to start the trial after three months, because after three months, the placebo rate of the Hawthorn being observed and so on decreases.

Chris Standaert: Mm-hmm.

Natalia Murinova: So, what you see in headaches if you really, really want to look at it, you need to really look at six months or twelve months outcome data, because that's when the placebo rate dramatically drops after three months, and it starts dropping after six weeks. So, whatever you induce the placebo, it's not sustainable, unfortunately. It would be greater if we could sustain placebo...

Kevin Walsh: Well, that may or may not be true, but we don't have that data to evaluate it. So, we really can't take that into account.

Chris Standaert: We only have 24 weeks. Right.

Natalia Murinova: Mm-hmm.

Kevin Walsh: I'm not very impressed by the botox results compared to placebo, but when I put this in the context of being a primary care physician who is caring for patients with these headaches that are debilitating, I don't see a reason in terms of safety or cost not to include this in the toolbox, because if you've gone through all the available therapies, and you've still not helped that person decrease their headache frequency, it would be nice to have another tool to use that may or may not help. I am impressed by the criteria that NICE uses for both recommending the use of it and also recommending when it be stopped. So, I could imagine a condition of kind of defining the parameters within which you would use it and when you would stop it that I would find acceptable.

Chris Standaert: Yeah, because it gets to...

Sheila Rege: From what I'm reading on the Preempt, that it was designed to be identical in design, and the only exception was the primary and secondary endpoint. So, the Preempt...

Chris Standaert: So, they switched them.

Sheila Rege: ...what?

Chris Standaert: They switched them. Is that what you mean?

Sheila Rege: No. No. They designed it to start exactly the same and the primary endpoint being headache episodes in the one and the second one was the change of baseline headache. So, maybe they did that on purpose and then decided to pull it. Maybe there was no funny business.

Chris Standaert: Well, if you pick two studies with two primary outcomes, you get two primary outcomes. Anyway, we're not trying to elude to the fact that there was some deliberate shenanigans here, but we're talking about how the data sort of... how actually the data that is there effects your interpretation of it, or how they set it up, yeah.

Gregory Brown: But the point of requiring organizations to pick a primary outcome is to avoid this.

Chris Standaert: Mm-hmm.

Gregory Brown: The fact that they had to switch says they saw the data. They didn't... they knew they weren't going to get their outcome or their approval, and they found a new primary outcome that they could meet.

Chris Standaert: Right.

Gregory Brown: I mean, that's...

Chris Standaert: That optic is certainly there, yes.

Gregory Brown: ...that's why, you know, if you go back before this concept, they picked as many outcome measures as they could. They analyzed the data, and then they said oh, this is a success, and they picked whatever measure they were successful. Well, if you pick enough measures, at least one of them is going to be statistically successful.

Joann Elmore: Yeah, and they were very clear in their methods that they changed it after they started. They said subsequent to study initiation, this is Preempt2, but prior to study completion in treatment unmasking, the protocol and statistical analysis plan for Preempt2 was amended to change the primary and secondary endpoints. They had already gathered all the data in the U.S. They just don't mention that.

Chris Standaert: And they were, even within that, again, back to Kevin's point, they were relatively exclusive in who they put in there. They excluded fibromyalgia. They excluded a few other things. They had the... they did a Beck of 24 as their exclusion. That's moderately depressed, not severely depressed. So, they excluded people who had moderate depression. They excluded however they defined fibromyalgia, whatever you might want to make of that diagnosis, but they kept other sort of syndromes out to keep it as a clean group, which also gives you... [inaudible] conditions gives you options there, too, because that's the people they use it in, but something there... there are some questions as to the statistical nature of how their data was derived or directed and the magnitude of benefit or question. Safety... so Laurie brought up safety. So, safety? Are there safety concerns for botox? I mean, it definitely makes you weak. I mean, that's what it does, you know? When you're getting in your forehead and the sides of your head and your neck basically, and in your traps.

Kevin Walsh: Yeah, but the side effect profile of topiramate is ugly. I... compared to that, this is small. I don't have a problem with it.

Chris Standaert: Yeah. I guess does it displace [crosstalk].

Gregory Brown: I'm seeing a side of you I've never seen in a discussion before.

Kevin Walsh: I know. I had this revelation where I kind of put on my clinical hat and said yeah, but you're up against, kind of you're up... I mean, I often feel up against the wall with these patients.

Chris Standaert: Mm-hmm. Yeah. It doesn't displace Topamax. Data... was the data on drug utilization... did it, did botox result in less utilization of other medications? You said that was in there somewhere but you didn't present it?

Andrea Skelly: Yeah. I'll have to look it up. [inaudible]

Chris Standaert: It's not a benign thing to do to somebody necessarily, but...

Gregory Brown: So, how...

Chris Standaert: ...using it short-term.

Gregory Brown: ...so if someone comes to you for treatment, how often do you do these injections?

Natalia Murinova: To me, actually, surprisingly I don't use a lot of botox in my practice, but it is exactly, you know, as Kevin said, in the toolbox of... it is available. It's not firstline therapy. In the past, actually currently I'm not using it for that, but I used to use that to get people off medication and I would use it only once or twice, you know, and that was it. Making it really, really clear to patients it's not an ongoing longterm therapy. Most people do not want botox as a longterm therapy. For people... what no one mentioned here, most people with migraine have central sensitization. So, if you do botox for them, it's very, very painful compared to cosmetic botox in people who don't have migraines. So, if someone doesn't have migraine, we're talking it's not very painful. If someone has migraine, it's extremely debilitating to have botox done. It's not something...

Chris Standaert: 30-something injections you're getting.

Natalia Murinova: ...right, it's 31 injections. So...

Gregory Brown: How often do you do... I guess...

Natalia Murinova: ...so, then you would do it for periodical every three months for a period of a year, right, you know? Most people currently though would say that even after doing two trials, you know, that's how most practitioners would try it. If it's not doing anything, they would not continue doing that. The biggest dilemma is more when do you discontinue treatment that is 'considered effective,' and this is really not well-defined currently in American Health Literature.

Gregory Brown: [crosstalk] literature?

Natalia Murinova: Or any, you know, health literature. So, they've tried to do, let's say, Topamax discontinuation in Germany to try to place. So, they didn't look at botox but they said, OK, after we, let's say, use it for three months if effective and we stop it, will that benefit sustain, and I can tell you right away that all botox does is decrease the [inaudible] production of chemicals. So, CGRP substance B. It does not do anything to increase the anti-pain production of chemicals. It does not increase serotonin, dopamine, norepinephrine, and so on. So, these kinds of treatments are super effective only if you can motivate the people to change their lifestyle and start

exercising, you know, normalize their weight. So, the modifiable risk factors for migraine are currently well defined, and it is BMI over 30, not addressing sleep, not addressing exercising, not eating vegetables and so on. So, if you're not addressing those things while you use the botox as your agent to allow people to have less headaches, because most people will come to you with debilitating headaches and will tell you that they cannot exercise or do anything. So, if you are clever enough and can use the botox and say, OK. This is not a longterm solution. This is a short term, and that's why no one has studied it for that, but that's... I would use it in clinical practice and have used it in clinical practice as saying, OK. You know, Kevin came to me with daily migraines, you know? This is an option to get you to make sure that you can do all the other things you need to do in order to get out of headaches. So, that's what is currently missing is the multimodal approach that most savvy physicians, like Chris would tell you in back pain, that you have to use multimodal approach to get people out of back pain. So, to me, you need to use multimodal approach to get these people out of chronic migraines. So, there is a study from Scandinavia that compares using topiramate versus exercise versus biofeedback, and I'm going to shorten this and it shows that within three months, it takes a minimum three months, you will improve with all three, but only about 30%. So, what we then sell is that we want to improve 90-100%, you need to use multimodal therapy, and that's what we see very effective in clinical practice. So, botox on its own, not enough.

Sheila Rege: So, the maximum botox dose of 360 whatever the units are...

Natalia Murinova: 155 units.

Sheila Rege: I think on the FDA then they say 360 units as a maximum, no?

Natalia Murinova: Currently, for migraine, chronic migraine is 155 units. That's the...

Chris Standaert: For the drug, in general, it's used for a lot more than migraines. For the drug, in general, you don't go over 360.

Natalia Murinova: But is that over some period, you know, 90 days?

Chris Standaert: Within three months.

Natalia Murinova: 90 days.

Chris Standaert: It's an antibody issue. That if you get too high too frequently, you induce antibody formation, and then it doesn't work.

Seth Schwartz: I think we're wandering.

Andrea Skelly: So, if you want information on the medication use [inaudible]. On page 156 of the report, there is a forest plot, figure 13, that describes the pooled analysis across the two Preempt trials and then some limited information from the Freitag trial regarding medication use, and you can see that there is a discrepancy between the Preempt1 and Preempt2. Preempt1 might find a statistically significant difference between the

two treatments with regards to medication use. The Preempt2 [inaudible] because the heterogeneity was not statistically significant. Freitag, we really can't draw a lot of inference from that because the confidence interval is so wide and it's such a small study. So, that's for chronic migraine on page 136. Now, for chronic tension type headache botox versus placebo on page 194, it [inaudible] but on the fourth page, it says medication use, and again, there were no statistical differences between the botox and the placebo group with regard to reduction in the percentage of days, analgesic use over a 12-week period. [inaudible] for eight weeks, and another trial not statistically significant. So, that's page 194 for chronic tension headache. Then, on page 221 for chronic daily headache, again, there wasn't a statistically significant difference. This particular study looked at patients who were placebo responders during a run-in period versus placebo nonresponders during a run-in period, but in either group there were no differences between botox and placebo with regard to a certain medication intake days up to 26 weeks.

Chris Standaert: And so since these studies excluded people on chronic prophylactic medications, it looks like they don't show any evidence of reduction in medication or medication related events by using botox.

Andrea Skelly: I would have to...

Chris Standaert: That's how I would take that.

Andrea Skelly: ...yeah. I don't know...

Chris Standaert: That's how I would take that, yeah?

Joann Elmore: Which studies are you talking about?

