

Copies of the audio recording for this meeting are available by request to: shtap@hca.wa.gov.

Health Technology Clinical Committee Public Meeting

May 15, 2020

Josh Morse: Good morning, everyone. This is Josh Morse with the Health Technology Assessment Program. It is a couple minutes after 8:00. We have a quorum checked in. There are two names who I do not see quite yet, Seth Schwartz and John Bramhall. If either of you are on, and we don't see you, perhaps you could raise your hand. Or we'll keep checking for you.

Welcome to the Health Technology Clinical Committee meeting for May 15th, 2020. This is our first virtual meeting for this group with actions on an agenda. I'd like to do a quick note here with Dr. Novotny. Dr. Novotny, can you hear me?

Edward Novotny: Yes. No problem.

Josh Morse: Thank you for joining us so early. You are the clinical expert, and we're very grateful for your participation. The topic that you are the clinical expert for is scheduled to take place later this afternoon. You're welcome, obviously, to stay for this meeting, but you're not required to if you don't want to until around noon.

Edward Novotny: Alright. That's fine. I just wanted to make sure everything is working fine.

Josh Morse: Excellent. I really appreciate that.

Edward Novotny: Sure. OK.

Josh Morse: OK. Dr. Rege, I think we are ready to go if you are ready to go.

Sheila Rege: OK. Good morning. Sheila Rege here. Can you hear me?

Group: Yes.

- Sheila Rege: Well, welcome to our first telephonic go to webinar meeting. I do want to introduce two individuals. And one is our clinical expert for the tinnitus, Dr. Jay Rubenstein, and the Ph.D. Director of University of Washington the Hearing Research Center and Professor of Head and Neck Surgery at the University of Washington and Bioengineering. Welcome and thank you, Dr. Rubinstein.
- Jay Rubenstein: Thank you. Good to be here.
- Sheila Rege: And we also have a new committee member. And Conner, I had talked to him yesterday. Tell me how to pronounce your last name.
- Conor Kleweno: Sure. Often, that's a tough one. It's Kleweno.
- Sheila Rege: Kleweno. Great.
- Conor Kleweno: Yeah. The W is a V sound. So, that's the confusion.
- Sheila Rege: Perfect. Do you mind telling us, as a new committee member, kind of just a couple sentences about yourself?
- Conor Kleweno: Sure. So, I am an associate professor of Orthopedic Surgery at the University of Washington. And I practice out of Harborview as an orthopedic traumatologist. My background is in biomedical engineering, which I studied at the University of Washington it seems like a long, long time ago now. I just have a really strong interest in being a part of this committee and helping out in any way that I can.
- Sheila Rege: Perfect. Welcome. Now, I'm going to turn it over to Josh for any program updates before we look at our previous meeting business. So, be prepared after Josh about the . . . we need to pull up the January meeting meetings. Josh, I'll turn it over to you.
- Josh Morse: OK. Thank you. Let me see. Let me just swap these. There we go. OK. I would also like to make an introduction. I would like to welcome Brit Reddick who is the new Health Technology Assessment program manager. Brit is new to the program about two months ago. She started on February 1st, comes from a previous appointment here in the Health Care Authority in our policy division. We're super excited that Brit's on board. This is her first Health Technology Clinical Committee meeting. I would just like to welcome her. So, if you haven't already had contact with Brit, welcome aboard, Brit.

OK. So, I'll go through our Health Technology Assessment program update. So, we have a couple housekeeping slides and a couple reminders. If you're participating by phone, it's OK to mute yourself, but please don't put us on hold. We'll be watching for inadvertent noises and may need to mute if there is any background noise. If you're not already familiar, there are a variety of webinar controls for you to use. Here are some of them. Moving on to today's agenda.

So, this morning, we will be talking about tinnitus, noninvasive, nonpharmacological treatments, and the afternoon topic is vagal nerve stimulation for epilepsy and depression. We will start with tinnitus after we go through the previous meeting business items.

Meeting reminders: As with all of our public meetings, this meeting is being recorded. A transcript of the meeting will be made available on our website some weeks after the meeting. When participating in discussions, please state your name and obviously, you are using a microphone today. To provide public comment during today's meeting, we're going to ask you to raise your hand if you're an attendee. And then we will ask you to help us with your name, as we record who is making the comment if you haven't signed up in advance so that we have on record who is making public comment today.

A little bit of background about the program. Multiple state agencies participate to identify the topics that are reviewed. And then, these agencies implement the policy decisions. These agencies include the Health Care Authority that manages the uniform medical plan for public employee benefits, as well as the school employee benefits programs and the Medicaid program, or Apple Health. Also participating is the Department of Labor and Industries, and the Department of Corrections also uses the policy decisions from this program, as well. The state agencies implement the decisions from the Health Technology Clinical Committee within their statutory frameworks.

A little bit of background about the program. The Health Technology Assessment program is administrated by the Washington State Health Care Authority. It was created in 2006 through legislation. It designed the program to use evidence reports and this panel of clinicians to make coverage decisions for selected medical procedures and tests based on the evidence available for their safety, efficacy, and cost-effectiveness.

The purpose of this program is to ensure that medical treatments, devices, and services that are paid for with state healthcare dollars are safe and proven to work. We provide a resource for the state agencies

that are purchasing healthcare. We develop scientific evidence based reports on these medical devices, procedures, and tests. We facilitate this independent committee of healthcare practitioners who help determine which medical devices, procedures, or tests meet the test for safety, efficacy, and cost.

This is a high level overview of the HTA process. We follow these steps for each topic. The Health Care Authority director is authorized to select technologies for review in this process. We develop key questions to shape the reports for the topics that have been selected. We then use contracted technology assessment centers. These folks produce the evidence based reports. This information is then brought to the Health Technology Clinical Committee for consideration, and the committee makes draft and then final determinations based on that information. There is a little over 100 days of public comment opportunity for each topic that goes through this process, and at the end, the agencies are charged with implementing these decisions.

This is our calendar for 2020, as it stands at the moment. Today is May 15th. We are doing a re-review of vagal nerve stimulation and a new review of tinnitus treatments. On June 12th, we will have a new topic of stem cell therapy for musculoskeletal conditions. This was originally scheduled for March, a month and a half ago, and we were forced to reschedule that meeting. So, we'll be holding another webinar in June. July 10th is our typical followup meeting from May meeting, which will now include the June meeting as well, and that will be a webinar or a phone conference. It's usually an abbreviated meeting of about an hour. September is the typical timeframe for a committee retreat. November would be the next active public meeting for decision making. We do not have a topic identified for November at the moment. So, that's our current schedule.

To participate in the HTA program, please visit our website on the Health Care Authority website. You can sign up to receive HTA program notifications by emails using our gov delivery system. Anyone may provide public comment on topics that have been proposed for review on key questions, on draft and final reports, and on draft decisions. Anyone is welcome to attend these public meetings of the Health Technology Clinical Committee, and to present public comments directly at these meetings. Additionally, anyone may nominate technologies for review through this process.

If you have questions, you can contact me, the HTA program director, and you can find information about how to do that through our HTA website. Alright. Thank you.

So, we will move on to previous meeting business, including the January minutes. We will switch. Sheila. I will turn it back over to you.

Sheila Rege: The January meeting minutes are being projected. Our clinical expert at that meeting was Dr. Chang. We had a quorum. We now need to review that, and I will accept a motion for approval.

Tony Yen: Move to approve.

Mika Sinanan: Second.

Sheila Rege: Any comments on it? Otherwise, Josh, should we all raise our hand to approve? Or would you like that done verbally?

Josh Morse: I'd prefer to do it . . . that's a great point. So, throughout the day when we do voting, I think we'll do, I'll do a verbal roll call please. I am keeping a record, as we go through that. Is that OK with you, Dr. Rege?

Sheila Rege: That works.

Josh Morse: So, first we'll check and see if Dr. Bramhall has joined. We need to unmute all committee members, Brit, if you can do that. I don't see Dr. Bramhall quite yet. So, Brit is going to unmute everybody, and I will read off names in alphabetical order.

Brit Reddick: I am not going to unmute everyone, because everyone already has that ability, except for it looks like Dr. Bramhall. So, everyone should be able to unmute themselves at this point when they need to on the committee, but if you have any issues, please send a note and let us know.

Josh Morse: Thank you. Oh, there's John. I'm sorry. OK. So, we'll start from the bottom here. Tony do you approve the minutes?

Tony Yen: Were you asking for Tony Yen?

Josh Morse: Yes, Dr. Yen. Sorry.

Tony Yen: OK. I'm just checking. Yes. I approve.

Josh Morse: Dr. Walsh?

Kevin Walsh: Approve.

Josh Morse: Dr. Sinanan?

Mika Sinanan: Approve.

Josh Morse: Dr. Schwartz?

Seth Schwartz: Approve.

Josh Morse: Dr. Rege?

Sheila Rege: Approve.

Josh Morse: Dr. Mischley?

Laurie Mischley: Approve.

Josh Morse: Dr. Kleweno?

Conor Kleweno: I'm assuming I abstain, since I wasn't present.

Josh Morse: Thank you. Dr. Friedly?

Janna Friedly: Approve.

Josh Morse: Dr. Hearne?

Chris Hearne: Approve.

Josh Morse: Dr. Bramhall. It looks like you are muted.

Britt Reddick: So, I just, he will just need to enter his audio pin. And once I see that is in there, then I will unmute him, and he will be able to speak. So, it might just be another moment.

Josh Morse: So, John, we will get your vote when we have audio connection with you. Thanks. OK. So, the next item on the agenda is, let me switch back. The final coverage decision for whole exome sequencing. Christine, are you ready to show this information?

Christine Masters: You're looking for the wording on the decision?

Josh Morse: That's OK, Christine. I'll project it.

Sheila Rege:: Yeah. That would, that would help, just be . . . this is Sheila, sorry, speaking.

Britt Reddick: This might be a good moment to test committee member, Dr. John Bramhall's, audio. I have unmuted you. Are you able to speak?

John Bramhall: Yes. Can you hear me OK now? This looks like it's connected now.

Britt Reddick: Great. Thank you.

John Bramhall: Awesome. Thank you. So, just parenthetically, I approve the minutes as they were reported.

Josh Morse: Thank you so much. Thank you, Dr. Bramhall. OK. So, you should be seeing on the screen, I will scroll through. These are the meeting materials from the previous meeting business. They are available on the website, and I will project them, as well. This is for the whole exome sequencing decision. This was a draft decision that was finalized by the committee in the January meeting. So, it's been a few months. I apologize for the gap in time here. So, I'll scroll through this, and if you have questions, please let me know. So, the first document shown here shows the timeline for this review. It shows that this was originally selected back in March of 2018, and there were two comment periods in the selection process, 15 days and then 32 days. The draft key questions were then published. The final report and then the public meeting with the draft findings and decisions, and the original committee meeting for this topic was in November.

We received no public comment on the final decision. So, there are no comments to consider right now. When there are comments, these are the questions that the committee considers. I will read those now. This will be relevant to the next decision we look at. So, based on public comment was evidence overlooked in the process that should be considered? Or does the proposed . . . do the proposed findings and decisions, does the document clearly convey the intended coverage decision based on review and consideration of the evidence? So, this is the end of the committee's decision document. Then, the committee makes a final vote. Does the committee approve the findings and decisions document with any changes noted in this discussion? And if you do, you know, approve this, what I'm about to show you today, then this document will be final.

OK. So . . .

Sheila Rege: Josh, if I can ask. Can I ask a question?

Josh Morse: Of course.

Sheila Rege: Going back to that last screen, just in process for the committee members, if somebody wants to stop you at some point, should they raise their hand? Or type in a question? What is our preference as a committee?

Josh Morse: Brit, can you help with that?

Britt Reddick: It's probably easiest to just send a note through the question box.

Sheila Rege: OK. Does everybody know how to do that, going through the question . . . there is a question box on the top? If anybody has trouble with that, then speak up at some point. Does anybody . . . is everybody OK that if you want to stop it, if you can't figure out the question box then just speak up.

Kevin Walsh: This is Kevin Walsh. I don't see a question box on the Goto Webinar page or additional . . .

Sheila Rege: So, then you will speak up if you have any questions.

Kevin Walsh: OK.

Sheila Rege: OK. Sorry, Josh. I just wanted a process in case people had questions.

Josh Morse: No. That's great. Thank you. Very helpful. So, what is on your screen now is the draft language from the January meeting for whole exome sequencing. It's a very detailed determination from the committee. If you'd like to go through it line by line, please let me know, and I will just leave it here for now.

Sheila Rege: Given that there were no comments, and I know we spent a lot of time looking at this, we can discuss it further. Or somebody can make a motion for approval of the final coverage. So, this would be the final final on the whole exome sequencing.

Mika Sinanan: Motion to approve.

Kevin Walsh: Second.

Sheila Rege: Open for discussion. Please speak up if you have any discussion. Otherwise, we can go ahead and I am going to wait five seconds. We'll go ahead and vote on this. Josh.

Josh Morse: OK. We'll go through the roll call. John Bramhall?

John Bramhall: Yes. I vote to approve.

Josh Morse: Chris Hearne?

Chris Hearne: Approve.

Josh Morse: Janna Friedly:

Janna Friedly: Approve.

Josh Morse: Dr. Kleweno, I assume you abstain?

Conor Kleweno: Abstain. Yes. Thank you.

Josh Morse: Dr. Mischley?

Laurie Mischley: Approve.

Josh Morse: Sheila Rege?

Sheila Rege: Approve.

Josh Morse: OK. Seth Schwartz?

Seth Schwartz: Approve.

Josh Morse: Mika Sinanan?

Mika Sinanan: Approve.

Josh Morse: Kevin Walsh.

Kevin Walsh: Approve.

Josh Morse: Tony Yen?

Tony Yen: Approve.

Josh Morse: OK. It is nine committee members approve, one abstain. Thank you, very much. OK. The next item from the previous meeting business is the cell-free DNA prenatal screening for chromosomal aneuploidies. This was considered at the meeting on January 17th, 2020. The committee voted eight to cover unconditionally with two to cover with conditions. The draft decision is cell-free DNA prenatal screening for chromosomal aneuploidies is a covered benefit. This is the determination document. This is the overview of the timeline for this topic selected in 2018, considered at the public meeting on January 17th, 2020, and here for consideration as our final decision. There were three public comments received on this draft decision. They are listed here with the names and who these folks are representing. Two of them cited evidence. You'll see the letters here. These are all available in the meeting materials for your consideration. Dr. Rege, I'll turn it over to you [inaudible] related to these comments.

Sheila Rege: I'm sorry. You're not hearing me? This is Sheila Rege.

Josh Morse: Yes. There was a little gap there.

Sheila Rege: Can you hear me now?

Josh Morse: Yep.

Sheila Rege: Sorry. I was talking away, and nobody was hearing me. So, based on the comments, we had taken the decision that we would cover cell-free DNA prenatal screening for chromosomal aneuploidies for children and adults. Eight covered unconditionally. Two covered under conditions. So, do we need to revisit that? Or are we comfortable with that? And I will open it up for discussion.

Mika Sinanan: I read through the comments. My takeaway was that they were supportive of the unconditional coverage and the benefits of this technology to patients, especially rural patients, patients who otherwise might have to travel long distances to get other forms of evaluation. So, it supported the majority . . . the comments seem to support the majority of the committee's recommendation that it be an unconditional coverage decision.

Sheila Rege: Any other discussion? I'm going to wait five seconds. If not, then we will go to a roll call for voting to approve the final coverage determination that we had come up with at the last meeting. OK. I think we did a good job, as a committee. I think there was support with the comments. So,

we'll go for roll call on approving the final final coverage language. Josh, I'm turning it back to you.

Josh Morse: OK. Do you want to seek a motion and a second?

Mika Sinanan: I vote to approve.

Sheila Rege: Thank you, Josh. A second?

Janna Friedly: I second.

Josh Morse: Thank you. OK. So, we'll go through . . .

Sheila Rege: So, if there's no more discussion, we will go for, yeah. We'll do a vote.

Josh Morse: We'll do a roll call. John?

John Bramhall: Yes. I approve. Thank you.

Josh Morse: Thank you. Chris?

Chris Hearne: I approve.

Josh Morse: Janna?

Janna Friedly: Approve.

Josh Morse: Conor. I'm assuming abstention?

Conor Kleweno: Yes. Abstain.

Josh Morse: Thank you. Laurie?

Laurie Mischley: Approve.

Josh Morse: Sheila?

Sheila Rege: Approve.

Josh Morse: Seth?

Seth Schwartz: Approve.

Josh Morse: Mika?

Mika Sinanan: Approve.

Josh Morse: Kevin?

Kevin Walsh: Approve.

Josh Morse: Tony?

Tony Yen: Approve.

Josh Morse: Thank you. That is nine approve, one abstain. OK. That concludes the cell-free DNA topic from the previous meeting business. Thank you, very much. We will switch back to our agenda.

Sheila Rege: Here, you know, as we get the new topic on tinnitus, we're going to go in that order. We're almost on time. So, that's good. If we can hold our questions, because of the format until we come in with the question and answer session at 10:10, I think that may work best, but if you have to ask a question that would be hard to come back to, then you're going to either put a question . . . type a question thing there or speak up. So, we're ready. We're going to move onto the topic for this morning, tinnitus.

Josh Morse: OK.

Sheila Rege: Handing it back to the agency representative.

Josh Morse: So, presenting the tinnitus topic is Dr. Zerzan. Judy, can we test your audio?

Judy Zerzan: Yes.

Josh Morse: I can hear you. Great.

Judy Zerzan: Good morning.

Josh Morse: And I will switch control to you. Do you wish to present your own slides?

Judy Zerzan: Yes. I am prepared to present my own slides, which are what you should all have.

Josh Morse: OK. I'm switching the screen to you.

Judy Zerzan: Okie-doke. Are they there?

Josh Morse: Yes. They are.

Judy Zerzan: Perfect. Good morning, everyone. This is so fancy. I miss seeing your faces, and I am pleased to chat about our first topic of the day, which is tinnitus, noninvasive, nonpharmacological treatment.

So, this will be the order of my presentation, talking about the clinical questions, our policies, utilization, evidence summary, and recommendations from AMDG.

So, what is tinnitus? Tinnitus is the auditory experience of ringing, buzzing, roaring, hissing, some sort of noise in the ears. The word of the day for all of this is heterogeneity. The word of the day could also be variability, because both tinnitus itself is quite variable in presentation and the studies I am going to summarize today are super variable and very different. So, it is a little bit hard to compare things. So, tinnitus can be either subjective or objective. Objective is when there is an anatomic feature that's causing the tinnitus. That is not the subject that we'll be addressing today. So, it is more the subjective side sensation of tinnitus. It can be constant or intermittent. It can be pulsatile or rhythmical. There are a variety of sounds. It can be in one or both ears. The NHANES study, which follows people longitudinally over the last couple of decades. It has varied somewhere between 7 to 14% of the U.S. Population is estimated to have problems with tinnitus at least once. The main problem with tinnitus is that it is quite a bothersome symptom. It is very difficult to treat. So, as a result of that there can be a number of comorbidities that either develop because of the tinnitus or perhaps are amplified from the sound, but include depression, anxiety, hearing and concentration difficulties, and sleep disturbance.

The clinical questions are, what is the effectiveness of noninvasive, nonpharmacological therapies for the treatment of bothersome, subjective tinnitus? What are the harms associated with those therapies. What are the costs and cost-effectiveness of these sorts of treatments? I just want to pause here to say that we are not talking about hearing aids, although some tinnitus can be caused by hearing loss. Hearing aids can be an effective treatment. It's a little bit difficult, because some of the studies excluded people with hearing loss. Others included them. Some of the studies included hearing aids, as part of the therapy. Most did not, but we are not talking about hearing aids for this review. Then, we are also not talking about pharmacological treatment. So, there are a number of drugs that can be used to treat this condition with, again,

variable degrees of success in that, but those are not in scope for this review.

The agency medical directors' concerns for safety was medium, for efficacy was high, and cost was high.