Chris Standaert: The one... everything.

Joann Elmore: Preempt1 and Preempt2.

Chris Standaert: No. They don't show... they don't show a significant drop in medication use.

Joann Elmore: That is correct, and many, many of them, like, over 60% were using multiple...

Chris Standaert: Yeah. Yeah. And they excluded people on prophylactic medications the month before the study started. So, therefore they didn't change. These are about acute medications they're referring to.

Andrea Skelly: Correct.

Chris Standaert: The Tylenol and stuff. So, anyway...

Andrea Skelly: Correct.

- Chris Standaert: ...using botox to decrease medication side effects, I'm not sure we have data to say that.
- Andrea Skelly: Correct.
- Chris Standaert: So, Seth, I was going to our tool and get us back going.
- Seth Schwartz: I was trying to do that preemptively.
- Chris Standaert: I'm with you. We'll go to our tool. Let's talk about botox. So, page five of the last section of your book. So, what we're gonna do. So, again, we have to go through this issue of safety, efficacy, and cost and where the data takes us. Since we're... we're going to do this twice. So, there's one for botox. One is for the other things, I suspect, and I'll just flip them a little bit as we do it. So, adverse events in terms of safety, what kind of adverse events are we thinking about. There clearly is weakness, neck pain, swallowing difficulties, all directly related to botox. So, are there important safety outcomes? So, like, again, death, not an issue here. We didn't see infections. So, real critical health outcomes. They mentioned severe adverse effects, but they didn't tell us what they were, yeah? That's a bit bothersome.
- Andrea Skelly: I made the assumption when I was preparing that the assays were standardized, like in drug trials. They were using the same criteria and assay for technology trial would be the same as a significant adverse event for a drug trial. Is that not true or?
- Gregory Brown: I don't think so.
- Andrea Skelly: OK.
- Gregory Brown: I mean, the FDA may have standards, but that doesn't mean that the clinical trials have any standards.
- Chris Standaert: Yeah. They can decide what they think is significant, I think, and then not tell you what that is. Yeah. So, it's a double secret significant effect. Single, yeah, we're really blinded. We're blinded from the serious outcomes. So, that's a concern there. So, anyway. So, there are important outcomes in terms of safety, some of which are relatively more minor but might be persisting for awhile and they might certainly inform patient choices on repeating the procedure. Major... we don't have a lot of data... I didn't see data on major medical concerns, again death, MI, that sort of thing.
- Carson Odegard: Wasn't there something on having allergic reactions.
- Natalia Murinova: Yeah, allergic reaction to botox.
- Carson Odegard: Is that considered under just a minor adverse effect or is that something that's serious?
- Chris Standaert: I've never seen an allergic... I assume you could have it, I just personally have never seen or heard... I assume that would be, like, a... I assume it could be anything from a rash, a local reaction, to anaphylaxis, I would guess.

Carson Odegard: Yeah, right.

Natalia Murinova: There is report that you could potentially have reaction, but yeah, I've never seen one in my lifetime.

Chris Standaert: I didn't see them in the studies.

Natalia Murinova: The studies didn't have any significant and all of the side effects are reversible.

Chris Standaert: We have a lot of adverse effects here, but I don't have a lot of patients. Yeah, so various weakness. So, we have things like weakness, paresthesias, all that sort of thing, but they're unusual effects, like an allergy you might not see it in the study of 1000 patients. It might take 10,000 patients to see one, and we don't have that.

Sheila Rege: It says 5% neck pain and muscular weakness. [inaudible]

Natalia Murinova: But that's because of that... the protocol [inaudible] changed how botox is being injected for chronic migraine, you know, so currently no one would inject into the neck for chronic migraine.

Sheila Rege: That's changed now?

Natalia Murinova: Yeah.

Chris Standaert: So, in the data we have, we have more weakness of various sorts. There'd still probably be ptosis and you can't pick up your eyebrows and all that sort of stuff.

Natalia Murinova: They also avoid ptosis by different injection technique for the most part now, so, it's not a big deal.

Chris Standaert: Other safety outcomes people saw? No. So, efficacy, this gets tricky, right? We have responders. We have episodes. We have days. We have severity of headache. We have functional measures, and these are different, you know? We had one study with days that showed statistical significance, but clinical we don't know. That's more the standard of what people are using, apparently, but not a huge effect size. Episodes and intensity. Not so different? No?

Gregory Brown: Well, if your responders were a 50% reduction in...

Sheila Rege: Yeah, they said it was a 50% reduction.

Gregory Brown: ...that's...

Chris Standaert: That's a responder rate. So, the mean...

Gregory Brown: ...but the definition of responder that they use was a 50% reduction in...

Chris Standaert: ...right, that was the mean intensity or mean...

- Gregory Brown: Yeah.
- Chris Standaert: ...frequency, right. Right. So, when they went to the responder level, they had a difference. Yes.
- Gregory Brown: Well, actually...
- Chris Standaert: Well, that's a response. Which way did they do? Which way did they go?
- Gregory Brown: Both.
- Andrea Skelly: The issue is days versus episodes.
- Chris Standaert: Right. Days...
- Gregory Brown: So, responders...
- Chris Standaert: ...versus episodes.
- Gregory Brown: ...50%... greater than 50% reduction in migraine headache days and then they also had decrease in mean migraine headache days per month. So, they had two RCTs for the responders and three RCTs for the decrease in mean migraine.
- Chris Standaert: Right, but the responders for days were better, but the responders for episodes were not, and the decrease in mean days was better, but decrease in mean episodes was not, right? So, it seems like the days are better, but the episodes, whatever measure responders are mean there are not. Which of those is more important? So, you get to what we always talk about, that, like, you'd like quality of life, right? So, it's yeah. You can measure days or hours or minutes or whatever and nobody thinks their life is any better, I don't know how much that helped you. We don't have... we have the HIT-6, but we don't have a tool that was really designed for chronic migraine. So, how do you measure... I don't know if we have a great measure of quality of life.
- Natalia Murinova: That's what the MIDAS and HIT-6 are supposed to [inaudible] the disability.
- Chris Standaert: Yeah, but you said they weren't really designed for...
- Natalia Murinova: They were not designed for...
- Chris Standaert: ...for chronic...
- Natalia Murinova: ...chronic, but they are still...
- Chris Standaert: ...for chronic migraine.
- Natalia Murinova: ...the only measures that are currently used in studies to try to address the quality of life. They don't have really a standardized quality of life measure.

Chris Standaert: And we seem to have data on the HIT-6 and data saying it doesn't make much difference on the MIDAS, and that's all... that's with placebo side [crosstalk].

Natalia Murinova: That's the problem with MIDAS is that I try not to use it in chronic migraine is because even if you have significant improvement as you go from daily headaches into just one bad headache or three bad headache days for a month, it's enough to still have really, really high scores. So, you might not improve dramatically on those, and so people then get very discouraged, because they look at it and they say, wow. My... I felt so much better, but my score doesn't seem to be getting better. So, I feel very clinically conflicted doing the Midas and HIT-6 in chronic because, you know, most people want to feel that they're putting a lot of work into getting better they actually have something that is improving. So, I think the headache days, you know, it's easier headache hours, severity off headaches and we require most of the people are supposed to have headache diaries that they fill out, and I think that's what most of the studies are moving towards, not just recall but actually record what you have.

Chris Standaert: And we've been talking about botox versus placebo, but when you throw it against the controls, it doesn't stand up as well against the pyramid.

Gregory Brown: Correct. I think the other thing I heard is that it's a multimodal approach. So...

Chris Standaert: Yes.

Gregory Brown: It's not like you're doing it in comparison to the control. You're doing it with the controls.

Natalia Murinova: And in real life, I would Topamax and botox. I wouldn't do Topamax versus botox.

Chris Standaert: Right, and they deliberately did not do that in the study, right? They said you can't do that. They took out the prophylactic medications.

Natalia Murinova: Yeah, but it would be much better comparison than Topamax alone versus botox with Topamax, like additional.

Chris Standaert: Or botox with Topamax and placebo with Topamax.

Natalia Murinova: Right. Exactly.

Chris Standaert: But they excluded that so they... I assume so they could, again, find the benefit, anyway. The study design. Cost? People find the cost data convincing? We were given cost data. It had some assumptions given the trials. Did you find it... was the cost data striking, meaningful? Either way? It costs more. Didn't the cost-effectiveness data we got sort of lean the other way, that it was cost-effective? Yeah. They made some assumptions, though. They made assumptions of continued benefit and other things that we didn't... and this is the... every... all these costs analyses, when they start doing that and saying... and we just assumed that this kept going, and we assumed that that didn't work. It's, like... I mean, immediately you spin your data.

- Sheila Rege: But that was not U.S. costs.
- Chris Standaert: No.
- Sheila Rege: I think those... so.
- Chris Standaert: No. So, our cost data is... we have some. The procedure, itself, is relatively spendy for the State as a whole. They're spending a couple million dollars a year on this. So, there are certainly cost concerns and our cost data on cost-effectiveness is fuzzy at best. So, in botox, any special populations that jumped out?
- Gregory Brown: We're focusing on chronic migraines right now, right?
- Chris Standaert: Age 18 to 65. So, they did not look in the older population, in terms of age. I don't know if they tried to break it down. I didn't see data on gender, on other factors.
- Natalia Murinova: 65, so it's not indicated for pediatrics over 18 and under 65.
- Chris Standaert: Alright. So, let's go to our nonbinding vote here and see what people think. So, we're talking about botox, onabotulinumtoxinA is what we're talking about. These are nonbinding votes. You have five choices in your yellow cards. Safety: Is there sufficient evidence that it is safe for the indications considered; unproven, less, equivalent, more in some, more in all.
- Laurie Mischley: Less safe?
- Chris Standaert: Less safe. So, is it less safe in some... compared to placebo or compared to its comparators?
- Josh Morse: Eight less, one unproven.
- Chris Standaert: So, efficacy: Is there sufficient evidence it has a meaningful impact on patients and patient care, again compared to our comparators?
- Josh Morse: One, two, three, four, five, six, seven some, one equivalent, and one unproven.
- Chris Standaert: And cost: Is there evidence that it is cost-effective?
- Josh Morse: One less and eight unproven.
- Chris Standaert: I don't know if we've ever had a yes. It'd be nice, but [inaudible] had lesses, so I guess we can use more than one card there. Alright. So, now we're down to the nuts and bolts of this one. So, is it going to be covered in some way or not? That wasn't a glowing vote compared to, say, some of the other things we've decided to cover. It seems unlikely people will go with cover unconditionally I have a feeling. Yeah. A lot of heads shaking. Do we want to talk about conditions, or are people leaning towards this being a noncovered thing? Would someone suggest it be not covered?

- Kevin Walsh: No. I like the NICE conditions... the conditions that NICE uses.
- Chris Standaert: Do we have access to the NICE conditions?
- Joann Elmore: It's about 103 or so if I remember correctly.
- Chris Standaert: Page 10 of this, if you just keep flipping past there on page 10. NICE does two things. They sort of define the conditions as roughly the conditions of the Preempt studies with chronic migraine. They specify sort of three pharmacologic prophylactic agents. They try to get at the medication overuse issue. They don't talk about depression or other pain syndromes, but then they also say... they define responsiveness as greater than 30% reduction in headache days per month, and if you're not really doing well with the drug, it should be stopped after two cycles, which is roughly you're at six months out by the time you're done with two cycles. So, if you...
- Sheila Rege: I like the less than 30% reduction.
- Chris Standaert: It seems... it's hard to say evidence wise, because we don't have the data there, but boy, it certainly seems like you'd like to... I mean, the worry here... the worry we often have is the genie in the bottle issue, right? If you start saying do this, and not everybody is thoughtful and has a multimodal approach in mind and has... goes through everything and they just... and if you do that and you're not tracking... if you say somebody has to respond, then you have to start measuring whether or not they're responding. If you're measuring without them responding, you'll figure out if you're actually helping them, and then maybe you'll do the right thing, you know? There's that component.
- Natalia Murinova: I think it's pretty much standard by now that most people know that botox, most insurances require that you have headache diaries. So, people are used to that.
- Chris Standaert: Yeah. That seems to be what... well, I don't know. Where are our insurance policies? Do they say that? We don't have those in here.
- Sheila Rege: I pulled AETNA, and it's about the same.
- Chris Standaert: About the same? So, it's looking for responders in a way, too, to keep it going.
- Natalia Murinova: It is, like, a standard currently, Chris, what NICE has.
- Chris Standaert: Did you find them, Chris? It's coming right up. So, was there someone who wanted to advocate for not covering who thinks our data... I'm not in love with the data.
- Joann Elmore: I'm not in love with the data, but I also take care of patients, and I see how terrible they suffer. I am worried... I keep going back to our evidence people saying, are we sure that they followed intention to treat analysis. How could they have done that when you had a higher loss to followup in the botox than in the control? So, I keep going back trying to sort of, like, understand there's 1.8 days difference, but we think there was unblinding of the placebo and I'm suspicious of their analysis, and I'm

suspicious that they changed their outcome, but yet, I want to help these patients. So, please tell me your guys' thoughts.

Chris Standaert: Wait. Dr. Skelly wants to talk.

Andrea Skelly: With regard to intention to treat, there are a number of ways that people conceive of it, and there are people who will follow a very strict set of guidelines. If you look at the Cochran handbook, which is what we tried to follow to the extent that we can, they suggest that if you've got missing data, you can impute and that's what this study did. They said they did intention to treat, and then they did impute data using last observation carried forward in order to make up for that data. Now, one can criticize last observation carried forward is a statistical option, but in terms of giving them credit or not credit, I think that based on the guidelines that we used, you know, that's what we came up with that recommendation. Some pay [inaudible] will not if you have loss to followup. [inaudible] for lack of intention to treat. So, there is some homogeneity in the guidance on what constitutes intention to treat.

Chris Standaert: So, you found it again?

Andrea Skelly: Oh, and they did prespecify that they did loss to observation carried forward.

Chris Standaert: Are they similar?

Sheila Rege: They go to hours and days of migraines reduced [inaudible] days from baseline or duration reduced by 100 total hours per month. So, I don't know if...

Chris Standaert: Yeah, but...

Natalia Murinova: ...the expert [crosstalk].

Chris Standaert: ...we have nothing on hours, right? We have no data on hours. I don't want to go there. We got nothing. Yeah, I agree with Joann that the data is suspicious, the structure of it is suspicious, and you know if you cover it, you're not incentivizing somebody to actually do the right study is a little bit of a problem, but...

Sheila Rege: [crosstalk] bring it back?

Chris Standaert: ...no. We, I mean, we have the ability to say no. We are not convinced by the data. We don't think this supports the use of this given what we view as cost and safety factors. That is within our prevue. If more data becomes available, it gets... it can be reconsidered, yeah, but we don't have the ability to say, like, somebody, like, you know, Medicare and say cover with evidence development, right? We don't... we can't do that. So, that's not in our scope, but at the same time I agree, you see patients with this, and it's debilitating and, you know? I suspect if you had somebody who had side effects who got weak and had one less headache day a month, they're not going to do it again.

Natalia Murinova: What many states have moved towards, and I'm not saying that's the correct or not, is having only experts use the treatment. So, that's where California moved to where you take it, and that's why you have to be careful, too, you know, where they say, OK. You have to be a neurologist certified in headaches, you know, to be able to use, you know, the treatment. So, that's how they have limited it, but I think most of it...

Kevin Walsh: That just limits access.

Natalia Murinova: ...exactly.

Chris Standaert: Yeah. So, then you have to make sure you have headache neurological specialists around the state, which I'm not sure we do.

Natalia Murinova: Exactly. So, I don't think that that's the option.

Chris Standaert: Yeah.

Natalia Murinova: So, I think that most people... that would be just me, then.

Chris Standaert: Yeah, I mean, I think by requiring headache diaries is essentially what you're doing, at least requiring people to start tracking what they're doing, and the people who are cavalier will not be able to be cavalier, because they'll have to have the data to support what they're doing. They'll have to document all this. That means, they have to be trying and as soon as you start trying to do that, you learn stuff. I mean, do we go to the Preempt things and say depression? Do we put those in there so people have to at least start looking at that?

Natalia Murinova: Actually, botox is now being approved by the FDA for depression treatment. I don't know if you've heard that.

Chris Standaert: I haven't heard that, but that's not really, yeah. So, my issue is the Preempt people said, you know, if you have a Beck of 24, we're not going to do this.

Gregory Brown: Well, I think there's one thing to do it for a clinical design to try and get clean enough data to find a result.

Chris Standaert: Mm-hmm.

Gregory Brown: Then, there's the real world of saying, you know, if you've got depression and a headache, we can't treat you is being a clinician in the...

Natalia Murinova: OK, but the...

Chris Standaert: No, but that's why things don't work in the real world when they work in studies, because people violate the inclusion criteria the studies were designed to stratify people in a way that would allow people to benefit. If you ask them to look, at least, then... it's not that... you would hope people wouldn't say, oh you have depression,

I'm not going to treat you. Say, wow, you're pretty depressed. Maybe, we should treat that, too, right? That's what you would hope.

Natalia Murinova: So, currently, from the data with chronic migraines, and we have done that data is more than 70% of people have significant anxiety and depression. So, pretty much...

Chris Standaert: I'm sure they do.

Sheila Rege: So, that'll cost \$525.

Natalia Murinova: ...if you have chronic migraine, it's more than likely than not that you have comorbid depression and anxiety. So, to exclude those patients, you would be excluding treatment.

Chris Standaert: No. I wouldn't be excluding. So, I don't think that's correct. So, I'm saying in the studies where they showed there is benefit, they only did it in people who had mild to moderate depression only. They didn't do it in people who were severely depressed. They didn't demonstrate benefit in those patients. So, I don't know if...

Gregory Brown: They weren't enrolled in the study.

Chris Standaert: They weren't enrolled in the study, right.

Gregory Brown: Right.

Chris Standaert: So, is that... that's... again, we can follow that if we want and say, you know, it's, again, it might be one of two things. It might restrict who gets it, but it also might expand mental health care for those people who have advanced severe depression, if you look at it that way, but you don't know that that would happen.

Joann Elmore: Some of us are a little confused about the total cost of this in that some of the paperwork we have lists a couple hundred dollars per treatment. There's websites that say it could be \$8000 to \$20,000 per year. How much...

Natalia Murinova: I don't know how much the current Medicare or Medicaid rates are, but I can tell you the commercial insurances. Commercial insurance is about \$2400 per treatment, so it's times every three months times four.

Chris Standaert: That includes the drug?

Natalia Murinova: Yes. That includes the drug.

Joann Elmore: And the doctor's visit, everything, and yeah.

Chris Standaert: So, it's \$5000 for three... you know, two injections over six months [crosstalk].

Joann Elmore: For an extra day a month of hopeful improvement.

Chris Standaert: Mm-hmm.

Joann Elmore: A day and a half.

Chris Standaert: Mm-hmm.

Joann Elmore: A month.

Natalia Murinova: And in clinical... that's the good news in that clinical real-world, you see much significant, you know, much more significant improvement if it works. So, I think that that's either it works or it doesn't work, and as Chris mentioned, you know, the people where it usually doesn't respond, it's very severely unaddressed depression and anxiety, but botox does help the depression, as well.

Chris Standaert: So, what do people think? We have inclusion criteria up here from NICE. What did Dr. Johnson say, exactly? See, they threw in the psychiatric conditions, comorbid treatment of psychiatric conditions. Oh, that's hers. OK. Sorry. Thank you. So, what do people think? I think NICE is... I think NICE had defined chronic migraine better, and I think it... I think it... I think the cutoff criteria of if this isn't working after two treatments, and you don't really have somebody who is clearly responding in a fairly meaningful way, you need to stop this.

Kevin Walsh: Well, I think that in the face of there being kind of equivocal benefit. This is the only way I would support it, because at least you're saying, we're going to hold you to some kind of outcome measure, and if you don't meet that outcome measure, you stop the therapy.