Continuing this, there are four different types of treatment that are covered in this review. First is sound therapies. So, sound therapies, there are 72 different kinds of sound therapies that are approved by the FDA. These include things like sound generators, sound maskers, and altered auditory stimuli, hearing aids that include sound masking or sound generating noises. It's a variable of different kinds of therapies. The second type of treatment included is repetitive transcranial magnetic stimulation. This is used for a variety of disorders and is used in tinnitus. It's for delivery of multiple electromagnetic pulses to the scalp. Third is cognitive behavioral therapy, which is a psychotherapy approach to reduce the distress associated with tinnitus. Then finally, the last one is tinnitus specific therapies. So, this is tinnitus retraining, tinnitus masking plus counseling. Some of this involves music or total sound. So, again, this is another sort of bucket of variable intervention. I should also mention that repetitive transcranial magnetic stimulation is not FDA approved for the treatment of tinnitus. It is FDA approved for other conditions.

So, the first State agency policy, sound therapies, L&I covered sound masking. It's not mentioned in other policies. The repetitive transcranial magnetic stimulation is not covered. Cognitive behavioral therapy is covered in general. There isn't a specific nod for tinnitus, but in general, cognitive behavioral therapy can be covered for a variety of conditions. Then, tinnitus-specific therapies, there is either no policy or it's not covered.

This is pretty similar to other carrier's coverage. This is a chart that is a little odd to look at. If there is a blank space, that means there is no mention of either coverage or non-coverage. So, down the left of the chart is different carriers. Along the top are the four types that we looked at, and also a column for there is just no policy. So, for Medicare and Premera, there is no policy. The other carriers, you can see the NC cover and noncovered. So, other carriers have specific therapies that might be called out as noncovered with no nod as to whether other things are covered or not. Then, CIGNA is the only insurer that calls out the coverage for tinnitus for cognitive behavioral therapy.

Looking at the utilization, this first slide is Medicaid, and the top chunk is the fee for service population, and the bottom chunk is the managed care population. It's divided into fiscal years for the last three years. So, 2017, 2018, and 2019 with a final column being sort of the overall, um, average or use over that time, and the number of unique individuals. So, fee for service is smaller population, as reflected in those. We looked, and pulling the claims, all claims have tinnitus in the first diagnosis space. Because this is a variety of interventions and some of the codes, including cognitive behavioral therapy are hard to tell what it's used for. We just looked at things with tinnitus in the first diagnosis state. So, this may be a little bit of an undercount if things are being used for other things. Or if hearing loss, for example, is put in the first space and tinnitus in the second space. That would not be captured here. So, looking at the number of days where people had claims. For the Medicaid fee for service population, it's around 200-ish or a little over. Most people had an average of almost two days of treatment with the maximum number of treatment days in a year ranging from 5 to 10 in the fee for service population. The paid amount you can see there has slightly increased over time, and the average payments per individual have also been increasing over time a slight bit for the Medicaid fee for service population. The managed care population is a much larger population. So, not surprisingly, the number of people with at least one procedure or service for tinnitus is higher, just under 2500 people. The number of procedures that happened are also higher, although the number of average treatments in a year is about the same, just under two. The paid amount here is much higher, although it has not grown over time. It's relatively flat. The average payment per individual are smaller than on the fee for service side. Here's the utilization for Washington L&I and also UMP. So, for worker's compensation claims per year, you can see that tinnitus is more common in the Medicare population, which isn't really surprising. There is a similar number of average procedures over the course of a year in terms of days, but more days per individual, and total payments are also much higher than the other population, which again isn't surprising given that Medicaid has a lower reimbursement. Then, that second chunk is the public employees and UMP. The individuals with at least one service for tinnitus in the first line has been growing over time, just a little bit over 700 individuals, and the paid amount grew a little bit from 2017 to 2018, but otherwise has been fairly stable.

So, diving into the review, um, our reviewers found five practice guidelines. I only put four here, because one of them was from the VA, and it was focused on traumatic brain injury. Tinnitus can be a feature of that, but it didn't mention specific tinnitus therapies. So, I left that out of

here. All of these guidelines are of moderate quality, and you can see that many are from other countries. I put across the top the four different types of treatment that this review looks at. For Sound Maskers, either they were not mentioned, and there was no recommendation. The American Academy of Otolaryngology said that Sound Maskers could be an option with something like shared decision making for people to see if that was an option that was right for them. The rTEMS therapy, two of the guidelines were against using this for tinnitus. That last one, which is an association that uses rTEMS, said that there is a possible but partial intransient benefit to rTEMS to helping with tinnitus symptoms. CBT in three of the four were recommended or strongly recommended, as a treatment for tinnitus. Then, tinnitus specific therapies, only the Germany guideline recommended against covering these types off therapies for tinnitus.

So, the evidence summary back to there was a lot of heterogeneity and a lot of variability in these studies, but we found 59 studies that were recorded in 69 articles over that time span. All were rated as low or very low quality. In terms of effectiveness, these studies use a lot of different types of instruments. So, the review looked at three different domains of effectiveness. Tinnitus distress and disability, psychological measures, including depression and anxiety, and then quality of life. You can see that the number of instruments used across all of these studies was quite numerous. I also added here some of the instruments have a defined clinical meaningful difference, but most do not, which, again, I think makes this body of evidence pretty variable, hard to compare, and hard to look at.

So, next, am going to dive into each of the four therapies and talk about their effectiveness, and talk about what we found, and look across the domains of our clinical questions, in terms of effectiveness, harms, and costs. So, on sound therapies, all of the studies were very low quality. About half were industry funded, and the sample sizes ranged from 30 to 136 people in them, which leads to a lot of variability and a lot of uncertainty about the results of these trials. So, for effectiveness in the domains of tinnitus distress and disability. There was either no benefit or unable to determine the benefit. In terms of psychological measures, there was no benefit or unable to determine the benefit. In terms of harms, there were no harms found in these studies. The cost was not reported.

Next, the evidence on repetitive transcranial magnetic stimulation. These studies were all either low or very low quality, so slightly better than the last one where there were some studies that were low quality.

The study size ranged from 6 to 153, and all included a sham control, but it was variable in how that sham control was set up, and some question of whether people who were getting the sham therapy knew which one they were getting. There were some trials that were a crossover. So, you either had the sham treatment first and then the real one, or the real one and then the sham treatment. In terms of effectiveness, for tinnitus distress and disability, no benefit was found. In terms of psychological measures, no benefit was found. In terms of quality of life, no benefit was found.

For the harms, it was unable to determine. Most of the studies recorded no harms. However, three studies described some adverse events, but they didn't report them by group. Then, cost is not recorded.

Third is the evidence on cognitive behavioral therapy. These studies included both therapist led CBT's and also some interventions that were either internet or book led. So, sort of a self-study CBT. All were low quality evidence, except they were very low on quality of life. So, in general, these were a little bit better studies. There were 13 of the studies in here that were either group therapist led or individual therapist led. Then, there were nine internet or book self-guided ones. That internet and book self-guided ones, the results were a little bit less strong in terms of a comparison between the two, but still there. The CBT interventions included relaxation and coping strategies with the duration of six studies being six weeks or less and ten studies being a little bit longer in the 8 to 12 week range. The study size ranged from 20 to 304, and some of these studies had significant differences and some didn't. So, again, even though the overall the evidence in this category has the most strengths, there was still a fair bit of variability. So, in terms of the effectiveness, there was a benefit for tinnitus distress and disability found that CBT helped with symptoms of tinnitus. Similarly, there was a benefit for psychological measures and for quality of life, there was no benefit found. This was only looked at in a book led group. There were no harms. Costs were not reported.

Then, finally, the evidence on tinnitus specific therapies. These studies were mostly very low quality, and a few low quality studies. The total sample size ranged from 39 to 492, but most were under 100 participants. The largest trial of 492 was usual care, defined as a hearing aid either with or without a sound masker versus tinnitus retraining with cognitive behavioral therapy. That tinnitus retraining with cognitive behavioral therapy was better in nearly all outcomes measured. Tinnitus retraining therapy was, again, super variable in these studies. Some used sound maskers. Some didn't. Some used music based therapy. It was

sort of a number of different things, as I mentioned earlier. Eight studies had statistically significant effects, but the significance of that clinically and the magnitude really varied by the measurements, the timepoints, in the comparison group. So, it was quite difficult to tell. Although in general, in terms of effectiveness for tinnitus distress and disability, there was a benefit. In the studies, it also used CBT principles. So, if you use some tinnitus retraining therapy plus CBT, or CBT like kinds of things, there was, in general, a benefit, and that wasn't seen in just the tinnitus specific therapy arm. For psychological measures, quality of life, harms, and costs was all unable to be determined.

So, the AMD recommendations for you to consider, for sound therapies, noncoverage with the note that our hearing aid coverage policy doesn't change. If hearing loss is present, absolutely hearing aids would be provided. For repetitive transcranial magnetic stimulation, noncoverage. For CBT, coverage. I think this may be a place that we could perhaps help people with tinnitus if we got more CBT being used for people with this disorder. Then, finally the tinnitus specific therapies noncoverage, because it seems that most of the studies where there was a benefit, there was also CBT principles involved, and that may be what pushed the benefit in those folks.

So, that is all for me, and I will pass this back over if I can figure it out, back to Josh.

Sheila Rege: While that's happening, Judy, thank you. Thank you, so much. That was a good summary of things. Your recommendations are available. Everybody has access to what's being presented also, because Josh or Brit had sent a PDF with a link. All the committee members should have that. We are at the time for public comment. I don't think we have any scheduled. Josh, I'm going to turn it over to you for the telephones or the public comments and how you want that to occur.

Josh Morse: OK. So, if you are attending the meeting and would like to make a public comment, we would ask that you please raise your hand and let us know. And we can work to unmute you. I am scrolling through. It looks like Jana Wiley has her hand raised. Brit, can you help unmute Jana Wiley.

Jana Wiley: Thank you, much. Can you hear me clearly?

Josh Morse: Yes. I can hear you. Would you like to make a public comment on the tinnitus topic?

Jana Wiley: Yes. I would. My name is Jana Wiley. I am a registered nurse and a senior acupuncturist here in Olympia, Washington. I have been personally seeing tinnitus patients for several years now, all based on referrals from Kaiser Olympia ENT department. All prescreened before . . .

Sheila Rege: Jana, Jana? If we, we . . . I forgot to mention the process. Your name, your conflicts, especially disclosing if anybody has paid for your time or travel here. And everybody has to go through that. So, if you'll just categorize that again for us. I'm sorry. Maybe I should have mentioned that before.

Josh Morse: And in addition, we ask you to limit your comments to three minutes, please.

Jana Wiley: I'll do my best. My name is Jana Wiley. I am a registered nurse and senior acupuncturist in Olympia, Washington. And I have no conflicts, but I did want to report that I have been seeing lots of tinnitus patients for several years now, all referred by Kaiser Olympia ENT department. We are seeing . . . and I just spoke with them on Monday regarding results that they've accumulated over years. This is a diverse population. Veterans, young, middle aged adults, seniors. They are seeing that as they refer patients, about three out of ten patients improve to varying degrees, some with 100 percent improvement. Some people have actually had some improved hearing loss situations happening, too. As far as the guidelines you're talking about, costs and harms, etc., the only harms that I can report for acupuncture is that generally the treatments are very well tolerated in general. People are surprised that it doesn't hurt. There was one small bruise in one case of 5 mm. This is over two years. Rare transient sharps with some patients with needle insertions that would resolve. Costs range between \$75 and \$105 per treatment. Generally improvements in 8 to 16 visits, some in just one to three visits. I know there was one person who was severely and profoundly impacted whose tinnitus resolved in one treatment using [inaudible] injection therapy [inaudible], and it resolved for eight months. She came back eight months later for another treatment that resolved. All treatments included addressing the comorbidities that you mentioned in this presentation. [inaudible] auricular therapy and was very helpful. Patients recorded improvements overall, including comorbidities. The impression was quite helpful for all. Some patients come back even a couple years later just to make sure that their tinnitus let's say muted or gone. So, I just wanted to record that, because I didn't see any mention whatsoever on the agenda items of this particular treatment. I do know that that [inaudible] practiced by the Veterans Administration have been

used. I also wanted to note that occasionally, I found that electro-microcurrent stem therapy utilizes acupuncture points with multiwave patterns, which could be exceptionally helpful. Several cases resolved right there on the treatment table. I am open for questions, but I do have another meeting in less than 30 minutes.

Sheila Rege: Thank you for the comments and for being so concise. Any other public comments?

Britt Reddick: I see Jianfeng Yang. I will go ahead and unmute you now so you can speak.

Sheila Rege: Again, name, conflicts and disclosing. Thank you.

Jianfeng Yang: This is Jianfeng Yang. I have Eastern Medicine practice since 1970. I have practiced the [inaudible] Medicine for about 50 years. In my clinic I train a lot of tinnitus patients. In my personal experience, if the tinnitus is caused by some stress and anxiety, or some other emotional impact, [inaudible] herbal medicine can work very well. Of course, we find a lot of patients who are aged people whose age is after 70. Their tinnitus is tougher to treat, but the tinnitus below 60, their tinnitus can be treated very well by acupuncture and herbal medicine. Of course, and also we have used like music therapy or sometimes just consultation, talk to the patients. Sometimes, their tinnitus is caused by stress, financial stress or work stress, or relationship stress. If we can talk and combine with herbal medicine and acupuncture. Sometimes, it works very well. The cost is not expensive at all. Like, I treat some tinnitus patients ten times, costs about each time, like, \$85 to \$110, depends on how long by the patient takes and needs to treat. So, in general, acupuncture and herbal medicine and also [inaudible]. A lot of physical therapy of Chinese medicine can work very well for this kind of patient. I hope this can be taken into consideration, because there are no side effects. There are no side effects. It works well for tinnitus patients. Thank you.

Sheila Rege: Thank you, very much, for that perspective. Any other public comments?

Britt Reddick: I'm not seeing any other hands raised and no questions in the question box yet. So, thanks.

Sheila Rege: OK. So, it's 9:02. If you would keep that open. So, please interrupt if somebody comes in and wants to ask a public question. So, keep an eye on that. Then, we will go . . . I don't know, Leila, if you're ready. We . . .

Leila Kahwati: Yeah. I'm ready, Sheila.

- Sheila Rege: OK. So, we're going to do the evidence report. Go ahead.
- Josh Morse: Perhaps now is a good time to introduce Dr. Rubinstein, as well.
- Sheila Rege: Yeah. In fact, I said something to Dr. Rubinstein, but if you would like to make a comment, Dr. Rubinstein? Your background?
- Jay Rubinstein: So, my name is Jay Rubinstein. I'm a faculty member at the University of Washington. I run Virginia Merrill Bloedel Hearing Research Center. I'm a clinical neuro-otologist in adults and children. I also run a laboratory that looks at both the development of vestibular prosthetic devices, as well as improvements in cochlear implants. I have an extensive history in the past in collaboration with Rich Tyler, who was the clinical expert on the report, of looking at the effects of electrical stimulation on tinnitus and have maintained a significant interest in tinnitus given the fact that I still see large numbers of patients who suffer from it.
- Sheila Rege: Great. Thank you, and welcome to the committee. We really appreciate your perspective treating this disease and having an expertise in it. Any other comments? Is anybody on the phone line?
- Jay Rubinstein: I have further comments on the report, itself, but I think it's probably better to save those until after it's presented.
- Sheila Rege: Correct. Yeah. So, we can kind of hear that and then what we're gonna do, Dr. Rubinstein, if it's OK, we'll do a break. Then, we have the committee discussion. We could do that, but if you have a burning question during the report, please feel free. We have the agency director and our evidence report expert present while [inaudible].
- Jay Rubinstein: Terrific.
- Sheila Rege: Anybody else on the phone line for public comment before we get started on the evidence report? OK. Let's go to the evidence report then. Thank you.
- Leila Kahwati: Hi, everybody. This is Leila Kahwati. Can you all see the slides? Are they showing in the full screen view?
- Josh Morse: Leila, they are not in the full screen view. I had the same experience. If you change, yeah, swap. There you go.
- Leila Kahwati: yeah. OK. Is that right?

Josh Morse: Correct.

Leila Kahwati: OK. Great. Perfect. OK. Good morning, everybody. On behalf on the Research Triangle Institute University of North Carolina Evidence Based Practice team, I'm happy to discuss the evidence report for noninvasive, nonpharmacological treatment for tinnitus. You can see our team listed here on the first slide.

I'm gonna go basically through a bit of background, though Dr. Zerzan covered a lot of it. So, I may go a little bit fast through some of it. We'll talk a little bit about our methods for compiling the health technology assessment, go through the results and conclusions. Then, we've designed this as a very . . . because of the heterogeneity that Dr. Zerzan mentioned, this is a fairly high level presentation, but you all have the full evidence report. If there are specific places you want to dive into specific details, there certainly should be time at the end of the presentation to do that, as you request.

Onto just a little bit of background. As Dr. Zerzan mentioned, tinnitus refers to the experience of ringing, buzzing, roaring, and hissing in the ears. The NHANES estimates the prevalence of between 7 and almost 15% among published studies. The kind of tinnitus that we're talking about today, as Dr. Zerzan mentioned is subjective to this. So, it's typically idiopathic or related to sensorineural hearing loss. It's not the tinnitus that results from underlying tumors or vascular lesions. There is not really a cure so to speak for this kind of tinnitus. Treatment is really aimed at reducing the perception and/or the reaction to the tinnitus noise. Due to the heterogeneity of the condition in terms of its etiology and how people experience tinnitus, there really is no one treatment that might be universally effective.

So, for the purposes of this health technology assessment, we considered four broad categories of intervention. So, we prefer to use this as our organizing framework for the evidence report. So, we acknowledge and recognize that there may be other therapies, other interventions that crossed these boundaries or don't fall entirely around these boundaries, but for the purpose of this review, this is how we structure things. So, the first category are the sound therapies. These are interventions that aim to use sound to either distract or decrease the perception of tinnitus, and there are three main types. So, there are sound maskers. So, these are devices that introduce sound using ambient or ear level devices, as is shown in the picture on the left of the screen. This sound is designed to mask the tinnitus sounds or distract the user, or a little bit of both. The

second kind of category that falls into this bucket are devices that alter the auditory stimuli. So, this is the use of music or other, like, nature sounds or pleasant sounds that are spectrally altered to emit noise at specific frequencies, often matched or designed to ask the tinnitus frequency that might be being experienced by the individual. Then, the third category of sound therapies are hearing aids that have sound generating or sound masking features. So, these are devices that provide the traditional application found in hearing aids, but they have additional sound masking features above and beyond application to try to address the tinnitus. These devices are typically only used in people who have both hearing loss and tinnitus.

The next category that we evaluated is repetitive transcranial magnetic stimulation, or rTMS. So, rTMS is a type of noninvasive neuromodulation intervention. With this intervention, an electromagnetic coil is placed next to the scalp, as seen in the picture on the right of the slide. Multiple pulses are emitted that are targeted to specific brain lesions. In the case of tinnitus, it's typically the temporal or the temporoparietal region. The intervention itself consists of multiple sessions of these pulses delivered over the course of days to weeks.

Next category is cognitive behavioral therapy. So, this therapy uses principles of cognitive restructuring and behavior modification to promote changes that reduce the distress associated with tinnitus or increase the person's ability to cope with the distress. So, as you all know, cognitive behavioral therapy could be used in a variety of conditions. So, tinnitus is just one of the many things that it can be used for.

Then, lastly, we have the category that we have termed for the purposes of the report, tinnitus specific therapy. So, these are interventions that often combine components of psychological or other therapies, usually sound therapies, as part of a multicomponent intervention. There are several examples of these types of interventions that kind of have name brands associated with them. So, tinnitus retraining therapy is one of those. Neuromonics tinnitus treatment is another. Tinnitus activities treatment, and then tinnitus masking counseling. So, we, for the purposes of the report, consider them as they are separate from CBT or sound therapies, because they sort of mix different components together.