Chris Standaert: We're going to scrap this and go to NICE. OK. So, go back to NICE for us.

Gregory Brown: I think one exclusion I would have included is fibromyalgia.

Chris Standaert: I mean, the idea is getting rid of other nonspecific pain syndromes that may have associated headache pain. I would say severe depression. I think they should be treating depression, but either way. So, it first changes to botox. So, this is first changes to botox... so, this is... get rid of that, because it can be a covered condition, right, not an option for the prophylaxis of headaches. So, it's in adults with chronic migraine, we're going to start. So, go down to... get rid of botox is recommended all the way down to... go to in adults. There you go. Nope. Leave the in adults. Then, after the word overuse, you're going to, yeah, break those down. Yeah. I don't know what the [inaudible] are. Oh, gotcha. Yeah. Take out the NR. Anybody else up for putting in fibromyalgia and/or depression? I'm seeing heads shake. Joann, do you think add? Do you think follow NICE? Do you think...?

Joann Elmore: Oh, I'm going to be quiet, because I'm actually thinking that I want to make a point. We keep approving, as a committee, things on miniscule data, and I am actually probably going to vote against, just because I want to finally let the drug makers know, we need better quality. So, I'm going to be quiet and maybe, as I listen to the conversation, I might change my mind.

Chris Standaert: That's the perspective of sort of not covering because the data is so...

Joann Elmore: Well, we, we keep ...

Chris Standaert: ...yeah.

Joann Elmore: ...yeah. I mean, I'm really conflicted, because I really...

Chris Standaert: I'm really conflicted.

Joann Elmore: ...really want to help patients, and I... I mean, my son suffered for a year and a half with terrible migraines, but this... you know, you were very articulate when you described there are side effects, you know? What is one day, one and a half day, you know? It's... there's problems with the studies. So, I'm conflicted. That's why I'm quiet and sitting back.

Chris Standaert: Seth, tell me what you're thinking.

Seth Schwartz: I mean, so, I think somewhat to most of the things that we see, I think there is... we have seen data from a reasonable quality trial that shows there is probably some benefit, albeit not significant... not dramatically clinically significant. There are side effects, but they're nothing that would really, in the scheme of things, be longterm detrimental to any patient in a condition where the effect of the condition is horrible for patients' quality of life, and already has limited treatment options. So, I would feel wrong, as a clinician, denying this treatment option, even though I'm not impressed by it at all, and I think it's reasonable to impose some relatively strict conditions on it, and I don't know what they should look like anything better than that. So, I'm comfortable with this. The 30% reduction I kind of think we pulled that out of thin air, but NICE probably pulled that out of thin air, but I think it's reasonable to say that there needs to be some measure of response. So, if that's what it should be, then that's what it should be.

Natalia Murinova: Most insurances, the commercial, they use 50% of migraine days. That's the...

Seth Schwartz: That would make a little bit more sense, since that's what the outcomes were that we looked at was, you know, 50% migraine days or something, you know, but we didn't look at anything that said 30%. So, that strikes me as a little odd, but I don't feel strongly one way or the other.

Gregory Brown: I also think it's self-limited if what our expert said is true that if they become sensitive to the injection, they're only going to come back for another injection if it really really helped them, you know?

Chris Standaert: People do stuff. I mean, people come back and make...

Natalia Murinova: Not for migraine.

Chris Standaert: ...healthcare choices that are not in their best interest out of encouragement of whatever system is encouraging them to do that. I don't know that, unfortunately, I don't think our system works that everybody is in a space where they feel free to say or communicate or otherwise decide that what is happening to them isn't the best thing for them, and it happens to them. I think that does happen, so I don't... I wouldn't, yeah. I don't know.

Seth Schwartz: I tend to agree with you on this one, Chris, but what I struggle with a little bit here is that, the placebo effect is a real thing, right? So, we have patients who are miserable. We're comparing this to the placebo effect, which we can demonstrate is real. We're seeing a little bit of benefit of both the placebo effect and the alternative realistically is nothing. So, the benefit...

Joann Elmore: That's a good point, because...

Seth Schwartz: ...for these patients is...

Joann Elmore: ...yeah.

Seth Schwartz: ...actually not the 10% better than placebo, it's the 70% better than nothing. So, I know that's not really the way that we think about it, but.

Chris Standaert: Laurie, what do you think?

Laurie Mischley: I think that this might not be an inappropriate time to introduce the acupuncture conversation, because I don't know that we have nothing. I mean, I think that we are making the assumption that we're going to dismiss most of the other ones, and I do think that the acupuncture conversation is worth having. I don't think it's all, you know, there's a little bit of data that says that there might be something that we are underutilizing, and it has been not as researched as we would like, but I think it's not correct to say that there is nothing.

Natalia Murinova: You go to botox, it's once, you know, every three months. How many acupuncture treatments, you know, because no one talked about that, do you need to get to the same, you know, reduction. Like...

Chris Standaert: Yeah. We don't know that.

Natalia Murinova: ...do you have to go three times a week, four times a week, you know, uh, once a week, you know? So, that's the, you know, how many times do you have to go. I'm not... I'm...

Chris Standaert: \$5000 is a lot of...

Natalia Murinova: ...I like acupuncture.

Chris Standaert: ...acupuncture.

Natalia Murinova: Yeah. Yeah.

Chris Standaert: You know? And I agree... I hear that a lot in the back pain world that, oh, if we don't do this, there's nothing else to do. Well, one, that doesn't mean you do a procedure you don't think works, and two, it's a multimodal problem, right? So, if the procedure you have isn't really as effective as you keep thinking or hoping it would be, you have to talk people into changing their lives in ways that help them, and in this case, these people take significant medication overuse, right, and BMIs are too high, and all... in fact, this is... the other, as you find some way to convince people to be healthy, and sometimes when a patient like this works, you can use it as a way to give them a window where maybe they can start to become healthy, which is what Dr. Murinova is saying in a multimodal world, that's what you would really try to do. Then, the question is, is this really useful in that setting, or is this a placebo, and that's the only thing people were getting.

Natalia Murinova: So, that's how you know exactly, as you pointed out, because within placebo, we would know within three months with placebo effect, it's gone. It's usually gone within six weeks. So, that's why, if you limit it to the six months, I mean, you're addressing both of those, you know, to make sure that it is not just, you know, placebo.

Chris Standaert: So, what do you think? Do you like this? Do you think, yeah? That works for you? Chris? Carson?

Carson Odegard: I like it. I think it could be shortened a little bit. I think that we could take out a couple phrases, I think. We know that it's 15 days per month. We know... I don't know where we got 30% reduction, but maybe that can be defined as something a little more broad. We don't have any data on 30% reductions.

Gregory Brown: 50% was one of the outcomes.

Carson Odegard: 50% as an outcome. You could put 50%, but...

Chris Standaert: Put 50% as a responder, if you can claim that it's headache days or you're claiming responders are 50%.

Gregory Brown: Well, the definition of a responder was that they had a 50% reduction.

Chris Standaert: I'm agreeing with you, yeah.

Gregory Brown: Never mind.

Natalia Murinova: The use of 15 days, because many people don't know what chronic means. So, some people will think if you have something once a month, you know, that it's chronic.

Gregory Brown: Oh, yeah. I understand that. I was just thinking that, you know for policymakers or whatever, they should know that.

Chris Standaert: I'm close to where Joann is. The higher the bar the better. I'd go with 50.

Laurie Mischley: Yeah. I like 50.

Gregory Brown: Yeah, 50'd be...

Chris Standaert: And if that's the responder in the study, then we have some real grounds for using that.

Joann Elmore: What about maximum number? The studies only went up to five total treatments. Are you guys going to just let them go on indefinitely year after year after year?

Laurie Mischley: You're already distancing yourself.

Natalia Murinova: Again, from a clinician point of view, I wouldn't be using it indefinitely. I mean, to me, you need to stabilize someone for, you know, one to two years.

Chris Standaert: That should be greater than 50% reduction by the way, I think. No? It must not.

Gregory Brown: Greater than.

Seth Schwartz: Finding lack of response is not adequate response.

Joann Elmore: If it says less than 30% [inaudible].

Chris Standaert: You can only do it if you have less than a 30% response.

Joann Elmore: No, but are you going to let them do more than five treatments in a patient? Lifetime? The study is only...

Kevin Walsh: We don't...

Joann Elmore: ...we don't know beyond five. So, are you just going to let them do more?

Gregory Brown: Well, no. So, the definition is not responding. So, the less than is correct. So, not responding is less than 50% reduction.

Chris Standaert: Oh, not responding. Yeah.

Seth Schwartz: So, essentially, why can't you just say just inadequate response to treatment and then defined as less than 50%?

Carson Odegard: Yes. Right.

Seth Schwartz: Yeah, but you...

Joann Elmore: But he's shortening it.

Seth Schwartz: ...is not adequate, or you could say is an inadequate response to treatment. I think it just...