In terms of the regulatory status Dr. Zerzan mentioned, as of last fall, there were 72 FDA approved sound devices. RTEMs does have FDA approval for the treatment of treatment resistant depression, acute

migraine headache, and obsessive-compulsive disorder, but it's not approved treatment for tinnitus. Finally, the State of Washington selected this topic for medium concerns for safety and high concerns for efficacy and cost.

So, moving onto our methods for the HTA. We have three key questions. The first question was around the effectiveness of these interventions for the treatment of bothersome, subjective tinnitus. The second key question was around safety. Finally, the third key question was around cost and cost-effectiveness of these treatments.

This slide it depicts and excerpt from our study selection criteria. Let me just move. I've got the, sorry. This includes . . . the way we scope the . . . what's going to be included or excluded from the evidence report. I'm not going to read every row to you, but I do want to point out a couple of key scoping decisions that were made early on in collaboration with the state to help you understand sort of what is in the report and what may not be in the report. So, first, we focused only on the four categories of the interventions that I previously described, the sound therapy, rTEMS, CBT, and tinnitus specific therapies. We did not include studies of other noninvasive neuromodulation treatments, psychological therapies other than CBT, or complementary and alternative medicine type therapies, such as acupuncture. We required studies to have a comparator group. This could be no treatment, usual care, weight loss control, delayed treatment, or sham treatment. We did not include active treatment control groups, as comparative effectiveness was really outside the scope of the report. For the key question on effectiveness, we required the use of psychometrically validated measures. So, for study designs, we limited selection to randomized control trials, or controlled trials. We did allow cohort studies with concurrent comparator for harms, but in fact, we didn't actually identify any cohort studies.

In terms of our methods for conducting the HCA, we searched typical evidence sources through last September. We conducted individual study risk of bias assessment on all included studies. So, this refers to . . . some people refer to it as study quality, but that gets confusing, because that's the terminology also used for grade for rating the bodies of evidence. So, we tried to use the term risk of bias to reflect the methodological robustness of the individual studies that are included in the review. We rate them as high concerns for bias, some concerns for bias, or low concerns for bias. We used calculated effect sizes and effect measures when the data was available and not reported by the study authors in the papers. Finally, we used a modified grade approach to

evaluating the certainty of the evidence. I wanted to say a little bit more about that on the next slide.

This slide is just a reminder of how grade words to evaluate the certainty of the evidence. For this report, we assessed outcomes in five domains. So, we looked at tinnitus distress and disability, psychological measures like anxiety, depression, and we also included sleep in that category, quality of life, adverse events, and cost outcomes. So, each outcome domain for each intervention and comparator is evaluated with grade. So, the bodies of evidence that are comprised of randomized trials, they start at a high certainty rating. Then, we downgrade that rating for concerns based on consistency of the evidence, precision of the evidence, which has a lot to do with sample size, the directiveness of the evidence, and study limitations, which is essentially risk of bias. So, bodies of observational study evidence, for example, cohort studies, would start at a low certainty and then can be downgraded for those same concerns, but they also could be upgraded for other features. I mentioned earlier that we used a modified grade approach. With a strict grade approach, every outcome at every various timepoint in followup is typically evaluated with grade. However, in this review, studies do so many different instruments and at so many timepoints, it did not really make sense to grade them all individually. Thus, we took an outcome domain approach and graded similar outcomes in a more aggregated way, and I'll say a little bit more about this on the next slide here.

So, on this slide are all of the various tinnitus specific distress and disability instruments that were used across the body of evidence that we identified. So, instead of rating the body of evidence for each of these measures individually, we basically graded all studies reporting any of these measures for each specific intervention and comparison. That's how we got to our certainty levels. So, even though there were many different instruments used to measure tinnitus distress and disability, I have noted the ones that were used most commonly at the top of the list. So, most of these, except for the visual analog scale, most of these are multi-item instruments. Some are longer than others. They include very similar things. Many of them have items that focus on measuring the loudness or the severity of the symptoms. Many of them also include items focusing on measuring the level of distress or impairment or disability caused by the symptoms, or the reactions to the symptoms, or the ability to cope with the symptoms, or the acceptance of the symptoms. So, even though they are all slightly different, some of them have more of a focus on the coping and the acceptance. Others have more focus on the distress and disability. Some of them, like the visual analog scale measures, are really just measuring pure loudness or pure

severity or an amount of annoyance. Table 3 of the full report offers a lot more details about these measures if you want to dig in. Some of them, as Dr. Zerzan mentioned to you, have minimally clinically important differences defined, but most of them don't.

Now, moving on, this is where I'm going to present a fairly high level of the findings. So, at the end, if there are specific things you want to dive into, we can certainly go that direction. So, first is a quick summary of our overall search yield where we screened just over 3000 titles and abstracts and ended up identifying 59 eligible randomized trials for this review. You can see on the slide how the breakdown looks by intervention type at the bottom of the slide. Some studies did report on more than one eligible intervention. So, if you were to add those numbers up, they won't add up exactly to 59, because they contribute to more than one comparison.

So, this is the evidence map with the topline summary of findings from the review. So, this is the sort of take home method. So, to orient you just a bit, along the left vertical axis are the three research questions. So, effectiveness, safety, and cost. Within effectiveness, we have studies providing evidence on three outcome domains. So, tinnitus distress and disability, psychological measures, and quality of life. The shapes within the grid represent the different bodies of evidence. So, the rectangles represent the sound therapies. The diamonds represent the rTEMS interventions. The circles represent CBT interventions. The triangles represent the tinnitus specific therapies. The number of studies in each body of evidence is represented by the K= number. Then, the number of participants for each body of evidence is located within each shape. That's the N number. Along the X-axis is the direction of effect. So, the shapes that are located over in the left most third of the grid are interventions that are more effective than the comparator. The comparators in these bodies of evidence are either no treatment, sham treatment, or delayed treatment. So, it's not comparative effectiveness. It's regular just plain effectiveness. The bodies of evidence that landed in the middle third of the grid are interventions that were no different than the comparator. The bodies of evidence in the right third of the grid are ones for which we were unable to determine a direction of effect. That is typically because there are inconsistent findings, mixed findings, or just not a large enough sample size to draw a precise enough estimate. Then, finally, the color of the shape represents the grade certainty level. So, red means we had very low certainty about that body of evidence. Orange means low certainty. As you can see, we didn't have any bodies of evidence that had moderate or high levels of certainty. That certainty level reflects not just risk of bias, but again, it reflects things like

precision, the consistency of the effect across studies, and directness of the measures used.

As you can see from the summary slide, the only interventions that have evidence for effectiveness in terms of tinnitus distress and disability are the CBT interventions and the tinnitus specific therapies. CBT was also effective in terms of psychological measures. For the sound therapies, the rectangles, we have several categories of interventions, some of which showed no difference from comparators, and others that had mixed effect. So, we weren't able to draw a definitive conclusion. That's why you see some of these rectangles sort of straddling the no difference to unable to determine sort of boundary. There did not appear to be any difference in safety outcomes for sound therapy. So, we were able to make a call on that. Then, for the rTEMS interventions, so these are the diamonds, we found no difference between active rTEMS and comparator groups with sham rTEMS in studies for any of the effect and its domains. The findings for rTEMS related to safety were mixed. Thus, we were unable to draw a conclusion about that. Lastly, we identified only one study that reported any cost outcomes. This was for a tinnitus specific therapy. The results suggested no difference in cost, but I will mention those results were very imprecise.

So, I'm going to go into a little bit more detail for each of the categories of intervention. So, I'm gonna start with CBT, because that's where we have the most robust evidence. This slide is an overview of the 21 trials that evaluated CBT. Just to orient you to the slides, the very top box, you can see the years over which these studies were published, so 1996 to 2018. You can see the range of sample sizes included in the studies and the duration of studies, which in this body of evidence was up to six months. Below this top box are a number of other study characteristics that might be of interest to you. I'll just mention a couple of them. First, these interventions fell into two sets of studies. There were 12 studies that used what we defined as therapist led interventions. So, these were interventions delivered either in person or over the telephone to individuals, or through an in-person group-based therapist led session. The second category of interventions were what we called self-directed or self-led interventions. So, these were CBT interventions delivered primarily over an online or internet platform, or through the use of a book or a manual that was provided to participants. Some of the self-led interventions did include some contact from a therapist, like a weekly email or a quick phone check-in, but the interventions, themselves, were primarily designed to be self-led interventions. There was one study that included both a therapist-led and a self-led study arm in addition to a control arm. So, that sort of is counted in both. Secondly, I wanted to

say something about the control groups that were used in these studies. The majority used a weightless control group, which is essentially delayed treatment. The drawback of this design is that the intervention can't be blinded. The other studies used an intention control group. This means that the control group got some or minimal contact, such as access to information resources or access to an online discussion forum, but they did not get the active ingredient of the intervention, specifically the CBT component. Then, a couple studies used both weightless and intention control groups. We did notice a small attenuation of effect in the intention control groups when you compare them to the effect sizes measured when using a weightless control group.

So, here is the grade summary of findings for the CBT interventions. The top row is the 13 therapist-led interventions. As you can see, we graded the evidence as low certainty for a benefit of the intervention on measures of tinnitus distress and disability, and for benefit on psychological outcomes, like, depression, anxiety, sleep. We also graded the evidence as low for no harm for the safety outcomes, but as you can see, this body of evidence only had three trials that contributed to it. The bottom row of this table is for the eight self-directed or self-led CBT interventions. As you can see, we graded this evidence as low certainty for benefit for tinnitus distress, disability, and psychological measures, but very low certainty for no benefit and quality of life. Again, that particular body of evidence only had two studies. No studies in the self-led interventions reported on any kind of safety or adverse events outcomes.

Let me give you just a little bit more detail on the CBT intervention. This really is the only category of intervention that demonstrates a benefit. It does, as Dr. Zerzan alluded to, it gets a little messy when you start scratching below the surface, because of the different measures and the timepoints used by the studies to report the effects, but first let me tell you a little about the therapist-led interventions. So, for tinnitus distress and disability measures, we had seven studies that reported outcomes using the tinnitus questionnaire. This was designated as the primary study outcome in four of those seven studies. The effect sizes in three of the studies that reported using effect sizes ranged from 0.81 to 0.95. If you recall, effect sizes are a standardized measure that basically takes the absolute mean difference between the intervention change and the control change. Then, it divides it by a standard deviation. So, it allows you to compare the size of the relationship, or the size of the effect, across studies that might use different instruments to measure the same concept. In general, an effect size of 1.2 or more is considered very large. Effect size of 0.8 is considered large; 0.5 is considered medium; 0.2 is

considered small. So, 0.81 to 0.95 would be considered a large effect size. All but one of those four studies also reported other measures of tinnitus disability and distress, including a visual analog scale for a specific component, such as, like, loudness, annoyance, or distress. Tinnitus disability questionnaire, and the tinnitus reaction questionnaire. Three studies reported using the tinnitus handicap inventory. This was the primary study outcome in one of the studies. The effect size is reported by the two studies reporting this effect size was 0.38 and 0.98. These studies also reported other measures of tinnitus disability and distress, the tinnitus function inventory and the tinnitus acceptance questionnaire. One thing I will say is that most studies did report more than one tinnitus distress or disability measure. In many but not all cases, the finding on the measure that was designated as the primary study outcome was confirmed by other secondary outcomes not consistently, but in general more times than not the findings were similar. Lastly, three studies reported measures other than the tinnitus questionnaire, the tinnitus handicap inventory. The tinnitus reaction questionnaire was reported in one study. These were studies that did report effect sizes. They only gave us the absolute mean differences. There was a 7.8 to 10.3 larger point improvement for the intervention group compared to control. This range was significant, statistically significant in one study but the significance was not reported in the other two studies. Just for context, the CRQ score ranges from 0 to 104. It does not have a minimally clinically important difference identified, but a difference of 7.8 to 10.3 corresponds to roughly an 8 to 10% difference between groups.

In terms of the self-directed interventions, we had four studies that reported using the tinnitus handicap inventory. This was the primary study aim in two of those studies. The effect sizes ranged from 0.56 to 0.70 across those four studies. Those were statistically significant effect sizes. In three of the four, they also reported larger improvements on other tinnitus measures that are listed there on the slide. Three of the studies reported using the tinnitus reaction questionnaire. It was the primary aim in two of those studies. One study reported an effect size of 0.28 at six weeks followup. This was not statistically significant. Another study reported a 12.5-point larger improvement on the CRQ. That was statistically significant, but when they reported the percentage that achieved a clinically meaningful reduction on the instrument, it was 13% in the intervention group versus 3% in the control group. That finding was not statistically significant. That particular study only had a sample size of 117, which may be contributing to the imprecision there. Then, one study reported no significant difference at six weeks but didn't actually give us the actual values on the instrument. I won't read through

the last two. There was one study each that reported the TFI and TRQ. Again, the overall sort of conclusion is that CBT appears to be effective at reducing tinnitus disability and distress. We did not really see much difference between the therapist-led and the self-led interventions, but overall, there does seem to be a signal that these can be effective.

Moving onto tinnitus specific therapies, this is an overview of the evidence base for these therapies. There were ten trials. You can see they were conducted between 2004 and 2017. Again, these are mostly studies conducted up to six months long. This particular body of evidence, none of the ten studies did enroll participants with hearing loss. In fact, one of the ten actually required hearing loss to be enrolled in the study. The treatment the comparator groups used in this category, two used usual care, six used weightless control, and two used attention control. I'm going to say a little bit more about the actual interventions used in this body of evidence. So, when we looked across this category, they sort of fell into two categories. So, there were seven studies of the ten that included sound therapy components. So, they had some kind of counseling or psychological component that was paired with a sound therapy component. The sound therapy component may have been a little different across the studies, but it definitely was included. The other three studies, were not particularly well described. We could not verify that they actually included any sound therapy. So, they may have mentioned sound therapy to participants, but we could not verify that participants were actually issued sound therapy devices or that they were used. So, we synthesized this evidence separately. So, for the group of studies that actually used sound therapy as part of the tinnitus specific intervention, this might be tinnitus retraining therapy or neuromonics. We found there to be low certainty of a benefit on measures of tinnitus disability and distress. So, that's the very top row on the slide. We were not able to determine a benefit with respect to psychological measures, quality of life, and we did not have enough information to determine safety and cost outcomes, certainly levels for that. In terms of the evidence base for the tinnitus specific interventions that did not use sound therapy, we did have low certainty that there was a benefit for those, as well. As Dr. Zerzan mentioned earlier, what we can't really tell from these bodies of evidence is how much of the benefit is really due to the psychological part of the intervention versus the sound therapy as the intervention. So, I think you may just want to consider that, as you consider the coverage criteria that she proposed.

In terms of the sound therapy interventions, there were 11 trials that fell into this category. Some of these went up to as long as one year. Of the 11 studies, 7 enrolled participants with hearing loss, 3 specifically

excluded participants with hearing loss, and one did not report hearing loss status. There were four types of interventions that fell within this category. So, three studies looked at hearing aids that included sound generators versus hearing aids alone. So, they were testing the incremental benefit of sound generator as part of the hearing aid. Four studies tested an altered auditory stimulus versus a placebo stimulus. So, these were studies that may have given randomized people to either receive altered music, so music that had been digitized and spectrally altered versus placebo music, so no changes made. Then, the third category were interventions that evaluated sound generators plus some other kind of intervention, such as providing education or information versus the information alone. So, that was testing incremental benefit of the sound generator above just information or education alone. Then, the fourth one was a really idiosyncratic type of intervention. This was an auditory attention training game. So, they randomized people to play this game that gamified basically the process of distracting yourself from the tinnitus noise to be distracted by another noise versus a placebo game, which was Tetris. So, that was sort of a one-off.

In terms of the grade, certainty ratings for these categories of interventions. So, for hearing aids with sound generating features, and again, this is in comparison to regular hearing aids. We have very low certainty for no benefit on measures of tinnitus distress and disability. Those were the only outcomes recorded by this study. So, we don't know anything about psychological outcomes, safety, or cost. For the group of interventions defined as altered auditory stimulus compared to control stimulus, again, we had very low certainty on all the outcome domains, and we were unable really to determine benefits for tinnitus disability and distress. That was because there were mixed findings. Some of the studies showed a benefit. Some did not. So, there was just too much inconsistency to conclude one way or another. We did determine no benefit from these kinds of interventions on psychological measures or safety, but as you can see, very low certainty. There was only one RCT for each of those outcome domains contributing to that grade. In terms of sound generators with information, education, counseling versus those things alone, again, we found very low certainty for no benefit on tinnitus disability and distress, and were unable to determine effect on psychological measures. Then, lastly the game I mentioned, we were unable to make a determination in terms of benefit to tinnitus disability and distress. I believe it was because the findings were far too imprecise. The sample size is only 31 in that study.

OK. Moving onto rTMS, here is the overview of the studies in this evidence base. There were 19 RCT's. Most of these studies were

conducted from 2007 to 2018. The duration of intervention was highly varied. There were a study or two that really just provided rTMS over like a session that occurred on one day versus other studies that provided rTMS three to five times a week for up to four weeks. Most of these studies, you can see, were conducted in countries outside of the U.S., and 14 of them enrolled participants with hearing loss. Three specifically excluded participants with hearing loss. Two did not report. In terms of the study design, nine of these 19 were crossed over RCT's. So, people were randomized to receive either the sham rTMS or the active rTMS in different orders. So, people served as their own control on the crossover studies versus the other 10 that were parallel assigned RCT's. So, people only received either sham rTMS or active rTMS. The crossover design is a little problematic, because it may result in people knowing which . . . seeing the difference between the sham and the active and being able to figure out which one they got first or second.

In terms of the grade ratings for rTMS, we found evidence, low certainty evidence, for no benefit on tinnitus disability and distress, very low certainty evidence for no benefit on psychological measures, and very low evidence for no benefit on quality of life. For safety, although we had 14 of those 19 studies actually reporting adverse outcomes, the findings were quite mixed. So, we really were unable to determine a direction of effect based on that evidence.

Moving onto discussion, this is just a reprise of the summary slide, now that we've gone through things in a little bit more detail. So, I just wanted to put that back up just to remind you where things fell out.

A quick slide about the limitations of the evidence. So, we have many high risk of bias studies in this evidence base. Some of it has to do with lack of blinding, which is not always feasible for some of the designs that use weightless controls. Some of this, though, has to do with just the rigor with which investigators design their studies or conducted their studies in terms of randomization methods, allocation concealment, outcome assessment, blinding, those kinds of things. Secondly, many studies had small sample sizes. This leads to imprecise effect estimate. That will bring down the overall certainty ratings within grade. Harms were not consistently ascertained. So, rTMS studies were the most common ones to actually report adverse events or harms. Most of the other studies did not routinely discuss how harms were ascertained or measured, or it didn't even report them. So, harms may be underreported across the body of evidence. As Dr. Zerzan mentioned, these interventions are quite heterogeneous. So, it's sort of difficult to put them all together and draw firm conclusions. Then, we had very

limited evidence for subgroups that might be a particular interest to the state, for example, people with tinnitus resulting from occupational noise exposure. We just did not have any studies kind of reporting out by those kinds of cell groups. Then, lastly, we only had one study that reported cost outcome. That was in the tinnitus specific therapy bucket.

In terms of ongoing studies, we identified 35 relevant ongoing studies that were registered in clinicaltrials.gov. Most of these are trials were interventions that had fewer than 100 subjects planned or enrolled. On this slide, you can see the different categories of interventions. So, you see most of the studies are focused on neuromodulation studies. Many, but not all, are focused on rTMS specifically, but there are other ongoing studies looking at some of the other intervention categories.