- Chris Standaert: Was there anything about this being indicated for longterm use? Right? Does... you know, for headaches? I mean, for dystonia, that's a lifelong condition, and you sort of just keep going.
- Chris Hearne: You get five treatments and it's one treatment every three months. So, that's, you know, in a year and a half range, which is kind of the range of what you're saying, one to two years of therapy. I think it's very reasonable to put some verbiage in there limiting it to that sort of ballpark.
- Joann Elmore: And when they have new data, we can reevaluate it.
- Chris Standaert: But what they said, you know, they said we don't do more than... we stopped at five cycles, right?
- Joann Elmore: And you guys are OK with other kind of opening it up for any kind of patient? They excluded those that are depressed. They excluded those that are above 65.
- Sheila Rege: What does the expert?
- Natalia Murinova: As I mentioned, you know, the majority of the people with chronic migraine will have depression. So, I would not exclude realistically the depression and, you know, it's going to be the chicken and egg. Most people would argue that they are depressed because they have chronic pain, and once you get them... and I can tell you that currently, the studies indicate that the genetic expression for pain is the same as depression and anxiety. So, once you activate genes of pain, you're inducing depression and anxiety. So, they go together. So, it's not chicken and egg, and the majority of these people, once they improve, their depression and anxiety improve as well.
- Chris Standaert: It's not depression on the whole. It's severe depression that they excluded, right? It really isn't... they didn't exclude people with depression.
- Joann Elmore: Severe things, psychiatric problems.
- Natalia Murinova: So, how would you define severe? So, then you would have to have some definition of what severe is, you know?
- Chris Standaert: So, the Beck Depression Inventory that they used. Severe is 31...
- Joann Elmore: I shouldn't have brought it up, 'cuz I don't like to sort of over-specify. I like keeping it simple and letting the clinician.
- Seth Schwartz: I think that's the point here. I mean, I think from a study perspective, I think they were trying to just get a clean response, but the reality is, that's not what we're going to have in real life, and it wasn't shown that it's inadequate in those patients. I think it's more a question of, are you appropriately defining chronic migraine or are you confusing the chronic migraine patient with somebody else. So, I think if you really are dealing with a chronic migraine patient, I don't think we need to restrict it. I think the

age question is a reasonable one, if there was a safety concern of doing it in older patients, or something like that, but I don't understand [crosstalk].

Natalia Murinova: There isn't. They were just doing it because they wanted to get some more effective [crosstalk].

Seth Schwartz: Yeah. So, I don't really have a... I mean, maybe we say in adults. I don't know if we want to get into pediatrics, because that's a different story. So, we could say...

Natalia Murinova: No. It was not... it was not studied in pediatrics.

Seth Schwartz: Yeah. So, I mean, here do we say in adults with chronic migraine.

Natalia Murinova: In adults.

Seth Schwartz: So, I think as long as we say adults with chronic migraine that's fine.

Joann Elmore: That's a good point.

Chris Standaert: No. It should be adults. It should be adults greater than or equal to 18.

Seth Schwartz: Yeah.

Joann Elmore: We don't on this, and we need to say in adults.

Seth Schwartz: At the top, what's... go over to the top there.

Chris Standaert: Yeah, the key question is adult. So, we don't have to say it. It already applies in adults, but we can say it. So, go up, Chris, go up to the top.

Joann Elmore: We just want to make certain it says...

Chris Standaert: And it does...

Joann Elmore: ...we can take botox to [inaudible].

Chris Standaert: ...it says in adults.

Joann Elmore: In adults. Good. You're set.

Chris Standaert: And [inaudible] should be. [inaudible] is not covered in people whose condition... so, our treatment is... should be... is terminated. Yeah, not... botox is a brand name. So, we can't use that. So, boNta works. The boNta thing works. It has to be translated to onabotulinumtoxinA. You have to put the actual word in.

Joann Elmore: Good job.

Chris Sullivan: Does that have to be up here, as well?

Chris Standaert: Yep. And it should be stopped to must be discontinued. So, it is not a covered benefit if they are not responding, essentially. This isn't a recommendation. NICE is a recommendation. We can say maximum of five treatments. So, add another paragraph, essentially. Where are you? No. Go to the bottom. Go there. It's just, go... add another paragraph or another line. You can say have received five cycles of... no. Get rid... just another sentence. Say maximum of five cycles or five treatment cycles. Are people OK with this? Yeah, that would be... I wouldn't make a bullet number three. It's not going to be discontinued. You're just going to say, you know, this is all... either way, yeah. There you go.

Natalia Murinova: Could we put something that multimodal treatment, like exercise, should be recommended to these patients, you know, adding something to, you know, because I mean, no one is doing that, but... because they don't know that that's what these people need, but that would be a nice way to...

Chris Standaert: As a clinician, I agree with you.

Natalia Murinova: I'm just asking.

Chris Standaert: No, as a clinician I agree with you. As a... looking at our data, I don't know how I say that.

Natalia Murinova: You know, the same... because you have that, you know, the medication always should be managed, you know, multimodal, you know, therapy is strongly recommended along with botox or something like that. Multimodal therapy.

Sheila Rege: Other therapies could be continued while botox is being delivered.

Chris Standaert: Well, this is just purely about botox. So, that's the tricky part. This isn't about treatment of migraines. This is purely about botox, right? So, it's not about... so we're one to go to PT or whatever, this doesn't say you can or can't do that. It's totally disconnected. Unfortunately, in the main studies we have, it's totally disconnected. That's the data we have.

Laurie Mischley: I was just going to say, I mean, if the data said botox plus exercise works better than botox alone, that would be appropriate, but.

Chris Standaert: Yeah. I would gladly say exercise, yeah. As a clinician, I agree. As a... looking at... from the data and what we can do. It's trickier for me. Yeah.

Female: Can I ask a quick question? Would it be helpful at all, in regards to the three prior pharmacologic prophylactic therapies, to say within two different classes of prophylactic medications so they would either try like a beta-blocker and a tricyclic, as opposed to three beta-blockers?

Male: Three prophylactic medications from three different classes.

- Female: From kind of two of the, you know, generally-accepted prophylactic migraine classes? Just throwing it out there.
- Chris Standaert: I don't know. We'd be [inaudible].
- Joann Elmore: It's a reasonable request.
- Chris Standaert: It's a reasonable request.
- Laurie Mischley: But that wasn't the inclusion criteria in these studies, though, so.
- Chris Standaert: No. It doesn't appear, I mean, even this doesn't appear anywhere in the data. I mean, are people really just going to try three straight beta-blockers not tolerating all of them? Like, I wouldn't think you would do that very often.
- Female: So, it just so happens that I did pre-authorizations for these procedures and yeah, you'll have someone say they tried three SSRIs and want botox, which generally considering, would not be considered typical prophylactic medication. So, yeah, they do.
- Joann Elmore: I think we could that.
- Chris Standaert: OK. So, add after prophylaxis therapies, put from two different classes of recognized agents, medications? If you want classes of medications used to treat migraine. That's what she's saying. Even getting medications that aren't really thought of as effective.
- Gregory Brown: I mean, we can't be writing recommendations based on people prescribing things.
- Chris Standaert: Say three recommended prior pharmacologic therapies. At least then, they're using drugs that are listed for migraines, but we don't have, we don't recommend, so.
- Gregory Brown: That's what I'm saying.
- Chris Standaert: I don't know. I see point, but I don't know how we can get there very easily.
- Natalia Murinova: We could just... three prior pharmacologic prophylaxis therapies, open a bracket, from at least two or more classes of drugs]. That's all. Two classes of drugs, two different classes of drugs.
- Chris Standaert: Classes of drugs? Classes of drugs, OK.
- Natalia Murinova: To treat migraines.
- Chris Standaert: So, I would add drugs and see what people think of it. We're just making our sentence longer. Yeah, we got more to talk about, so.
- Gregory Brown: Well, if we wait long enough, then the drive home is going to be much quicker.

- Chris Standaert: Oh, yeah. We're not waiting that long. Let's keep going.
- Josh Morse: I don't know that level of detail... it can't be worked with by the agency.
- Chris Standaert: OK. We may be cleaning up these words, I have a feeling, but.
- Josh Morse: I would add after covered benefit, the words, with conditions. That would be your... if that is... if that's the formal language of your conditioning.
- Chris Standaert: Yes. Covered condition... are covered... are covered benefit... are a covered benefit with conditions.
- Josh Morse: We can address the grammar if we need to.
- Chris Standaert: Yeah, the... get rid of that. Then we say [inaudible] in people whose condition inadequate... so that, we have, we have changed the language there. We have to fix that. So, in people whose condition, I would put has demonstrate inadequate response. Go back to where you were, because we have to change the lead stem. Down, down, down, down, number one. It doesn't follow from whose condition anymore. Just put has shown inadequate response to treatment. Nope, has shown inadequate response to treatment. There you go. Yeah?
- Joann Elmore: Are you guys happy with your 50% reduction? I mean, I'm impressed. I'm just sitting back here, but do you guys realize... no, but I hope that the...
- Gregory Brown: So, you were going to abstain on the first one.
- Joann Elmore: ...no, I'm, I'm still... I'm getting a strawed vote, and I'm assuming that everybody is going to vote for this. I'm probably going to vote no, you know, noncover, but you guys wrote that you are requiring at least a 50% reduction in headaches.
- Chris Standaert: Mm-hmm.
- Joann Elmore: Even in the Preempt1 and Preempt2, it went from 20 days down to nine days, you know? It's, like, barely there. So, you guys are being pretty strict. They're only going to be able to give them two doses.
- Chris Standaert: If it doesn't work then they...
- Joann Elmore: If it doesn't work, yeah.
- Chris Standaert: ...it's got to work.
- Joann Elmore: OK.
- Chris Standaert: Yeah. People OK? Vote. So, based on our view of the evidence and our discussion thereof, discussing the technology, safety, efficacy, and cost-effectiveness, this is not covered, covered unconditionally, or covered with the above conditions.

Josh Morse: I see eight cover with conditions and one no cover.

Chris Standaert: Since we pulled these three out of NICE, we're at least consistent with some published guidelines and they're a bit all over the place, and there is no national... there is no NCD on this, and we're probably not too far off from various society recommendations, but they are sort of all over the place a bit, too, and not quite as prescribed. Alright, so next, can you pull up that list of things from Dr. Johnson's... go back to Dr. Johnson's slide with those other things at the end. Those. So, trigger point, acupuncture, massage, we're going to go trigger point injections. No, we're going to see if we have to do them one at a time. So, trigger point injections, I didn't see any data for. It was... anybody, safety, efficacy, we have a data thing, right? Transcranial magnetic stimulation, anybody... there was some data on it, it was not great data, right? We're going to lump a bunch of these together, OK? Manipulation? We get good data on that in terms of migraines? There was a study on manipulation. All these studies were limited? For what? For tension, tension headache, yeah. So, manipulation, I'm not hearing data. We didn't have safety or cost issues there, necessarily, but not a lot of data. Massage? We had a sham massage study, which is fascinating. It didn't survey for blindedness when they were done, obviously. People overwhelmed for massage here? Huh? That wouldn't have been sham, versus active ultrasound, deep heat. OK. So, all four of those, I'm getting the same sort of feeling that we have inadequate data, essentially. We don't have data saying they don't work, but we have data that is not very convincing from an efficacy, safety, and cost perspective that they are worth... they are valuable to cover here. I heard a lot more talk about acupuncture from people.