To recap, in terms of clinical practice guidelines, we identified six CPG's that addressed tinnitus treatment. One was very narrowly applied, just to specific population of persons with traumatic brain injury from the VA, and another was limited to rTMS. So, I didn't put them on this slide, but they are summarized in the report. On the slide here, I have summarized the four more relevant guidelines. The guideline from the National Institute for Clinical Excellence, NICE, was just published, I believe, in March. We assessed its quality as a 7 on the AGREE-II rating scale where 1 is the worst possible quality CPG, and 7 is the best possible quality. This guideline recommends CBT for use and basically called for more research on the three other categories of intervention. The other three guidelines on here also all recommend CBT but were not entirely consistent across the other intervention categories. So, two of them, the European Consensus and the American Academy of Otolaryngology Head and Neck Surgery recommend against rTMS. The German Medical Society recommends against tinnitus specific therapies. Regarding sound therapies, three of the four called for more research so did not make a specific recommendation for or against sound therapy. So, that's why there's question marks on the chart. The American Academy had a soft sort of optional recommendation for the use of sound therapy in selected patients where clinicians felt it might be useful.

In terms of payer policy, so CMS interestingly had a national coverage determination prior to 2014 that stated tinnitus masking was considered experimental and was therefore not covered. However, that NCD was removed effective December 18, 2014. So, in fact now they currently don't have an NCD at all. In terms of the other payers, Dr. Zerzan summarized this in her introduction, but basically many of the interventions, the payers do not have any policies one way or another regarding coverage for specific tinnitus treatments. CBT is not

prohibited, but it's not also . . . there is no specific policy calling it out for use in tinnitus. So, it's a little bit confusing to interpret, I think, some of the policies around CBT, but most all the payers agree . . . or the majority of payers do not cover rTMS, and there are about five of them that don't cover sound therapies, but the rest are sort of silent on the issue.

Finally, limitations of our health technology assessment. We, again only include peer review journal publications in English. We did not evaluate the comparative effectiveness of interventions. We did not evaluate neuromodulation interventions other than rTMS. There are some out there that are a direct current stimulation directly on the scalp and things like TENS units. Those were not in scope. We did not evaluate psychological interventions other than CBT, unless it was, again, a part of a multicomponent intervention like tinnitus retaining therapy. Poor study reporting for a lot of these multicomponent interventions means it's possible we might have misclassified some interventions or excluded some interventions. Then, finally this HTA was not scoped to evaluate medications, lifestyle modifications, or alternative and complementary therapies or invasive interventions, like cochlear implants and such.

So, in conclusion, we concluded low certainty that CBT or tinnitus specific interventions that combine psychological counseling with sound therapy offer some benefit for reducing tinnitus related distress and disability. We concluded with very low to low certainty that sound therapy alone and rTMS, as was used in the studies, may not be effective. Across the body of evidence, harms were poorly ascertained and reported. Then, we concluded with very low certainty that there may be few to no harms from CBT or sound therapy and insufficient evidence to determine harms from rTMS and tinnitus specific therapy.

So, I will pause there and see if there are any specific questions that you have about the evidence.

Mika Sinanan: I have a question that perhaps you can answer, or Dr. Zerzan. By the percentage prevalence in the population, there should be tens or 100,000 people with tinnitus in the Medicaid population. The numbers that were quoted in Dr. Zerzan's slide and the numbers in these RCT's all suggest a much lower total population that's getting treated. So, are the other 90+ percent of potential patients simply not getting treated? Or are those the people who are getting acupuncture? Do you have any idea about that?

Leila Kahwati: Yeah. I'll take that question first. Then, Judy, if you want to chime in. So, it depends on how the prevalence estimates are gathered. So, for

example, NHANES, which is community samples, asks people about symptoms. So, that just represents the people who report the symptoms. Not everyone who has tinnitus is going to find it bothersome or it be severe enough for them to present for evaluation or treatment. In fact, some people have it. They might want to know why am I having it, but it's actually not bothersome to them enough to actually want to do anything about it. Does that make sense? So, I think the people that are enrolled in trials are actually a lot, most of the studies have inclusion criteria requiring people to have bothersome tinnitus, or that they have had it for a long enough duration, and they meet a certain severity level on one of the measures of tinnitus disability and distress to be even enrolled in the study. So, I think the people that are in the trials are the tip of the iceberg so to speak.

Mika Sinanan: Thank you. That's helpful.

Judy Zerzan: I think also the . . . I totally agree with that answer. Then for our claims data, we only looked at tinnitus in the first diagnostic field. So, that's some of the problem. It's hard to tell exactly, especially since some of these interventions are pretty mixed what thing it is people are getting. So, I agree. Those are billing . . . And these trials are the tip of the iceberg.

Mika Sinanan: Jay, do you have any comments about that question?

Jay Rubinstein: I do. So, the vast majority of people with tinnitus have sensorineural hearing loss. So, when somebody comes in with a chief complaint of tinnitus, where the first diagnosis will typically be sensorineural hearing loss. The second diagnosis will typically be tinnitus. So, I suspect that plays a big role in the differential that you commented on.

Mika Sinanan: Thank you. That's helpful. The implication of that is that the subset we're looking at are the people who have tinnitus as the principle symptom. They have either minimal or don't report hearing loss. Is that right?

Jay Rubinstein: No. That's probably not right. It's just sort of random nature of what the first or second diagnosis would be. If their hearing loss is minimal, like I said, virtually, not everybody, but the vast majority of people with tinnitus have sensorineural hearing loss, but that sensorineural hearing loss could be fairly minimal and not disabling in and of itself. Or, they could also have disabling sensorineural hearing loss with tinnitus. So, I suspect what ends up one and what ends up two for primary or secondary diagnosis, is sort of what leaps out the most. Is the person's

hearing loss the biggest problem? Or is the person's tinnitus the biggest problem? Does that make sense?

Mika Sinanan: As a followup question to that, how often do people get multiple types of therapy? In other words, do they get one of these special hearing aids that has both sound interference, as well as hearing augmentation, plus something else? Or is it usually only the hearing aid?

Jay Rubinstein: So, again, the vast majority of people who need a hearing aid and acquire one will, and who have tinnitus as well, will not have tinnitus maskers added to their hearing aids. I think part of why the academy recommends keeping masking as an option is, there are a small group of patients who really find the masker much less annoying than their tinnitus, but in most cases, while masking is very effective at reducing the perception of tinnitus, many people find the masker as annoying or more annoying than their tinnitus. So, it's not a very widely used therapy. As opposed to hearing aids, where the majority of people who wear hearing aids and have tinnitus find that their tinnitus is reduced through the use of their hearing aids alone.

Mika Sinanan: Thank you.

Janna Friedly: May I sort of follow up on this line of questioning. This was something that I struggled with in terms of interpreting the results of this report, was separating out people who have hearing loss versus people who don't and how, given that the vast majority of people, it sounds like, have at least some degree of hearing loss. It sounds like a wide range of severity of hearing loss, how do you interpret the results of these studies? How does this impact the studies as presented and the results, and how we should interpret these? That's sort of a broad question, I know.

Jay Rubinstein: Is that being posed to me, Janna?

Janna Friedly: Yeah. I think so.

Jay Rubinstein: Well, you know, if you restrict the study to people who have no hearing loss at all, you're studying a very atypical group of tinnitus patients. Then, the question in a large scale study always arises. Well, how did they define hearing loss? Does the person have 30 decibel thresholds at 8 kHz? I call that a hearing loss, because that's an abnormal result, but that's again not an individual who will complain about their hearing. They'll only complain about their tinnitus. So, if you truly restrict studies

to people who have measurably normal hearing, you're talking about a very small group, and it's an atypical group.

John Bramhall: Could I just ask a question that may be related to the presentation by Judy. I just have sort of a subjective question. It looked like when people are being treated with cognitive therapy in the State, it looked like there was a sort of a single day of treatment, I assume a single treatment, and the cost was a couple of hundred dollars. So, I'm wondering just objectively, when people get cognitive therapy, is it a single session, and then they're on their own? Or, 'cuz, I would have thought that cognitive therapy would take, pace over a period of time rather than a single episode. Maybe I'm misreading the information. Can anyone comment on that?

Judy Zerzan: CBT is for sure not a single thing. In the studies presented, it was anywhere from 6 to 12 weeks usually. I think what that reflects is, again, the bias because this is such a heterogeneous type of condition and what treatments are done. I think for CBT, because there isn't a specific callout about tinnitus, I suspect that most CBT done by behavioral health professionals is labeled anxiety, depression, sleep problems, some of the other comorbidities with maybe tinnitus second. So, similar to the hearing loss is likely an initial diagnosis, I think if you're using CBT, probably these other things are the first diagnosis, and tinnitus might be second. So, I think it's all in a matter of this data is really hard to capture.

John Bramhall: OK. Thank you. That's helpful. Thank you.

Conor Kleweno: I had a question about the data specifically, the effect size in the seven randomized controlled trials that showed benefit. Is there a clear accepted threshold that was met for the studies that showed benefit, particularly given if there is any bias related common criticism is where statistical significance is highlighted, even though that's just based on the standard deviation without paying respect to the effect size, and it's relationship to a true clinically meaningful effect size.

Leila Kahwati: Thanks for that question. So, I don't recall off the top of my head. I'd have to go back and look, but that definitely is an issue across this body of evidence in terms of many of these instruments don't have an NCID defined. That's not been established. So, I can get back to you on that question. I just don't recall off the top of my head whether the point . . . I know the 0.81 to 0.95, those were all statistically significant effect sizes, but I do not recall how they map to clinically important differences.

Conor Kleweno: Thank you. That may be something that the clinical expert provides some comment on, as well, as we further discuss it. Just because it's easy to show the difference based on a heterogeneous population if you have a lot of . . . depending on the standard deviation.

Jay Rubinstein: I'll follow up on that. Jay Rubinstein here. The experience is, it's very difficult to show an effect, and we haven't talked about it yet, but as in Dr. Kahwati's background slide, where there's an elephant missing from this discussion, which is the perception of the tinnitus itself, as she introduced. Tinnitus consists both of a percept and of a distress caused by that percept. This review has really focused on the distress caused by the percept and has not addressed at all the percept itself. Typically, the visual analog scale that you've heard about is not always commonly related to what's the loudness of the tinnitus that you experience. That loudness can also be measured acoustically with a pretty good degree of reliability, although that's not typically done in these large scale studies, because it's so time consuming, but one of the findings in all of these studies has been that no matter what you do with the exception of masking, you don't reduce the loudness of the tinnitus percept, but you can reduce tinnitus distress. I'm not an expert on effect sizes for distress. I can't really comment on that.