Gregory Brown: Wait. Wait. Wait. Before you go, let's just cover those four.

Chris Standaert: Let's cover those four.

Josh Morse: Which four?

Chris Standaert: So, we're going to, this is for trigger points, acupuncture, massage, transcranial magnetic stimulation and manipulation.

Josh Morse: We're going to [inaudible] acupuncture.

Chris Standaert: So, you have to go back to your nonbinding vote, first, right? We have to do that. So, this is a yellow card vote. So, for those four collectively, trigger points, massage, magnetic stimulation, and manipulation, safety. Is there sufficient evidence that... I haven't even looked up yet, and I have this weird feeling it says unproven all around me, but is there sufficient evidence that proves the technology is safe for the indications considered?

Josh Morse: Yeah, I see nine unproven.

Chris Standaert: This is for all four of them. For efficacy and effectiveness, is there sufficient evidence the technology has a meaningful impact on patients and patient care?

- Josh Morse: Nine unproven.
- Chris Standaert: Cost-effectiveness, is there sufficient evidence that the technology, that all these technologies, are cost-effective for the indications considered?
- Josh Morse: Nine unproven.
- Chris Standaert: Based on the evidence about the technology, safety, efficacy, and cost-effectiveness in the setting of chronic migraine, trigger point injections, massage, transcranial magnetic stimulation and manipulation are not covered, covered unconditionally, or covered under certain conditions?
- Josh Morse: I see nine not cover.
- Chris Standaert: OK. Oh, boy, expert guidelines on these issues?
- Josh Morse: Can I just ask a point of clarification?
- Chris Standaert: Yep.
- Josh Morse: So, you did that specifically for chronic migraine.
- Chris Standaert: Chronic migraine.
- Josh Morse: You have already excluded other headache types [crosstalk]?
- Joann Elmore: Darn. We should have done it for all of them at the same time.
- Sheila Rege: Chronic headaches, yeah.
- Chris Standaert: We can do chronic tension headaches as one, unless somebody wants to pull one of these other technologies back into chronic tension headache.
- Joann Elmore: OK. Good idea.
- Chris Standaert: Right? So, let's... we'll get to chronic tension headache in a second.
- Kevin Walsh: I move that vote was all for the different headache types.
- Laurie Mischley: I second that.
- Chris Standaert: Well, we still have to go back and talk about it for migraine, so. We have to talk about chronic tension headache. That's for botox. We have to talk about chronic tension headache for botox if we're going to do it this way.
- Gregory Brown: But we're just going to do all?

- Chris Standaert: So, we're going to... we'll do everything when we get to chronic tension headache. OK. You don't think?
- Josh Morse: I think you don't with botox, because you've narrowed your conditions to migraine.
- Chris Standaert: To migraine?
- Sheila Rege: Yeah, we did actually.
- Josh Morse: Which leaves others as not covered.
- Gregory Brown: I second Seth's vote, motion.
- Chris Standaert: So, how do we do this?
- Josh Morse: If you want to go back and do that, that's fine with me.
- Sheila Rege: No, we'll just do it, do it all at once.
- Chris Standaert: No. Quick vote. So, all four of those for chronic tension headache. We went through the safety, efficacy, and cost data already. So, pull out your pink card again. So, we are following our structure here. Trigger point injections, massage, transcranial magnetic stimulation, and acupuncture in the treatment of chronic tension headaches based on evidence on their technology... based on their evidence of their safety, efficacy, and cost-effectiveness, the treatment of chronic tension headaches.
- Josh Morse: Nine not cover.
- Chris Standaert: So, then we are into acupuncture, and we have both chronic migraine and chronic tension headache floating in the air for acupuncture, and some people were more interested in acupuncture or more impressed the data, or more struck by the data in some way. Somebody want to talk about acupuncture?
- Laurie Mischley: As the token alternative medicine doc on the panel, I'll just say that I actually was surprised by the data. I actually underestimated what acupuncture would have to offer people with migraines, and when I started looking into the data a little bit, I found myself being impressed. I think we have already covered this issue of for-profit companies driving research, and it's tempting to start to think that these huge, huge expensive studies are the norm, and I just think if we're... we're always going to be disappointed by some of these complementary and alternative therapies. The size and scope of some some of these complementary and alternative therapies, given the healthcare system we find ourselves in. I mean, it's just... I feel like it's not entire... I want to keep a high bar for the quality of research we're looking for. I also want to realize that there are other forces at play, and we'll never see an acupuncture trial of the same scope that we have for botox trials, and it's easy for us to be bias, but when you see 1200 people in one study and 120 in another. So, I just want that to enter people's thinking. I do, like I said, I'm finding myself doing a lot of placebo research, and I am struck by, just as I was for botox with acupuncture. I think any time you give

a patient a lot of attention and you put some needles in them, you're going to get better outcomes than popping a pill, and I don't think that is completely useless. I think the record of safety is good. We have a couple trials here suggesting there is some efficacy over Topamax, and I just think that it would be a shame to... given how many patients suffer, how many limitations there are to available³ therapies, that this is a safe and relatively inexpensive intervention. I think it would be a nice tool to continue to have in the toolbox. In terms of intensity, I looked at what they did in the clinical trials, and it was two treatments a week for 12 weeks for a total of 24 treatments at 30 minutes each. The other thing, when they were looking at cost-effectiveness, a lot of it was coming... what they were talking about is, it depends on who is doing the treatment. If you have a primary care physician doing the acupuncture, it's a lot more expensive than if you have an acupuncturist doing the treatment. So, I don't know that we can parse that out, but I will say that we are fortunate to live in a State where we have access to a lot of acupuncturists. So, that may end up shaping the cost of this intervention, should we make it available.

Chris Standaert: Other people want to talk about acupuncture?

Chris Hearne: Does anybody know, or maybe the evidence vendor can talk to us about this briefly. What was usual care in the Vickers 2004 study? That's the 301 participant acupuncture versus usual care for chronic migraine?

Chris Standaert: What was usual care?

Chris Hearne: What was usual care? Oh, that's right. So, just whatever.

Andrea Skelly: This wasn't on. Did everyone hear me?

Chris Standaert: Mm-hmm.

Andrea Skelly: OK.

Chris Standaert: How are patients... I didn't read that study. So, this issue of patients, how were they recruited? Were they patients who came to an acupuncture clinic? How were they found? Were they randomized? Were they... that sort of thing. Were they people seeking acupuncture and weren't given it? How did they get?

Andrea Skelly: You know, let's look that up.

Joann Elmore: If you're talking about the Vickers paper...

Andrea Skelly: Yeah.

Joann Elmore: AAMJ. It was published in 2004. It consists of 12 separate clinical sites with a single acupuncture place and two to five local GP's, and they basically... the practices searched the databases to identify potential participants and then sent letters to suitable patients, 401 patients. They were randomly allocated to receive up to 12

acupuncture treatments over three months or to a control intervention offering usual care.

Chris Standaert: See, I thought the study design was always somewhat troublesome, because you're asking people if they want to be in this study. So, people who are curious about it then half get it and half get nothing. That, I don't know, in the back pain world, that always leads to whatever you did works, because they all want something. In the other group, you give nothing to. So, I don't know. That study design kind of bugs me a bit. It looks like the mean change in modest headache days is 1.2, any headache days 1.8.

Joann Elmore: 22 fewer headache days per year, 15% less medications, 25% fewer visits to GP's, 15% fewer days off. You have about a 35% improvement from the placebo, and they don't have a placebo arm. So, it's hard to compare this, you know? Is this just a nice powerful placebo, or is this... it seems like it's a tad better than a placebo.

Chris Standaert: It's interesting, if you go to slide 46 of Dr. Skelly's presentation on Page 23 of our thing, they have chronic tension headache, acupuncture versus active treatments. When you put something else in there that helps people. So, PT, exercise, physiotherapy of some sort, relaxation sort of thing. These are all small problematic studies, it looks like but no difference.

Joann Elmore: Well, actually in one of the tension headache studies with 90 patients, those that were randomized to the relaxation group, did better.

Chris Standaert: Better with relaxation?

Joann Elmore: Mm-hmm, number of headache free periods and headache free days. Both outcomes were better in those randomized to the relaxation group.

Chris Standaert: Kevin, you were talking about acupuncture. What do you think? What do you think of our data?

Kevin Walsh: I'm not impressed by the quality of the data, but in... on the whole, when you combine that with the cost, the safety, and again, thinking about patients who have tried and failed a couple classes of medications, I... in spite of the fact that the quality of evidence is low, I don't see that it is substantially different than the quality of evidence of the Preempt trials, especially when you start to consider how it might have been rigged.

Chris Standaert: Yeah. I'm highly suspicious of the Preempt things myself. They did include a sham, which would be nice in an acupuncture study. That definitely changes the outcomes when you look at studies of low back pain and acupuncture and sham versus no sham.

Kevin Walsh: Did it decrease the...

Chris Standaert: Doesn't... it, it... the studies that I'm familiar with, they all get better. There is a high response to sham or real acupuncture.

Kevin Walsh: Kind of like botox.

Chris Standaert: Huh?

Kevin Walsh: Kind of like botox.

Chris Standaert: Right.

Kevin Walsh: I'm not trying to say this is markedly better than botox. I'm just trying to say it's not... the quality of the evidence and the... it's not worse.

Chris Hearne: I agree. I don't think it makes any sense to cover botox with those conditions but not acupuncture given the similar sort of level of evidence.

Chris Standaert: Do you really think there's a similar level of evidence?

Seth Schwartz: No.

Chris Standaert: This is not a... these aren't randomized blind placebo control trials, right? Botox... yeah, botox has its issues, but they had an active placebo arm, which this doesn't.

Chris Hearne: Well, the Yang 2011 has an active placebo, or an active comparison treatment.

Joann Elmore: Which one was that?

Chris Hearne: That's the...

Joann Elmore: Migraine or tension?

Chris Hearne: ...Topamax, yeah.

Chris Standaert: Oh, the Topamax one, yeah.

Joann Elmore: Oh, but see, that's not the same as sticking needles in.

Chris Standaert: It's not the same as [crosstalk].

Joann Elmore: The placebo effect is markedly higher when you... when there's active needling, as opposed to just swallowing a pill.

Carson Odegard: I mean, if we go by that evidence, I mean, you're talking about for chronic migraine, right? Not tension. Are we lumping those together, because if you use the same kind of argument, manipulation is effective, even though it's low evidence.

Chris Standaert: Yeah.

Carson Odegard: For tension type headaches.

Chris Standaert: Yang is a four-week followup, right?

Carson Odegard: No. That's an 18-week.

Chris Standaert: The graph here of topiramate is four-weeks.

Carson Odegard: No. No. I mean for manipulation.

Chris Standaert: Oh, yeah. Yeah. Yeah.

Carson Odegard: So, there's an argument.

Seth Schwartz: The only difference, and the effect size is certainly bigger for the acupuncture in that Yang trial, but that's very problematic. I mean, I think we're still dealing with insufficient evidence. There's something there, but it's hard to say much about it. I think the quality of the trials are different than what we're seeing, even though there's questions about the quality of the randomized control trial, we have randomized control data for botox where this is not that. That's again, not to say that acupuncture is totally useless. It's just to say that I don't think we're seeing sufficient evidence that it is useful.

Joann Elmore: I do appreciate the discussion, especially you guys pointing out how, you know, it's not as costly. It doesn't have the... over half the patients having adverse events.

Laurie Mischley: And the stereotype a little bit here is my experience is that those 30 minutes while someone is on the table is an opportunity to intervene on lifestyle modification that is not often seen in conventional practice.

Chris Standaert: Yeah. Nobody studies that. Apparently, there's no money in actually sitting down and talking to people for a half an hour and then counseling them on their health. That doesn't seem to, like...

Kevin Walsh: Well, nobody pays for it.

Chris Standaert: Nobody pays for it. I mean, that's the truly...

Gregory Brown: They're playing Veggie Tales for subliminal suggestion for...

Chris Standaert: Yeah. You lost me. I know the cartoon, but I've never watched it, no.

Gregory Brown: Anyway, lifestyle changes. Never mind.

Chris Standaert: So, discussion document. So, safety, outcomes, acupuncture, adverse events. We don't have much data on adverse events. There would be some, but we don't worry about weakness or other sorts of things, but we don't have a lot of data, frankly, safety data. Efficacy, we talked about reduction in episodes and headache days. They have data on that. Whether we think the quality is there is a different question. Whether we think the comparators are all appropriate is a different question. They have data

on headache days. They have data on responders in that one study, Yang, they had responders, response to treatment. We don't have... I didn't see cost utility data on acupuncture, even the cost of acupuncture in the evidence. I don't know.

Joann Elmore: It had a lot of limitations. So, we can go on. I'm sure [crosstalk].

Chris Standaert: [crosstalk] care, suggests it's favorable but no active comparator, limited time horizon, limited sensitivity analysis. Gotcha. Special populations? They did bring up more severe headaches, maybe, are more responsive to acupuncture? That was their? Alright, unless there are other comments, we'll do our nonbinding vote. Safety, effectiveness, and cost.

Joann Elmore: So, are we doing chronic migraines and chronic tension headaches together with acupuncture?

Chris Standaert: I would opt to do that.

Joann Elmore: OK.

Chris Standaert: Unless...

Joann Elmore: I just want to clarify so [crosstalk].

Chris Standaert: ...unless somebody else wants to split them.

Joann Elmore: OK.

Chris Standaert: No? OK. So, we're going to do them together. Safety. Is there evidence that the technology is safe for the indications considered? Unproven, less, equivalent, more in some, more in all.

Joann Elmore: Compared to what?

Gregory Brown: Safety.

Josh Morse? One, two, three, four some. Please don't put your cards down. Let me write this down. Four some, two equivalent, at least... five some, two equivalent, and two unproven.

Chris Standaert: So, efficacy, effectiveness. Is there sufficient evidence this technology has a meaningful impact on patients and patient care?

Josh Morse: OK, one, two, three, four, five unproven, four some.

Chris Standaert: For cost outcomes and cost-effectiveness. Is there sufficient evidence this technology is cost-effective for the indications considered?

Josh Morse: Nine unproven, oh, eight unproven, one some.

- Chris Standaert: OK. I assume nobody is leaning towards cover unconditionally? Somebody who wants to propose conditions, I assume you want to... I assume you start with the ones we already have for botox or no for people who want conditions?
- Sheila Rege: NICE has coverage of acupuncture, the British agency.
- Chris Standaert: And there are conditions? Or they have...
- Sheila Rege: They have... they want, I can't even say these drugs, topiramate and propranolol, beta-blocker are unsuitable or ineffective, course of up to ten sessions, different than our literature, over five to eight weeks according to patient preference.
- Kevin Walsh: Can you talk into the microphone please?
- Sheila Rege: Oh, sorry. NICE does have language on how they would cover acupuncture, and they want a trial of medications, after which consider a course of up to ten sessions of acupuncture over five to eight weeks, and I think you can project it. I think I sent it. We can have it projected.
- Joann Elmore: It's on Page, acupuncture, NICE, Page 10.
- Sheila Rege: Is it there?
- Joann Elmore: I think so.
- Sheila Rege: OK.
- Chris Standaert: Yes. It is there.
- Joann Elmore: But maybe take a straw vote to see if people want us to type up coverage with conditions, and if the majority...
- Chris Standaert: So, someone who would advocate for conditions, if the conditions we had are what you would think, we can leave that. If you want other conditions, then, to hash through words, I would put out a straw vote about where people are leaning. People might be swayed by conditions one could describe. Do you have conditions you might propose? You don't have to type it yet, but, verbally.
- Laurie Mischley: The ones we're talking about and looking at would be where I would let, I mean, what we've already been talking about. I just...
- Chris Standaert: For the NICE ... regarding the acupuncture?
- Laurie Mischley; Yeah, your... the ones you just read for NICE were reasonable.
- Chris Standaert: They say for the prophylactic treatment of chronic migraine, which is interesting. I guess they recommend the same thing for botox. They say the same thing, both for treatment, they say prophylaxis.

- Laurie Mischley: Just compared to botox, I mean, we're looking at the percentage of patients achieving more than 50% reduction, and in this study, they're looking at 63 and 75% of participants meeting that criteria at four weeks. I didn't see that... did anyone see that presented that same way for botox? I mean, what...
- Chris Standaert: It was presented. They had topiramate.
- Laurie Mischley: How did it com-...
- Chris Standaert: They had about the double the topiramate responders, but they didn't have nearly as many responders as the acupuncture had. That's a couple slides before that.
- Laurie Mischley: Right. OK.
- Chris Standaert: But they had about a 30% response than topiramate. So, that's low, but still, botox wasn't anywhere near as high as that.
- Joann Elmore: Right.
- Chris Standaert: Those are high numbers, yeah? Yeah. If they would sustain. So, we're going to do a straw vote. So, uh, hands of people who want to talk about conditions. You don't have to say you're going to vote for them, but if you want to talk about conditions. OK. Let's put up the NICE conditions, those. Can you pull them, cut them, and paste them into a separate thing? Just that first paragraph right there on acupuncture. Stop. No. No. No. Stop. Yep. So, would your inclusion criteria be the same that you have these people with multiple medications, like, what we put in for botox, to get to botox you have to have the definition of chronic migraine and...
- Kevin Walsh: Treatment failure.
- Chris Standaert: ...you have to treatment failure and, yeah.
- Joann Elmore: Similar to the other.
- Chris Standaert: I'm assuming, uh, I don't, so. So, can you pull up the first paragraph from the conditions we gave you for Botox? So, that first paragraph. Granted, we'll change the word botox or whatever that, yeah, the longer version of that word to acupuncture. So, you've changed that to acupuncture as a covered benefit with conditions. I'm just talking... so, somebody who wants to do... who is proposing this. So, go down to three. So, in two, there are conditions [inaudible]. Next would be three. So, it says a course of ten sessions. So, that's going to be your third clause, right? Then, stop after weeks, yeah. So, get rid of can be considered and everything after that. Is that what, so again, somebody, those of you who want to talk about this, please.
- Chris Hearne: So, the two studies we have, have 12 sessions over three months and the other has one session per week for 24 months. So, we're... the data we have are looking at 12 to 24 sessions rather than 10.

- Chris Standaert: Yeah, but we don't have 24-month data from those studies, do we?
- Chris Hearne: 24 weeks, excuse me. They are weeks.
- Joann Elmore: 12-month followup.
- Chris Standaert: You said 24 months.
- Laurie Mischley: So, you're suggesting 12 to 24 sessions of acupuncture would be a covered benefit if the following conditions are met.
- Chris Hearne: Correct.
- Chris Standaert: I get there are other studies on acupuncture, but the equivalency to other active treatments bothers me as to why we're calling... I understand there's a study or two there, but you wonder about the same thing, you know? PT, exercise, manipulation, other active treatments to somebody, you know, compared to nothing and compared to a drug people don't like, it looks better. Compared to exercise, compared to PT, compared to whatever, it doesn't look better.
- Joann Elmore: And we actually have evidence here, whereas with botox we didn't. Here we do...
- Chris Standaert: Yeah.
- Joann Elmore: ...have randomized trials and the exercise and the relaxation did better. They were poorly designed. They were small size, but at least you have evidence if you want to add in.
- Chris Standaert: And this is set up as essentially an equivalent choice over botox. So, in some cases maybe it's safer, but...
- Joann Elmore: And cheaper?
- Laurie Mischley: I honestly agree with the folks here who think the evidence is not sufficient. I mean, I really do get that. I also know that we don't have really good therapies for migraine, and I'm looking and seeing that 75% of people in some of these studies are saying I feel better after this series, and it's hard, given the safety and the cost to not make this therapy available, given the therapists we have available in Washington State and the little teeny bit of data we had looking good, so.
- Chris Standaert: I think you could say that for all sorts of studies and all sorts of technologies that you find something that... an active treatment that people respond to and resonate with and have some interest in compared to something that they don't, and it works better in all sorts of pain conditions. We've seen this a lot. So, my only issue is calling this out as opposed to all the other things we have seen in that. You could theoretically change the word I n there. I don't doubt there's benefit to finding ways to get these people to be healthier, and if acupuncture is one of them, if exercise is one of them, I have no doubt that that actually might be beneficial. This is my perspective.

- Kevin Walsh: So, you're saying so like all kinds of other soft benefits?
- Chris Standaert: No, I would not favor this, because I don't see the data that tells me this is the thing to do, right, and I think the studies are not great. I think they're not blinded. I think they... when compared to an active treatment, it does the same as the active treatment if not worse than exercise or behavioral treatments in some way. That's what makes me question, and does it mean that we need better studies? Yeah. We need better studies.
- Kevin Walsh: I would just ask... I understand all that and it's valid, and I agree with it. At the same time, we approved botox when compared to topiramate, it was marginal to zero benefit, and then in one poor study, this is a lot better.
- Chris Standaert: In one poor study, right.
- Kevin Walsh: Costs... it costs less. Its safety profile...
- Chris Standaert: I don't know what I'd do with [crosstalk].
- Kevin Walsh: ...is better. I mean, there is an argument to say, let's be really rigid and if there's no evidence, it's no go. Sometimes, a lot of people feel that way, and sometimes if there's any benefit, people vote for a surgical procedure that's really expensive.
- Chris Standaert: I hear you. I'm expressing my... I hear your perspective, yeah.
- Kevin Walsh: No. I'm not...
- Joann Elmore: Can I hear some of the other member's comments before we go to a vote? Quickly?
- Carson Odegard: Well, I think, you know, if we're going to be very strict about this, my vote against manipulation was the fact that the evidence was so low, but then... but that was for chronic tension headaches and not for migraine. For migraine, acupuncture looks better, but still low evidence. So, it's really hard for me to accept the same low evidence for acupuncture and, I mean, if we're going to use the same criteria, we'd have to use it for manipulation, 'cuz that was the only other thing that really had the evidence backing it... at least for chronic tension headaches. So, that's my thought.
- Joann Elmore: Seth is watching the clock. Seth. Chris. Anybody else?
- Gregory Brown: I guess I agree with you, Carson. They fly or they sink together.
- Gary Franklin: Chris, can I say something?
- Chris Standaert: Yes, Gary.
- Gary Franklin: We have never covered acupuncture over these many years. We just... we've been working with the acupuncturists, and one thing you have to realize is when they do acupuncture, they also do about 20 other things. Now, I don't know what exactly was

done in these trials, but they do do a lot of other things, all of which are billed for, if you've covered it. So, we did agree, because we had multiple randomized trials on low back pain, we agreed to do a pilot. So, we agreed to cover acupuncture for only, I think, ten or twelve visits, period, with a recommendation to track outcome after the fifth visit and [inaudible] the next five visits if nothing's happened in the first five visits, but on. So, we're going to do a pilot on that, but we don't cover for anything else. So, to me, this should be relatively compelling evidence for you to make a coverage decision. You don't think it's actually very compelling at all. If you say to cover it, we're going to have to cover it, and that would be... we'd have to change our rules and everything. So, if it's compelling, that's great. That's what you guys do great, you know, but if it's not compelling, just because it's a noninvasive treatment when not much else works isn't a reason to cover it.

Chris Standaert: Low back pain patients, pilot and low back pain, pilot and low back pain patients is which one you're working on, yes?

Gary Franklin: We're working on the low... they're only... we're only going to allow it for low back in a pilot.

Chris Standaert: OK. Right. Greg, did you say what you're going to say? Oh, you said you agree with Seth. You agree with Carson. Alright. 5:07. Other discussion? You were about to talk Laurie. I don't want to cut you off.

Laurie Mischley: I agree that the data is not compelling, and I actually don't prescribe acupuncture or use acupuncture or refer for it. I mean, this is not something I'm arguing, necessarily, for. I just want to point out the insanity of looking at how much better the responses are to acupuncture from Topamax, and our criteria are, I mean, I get that's not our prevue. I just... we're in a... in a...

Chris Standaert: But you have to... you have to look at that study. It's a four-week outcome, right, with, again, an active intervention. So, it's... it, I see it, but at the same time, the study level is [crosstalk].

Laurie Mischley: No, I get it. I get it. My issue was the, anyway. It's not relevant to the vote.

Chris Standaert: No. Your thoughts are certainly relevant. Yeah.

Laurie Mischley: All I was saying is that it's... it's funny that we would even start with the if you've failed the thing that is looking to be less effective, then we'll move on to letting you do the cheaper, lower side effect thing that looks to be more effective.

Chris Standaert: Yeah, I don't know what the data on topiramate looks like.

Laurie Mischley: Right.

Chris Standaert: I don't know what the drug trials look like.

Laurie Mischley: Right.

- Sheila Rege: I agree with Carson, but I also think Laurie brings up a very important point. The drug companies have a lot of money, and they can go ahead and use fancy statisticians and stuff to fudge the data. When you look at an acupuncture trial, you don't have that. I actually have a partner who is a radiation oncologist who does a separate free of charge visit and does acupuncture on patients, and I look at my patients and say if you want that foo-foo stuff go see him, and some of them really like it, and it works. So, I'm glad we're doing a pilot study with some outcome data, but I do... but that was a good point that you brought up. This is something where there is not big corporate money coming into the study. So, I'm glad we had that discussion.
- Chris Standaert: Any more discussion? This is for migraine and chronic tension headache, so not just migraine, yeah? Migraine and chronic tension headache. So, that would be... we changed it to a covered benefit for chronic migraine or chronic tension headache if we're going to do that. Alright. So, our choices, based on our discussion and review of the evidence regarding safety, efficacy, and costs, acupuncture or treatment for treatment of chronic migraine, as defined on the board and chronic tension headache is either covered with conditions, meaning those, not covered, or covered unconditionally.
- Josh Morse: I see seven not cover and two cover with conditions.
- Chris Standaert: That was a good discussion of it. That was a good thing to bring up. Getting other treatments into the discussion is very useful, too. So, there are no national coverage determinations on this. There are a few payer policies on this.
- Josh Morse: Yes, and your determinations align with the American Academy of Neurology, at least for the botox, and there are some contradictory policies here from the United States, as far as Professional Society [crosstalk].
- Natalia Murinova: We [crosstalk] over 15 days.
- Chris Standaert: Yes.
- Josh Morse: So, I think you're good there.
- Chris Standaert: Alright. So, we're done?
- Joann Elmore: Do we need botox for tension headaches?
- Sheila Rege: Should we do that?
- Joann Elmore: We did all the other ones. We did botox for migraines. Did we throw the botox in with the other ones for tension headaches?
- Sheila Rege: Should we go ahead and do that just to make sure.
- Chris Standaert: OK. I don't know if we voted on botox for tension headaches.

- Joann Elmore: I don't think we did.
- Josh Morse: If you're not, yeah. Why don't you vote on that, and we have one other thing...
- Joann Elmore: I would love to leave also, but...
- Josh Morse: ...to do after.
- Chris Standaert: OK. So, botox for tension headaches. We talked about migraines. We didn't talk about tension headaches. The data was different, right? So, we've been through our data. So, based on our discussion of... do we have to go through the yellow cards, too, do you think? We talked about conditions. We were talking about migraines with the yellow cards.
- Josh Morse: I think you should do both.
- Chris Standaert: OK.
- Josh Morse: Because it doesn't sound like you're clear on.
- Chris Standaert: Yellow cards, migraines and tension headaches. Safety. Is there sufficient evidence technology is safe for the indications considered? Botox for tension headaches. Joann?
- Josh Morse: Safety for botox for tension headaches.
- Gregory Brown: For tension headaches.
- Josh Morse: Four less, five unproven.
- Chris Standaert: Efficacy for tension headaches, botox and tension headaches, sufficient evidence the technology has a meaningful impact on patients and patient care.
- Josh Morse: Eight unproven, one equivalent.
- Chris Standaert: Cost. Sufficient evidence the technology is cost-effective for the indications considered, botox for tension headaches, chronic tension headaches.
- Josh Morse: Nine unproven.
- Chris Standaert: Based on our discussion of the technology safety, efficacy, and cost-effectiveness, botox in the use of chronic tension headaches is not covered, covered unconditionally, or covered with conditions?
- Josh Morse: Nine not covered.
- Chris Standaert: So, there we go.

Josh Morse: Thank you.

Chris Standaert: Once again, I think we're in line with our national coverage decision and [crosstalk].

Josh Morse: We have two people who will not be at future meetings. These are their last meetings in person. So, yeah. Thanks. Dr. Standaert we have a going away...

Chris Standaert: Thank you very much.

Natalia Murinova: Where is Dr. Standaert going?

Josh Morse: And here is a letter of thanks. Thank you, very much.

Sheila Rege: I can't believe it. You are really, really leaving us?

Joann Elmore: I think we all have to say that without Chris and Carson, it's just not going to be the same. It's been many years. You guys have, I think, helped shape the direction, the way we think about evidence, our logistical practices, and entertained us all at the same time. So, thank you.

Carson Odegard: Thank you, so much. I'm going to miss you all.

Joann Elmore: I think you need to read the evidence reviews.

Josh Morse: So, our next meeting will be July 14th, and will be on the phone.

Chris Standaert: Phone, to review our determinations from today.

Gary Franklin: I do want to say something else.

Seth Schwartz: Thank you, very much.

Chris Standaert: Thank you, Josh. That's very nice.

Josh Morse: Dr. McCulloch will be receiving one, as well.