Sheila Rege: That's . . . oh, go ahead.

Leila Kahwati: I was just gonna respond at the . . . the effect size for behavioral interventions, 0.81 and 0.95, are fairly large effect sizes. We don't typically see that size effect in behavioral type interventions, if that helps.

Jay Rubinstein: Yes. Thank you.

Sheila Rege: That's very interesting and an important perspective, especially based on your experience, but what I would suggest is, we take a break now, but when we return, we can use our discussion aid and go around the room, discussing strength of the evidence for each outcome, as we see it, limitations, and just kinda go around the room with our thoughts. Is everybody OK with a ten-minute break? I'm hearing no dissent? We're going to . . . instead of signing back in, if everybody can just stay on mute and maybe then we can come back and save time signing back in.

Josh Morse: OK. So, reconvene at 10:12? Or are we gonna round it up to 10:15?

Sheila Rege: Is everybody OK with 10:15? Because we've been pretty good? We'll do 10:15 and steal some time from the lunch hour. OK. 10:15 we'll return.

Josh Morse: Thank you.

Sheila Rege: Welcome back. Maybe we could go around the room just kind of . . . I'm going to start alphabetically. John, you're going to be up. Just kind of let's discuss using the discussion aid to state effective improving health outcomes based on the data what our thoughts are and we felt were the limitations. John, are you OK starting us?

John Bramhall: Sure. Absolutely. So, I mean, the impression that I got when I read all the information, and thank you for the . . . I actually thought that the evidence based presentation was excellent. It was very well formatted and very well organized. So, I really appreciate that, Leila, particularly some of the graphics about this complicated pattern, because you've got four or five different treatments and several different outcomes, and a range of certainties. So, I thought it was well presented. The bottom line seems to me to be that the only intervention that appears to have objective support is the cognitive type approach. The electromagnetic doesn't seem to be very positively reviewed. The cognitive therapy, Mika made the point that this is a relatively high incidence in the population somewhere around 10%, maybe a little bit more. So, there's a significant number of people who have this complaint. There is apparently a lot less of that same population, a smaller number have distress caused by the complaint. So, we're dealing with something that's common, but its most of the time doesn't lead to seeking of medical attention. When medical attention is sought, it seems that the best intervention is some form of cognitive therapy, maybe with some music components and some sound components. So, I'm not impressed overall by the quality of evidence, but this is a common theme, Sheila. I think it's nothing to get too depressed about at this moment, but it does seem that many of the incidences that we look at historically, probably we're looking at them because the evidence base is thin. We don't tend to see and have to discuss and have to dissect therapies that are so clearly effective that we actually don't have to analyze them. The cognitive therapy seems to be safe to me. I mean, there's no evidence of danger or damage or harm that I can see. It seems to be very modestly effective in the randomized control small number of trials that were presented. I presume, I actually presume, that there is a subjective effective and benefit, which is seen by patients, which is more important to them than the randomized control data. For those people who elect to have the therapy, I suspect that there is some benefit to a significant proportion of them subjectively. We're just not getting a really good window on that. It seems like it's probably cost-effective, because the information that we got was that it was a relatively modest cost with a large number of people that are involved. We were presented with something around about \$200 per

episode therapy cost on average. So, it doesn't seem to be an incredibly costly intervention. It does seem to be modestly effective. That's my subjective perception about the cognitive behavioral therapy that we've been looking at. I know we'll have time later. I do have a question to Dr. Rubinstein later on perhaps. I'm just interested in perhaps the sort of biomechanical substrate for all this. What actually is going on when people perceive tinnitus? I know that probably isn't part of our remit, but I'm hoping there's an opportunity just to get informed about the sort of molecular structural level cause of the tinnitus, if it's known.

Sheila Rege: I think Jay, if it's OK with you, we'll just go around and you're gonna just tell us also, as a committee member, kind of your gestalt. Then, we'll just banter on questions and use your expertise and get your perspective based on your experience. So, you'll go, Jay, I'm just going in order of last name. So, you will go after Laurie or me. Janna, do you want to?

Janna Friedly: I do. I think in general I agree with Dr. Bramhall and his assessment. With one exception. My interpretation of the data for cognitive behavioral therapy is that actually the . . . looking at all the effect sizes, they are quite large. Even though we don't have great measures of NCID, it looks like the improvement is actually fairly substantial in size. It's moreso than the literature for cognitive behavioral therapy for chronic pain and a lot of other conditions. So, to me, that's a little bit surprising, actually, that the effect size is so large. It seems to be so effective. So, as John mentioned, I think we are hampered by the quality of the evidence overall for all of the different interventions, the heterogeneity. I am still struggling with trying to figure out how to interpret all of this for which patients because it seems that clinically most of the patients are going to have some degree of hearing loss. So, I'm just struggling a little bit with how these coverage decisions will be applied in actual clinical practice and how to interpret the results of these studies given that people with pure tinnitus is such a small subset of the patients. I think that's all I have.

Sheila Rege: That's good thoughts and good positions. Going on, Chris?

Chris Hearne: Yeah. I guess I don't have too much different to say. I think it's good to keep in mind that since tinnitus is so common in clinical practice, and the majority of people who have tinnitus will not seek any care for it. You could make an argument that perhaps those who do seek care for it have the most severe symptoms and might benefit the most from these sorts of interventions. I think that the issue of harms is always difficult. Sometimes, we don't have enough data to make really reasonable judgments about that, but in this case . . . I mean, sometimes we have to

imagine what harms might be possible. It's hard to imagine CBT in this context causing significant harms other than perhaps the time spent engaging in it.

Sheila Rege: I agree. Conor, would you like to comment?

Conor Kleweno: Yes. Thank you. I did write a question. I don't know if it's visible. I just had a clarification on if we are considering at all etiology. I noticed that L&I covers, or has some coverage benefits. Assumedly, that's due to occupational exposure related tinnitus. I would be very interested to hear Dr. Rubinstein's gestalt on all of this, but just a clarification question whether we at all will be taking etiology into account, or if there is any related sense from Dr. Rubinstein if there is a difference in expected treatment benefit related to etiology. I know that Leila mentioned that these studies, it was difficult to determine whether, in terms of inclusion, there was not a lot of information based on etiology. Other than that, I agree. I think that from the modalities we were evaluating, they all appear to be safe. It seems there is a benefit in terms of effect size for at least the CBT being effective. I will probably struggle a little bit more with the third point, which is value, and we will have differential thoughts on the different four categories that were listed in terms of whether they provide value, as well.

Sheila Rege: Yeah. Good point. I think Jay, you're going to have a lot of questions when we get to that part, because I'm hearing a lot. So, keep those questions in mind. We'll ask Jay that later. Laurie, would you have any . . .

Leila Kahwati: Sheila?

Sheila Rege: Yeah.

Leila Kahwati: I pulled up the data that Dr. Kleweno had asked about earlier related to effect size. Would it be OK to provide that at this point? I think he just kind of mentioned it again?

Sheila Rege: Yeah.

Leila Kahwati: OK. Brit, are you able to send the screen back to me?

Britt Reddick: Yes. Or Josh, do you want to hand it over to Leila?

Josh Morse: Yes. Thank you.

- Leila Kahwati: Alright. So, are you able to see? It's just a very plain vanilla Word document up there. Are you all able to see it?
- Group: Yes.
- Leila Kahwati: OK. So, Dr. Kleweno, you had asked me about the effect sizes and whether they were clinically meaningful differences. So, the three studies that used the tinnitus questionnaire, meaningful difference for improvement for deciding about improvement is five points. For deciding about deterioration, it's one point. So, in the study that had an effect size of 0.89, the between group difference between intervention control was nine points. So, it was more than the clinically important difference, and for this study that had the effect size of 0.95, the between group difference was 16.8 points. For the study with the effect size of 0.81, the between group difference was 9.5 points. So, I think they all were above the minimally important clinical threshold. So, that's for those three studies. I don't want to claim that this was universally true across all of the evidence, but I think in general, at least for the tinnitus questionnaire, we know what the clinically meaningful difference is.
- Conor Kleweno: Thank you. That was very helpful. That's three out of the seven RCT's that showed benefit. Is that correct?
- Leila Kahwati: Yes. The other four didn't give us the data, didn't report effect sizes, and didn't give us the data we would need to calculate effect sizes. Right.
- Conor Kleweno: Great. That helps a lot. That helps me understand. Thank you.
- Leila Kahwati: Mm-hmm.
- Sheila Rege: Thank you. Laurie, would you like to comment on . . . thank you.
- Laurie Mischley: Yeah. I largely agree with what other people have been saying. I, too, agree that CBT seems modestly and consistently effective. I'm not worried about harms. I do appreciate our expert calling attention to the treatment of the distress component of it. The only thing I would like to add is between 2001 and 2010, my practice was largely complementary and alternative medicine strategies for neurological complaints. I just want to nod to the public speakers, the community members who spoke up at the start of the meeting today. It was my clinical experience that patients who would come in . . . I don't do acupuncture myself, but I do appreciate that it was something that I feel like I can consistently heard in practice was that people did get benefit from traditional Chinese medicine. So, I appreciate them being here. I know that's beyond the

scope of what we're talking about today, but I would support CBT, as a treatment here. That's it.

Sheila Rege: OK. Thank you. Jay, would you like to comment and just . . . the same thing. Is it safe? Is it effective? Does it provide value? Your depth of experience is going to really help us.

Jay Rubinstein: I'll start by congratulating Leila on a very thorough systematic evaluation of a very challenging set of literature to try to create a cohesive hole out of, and the overall tone of the report is completely consistent with my own far less systematic review of the literature. I completely agree with the conclusions and the recommended coverage decisions. I'm a little puzzled by the absence of any commentary about tinnitus loudness. The reason for that is that the . . . to sort of give a gestalt on tinnitus, as we see about 15% of the population, 15 to 20% of the population has tinnitus at some point. There's actually pretty good numbers on what percentage of those go see a physician about it, and it's about 10% of the people who have it see a physician about it. About 10% of the people who see physicians have what we would call disabling tinnitus, which is tinnitus that really puts a crowbar into their quality of life. So, that's still a fairly large number, but it's only 1% of the overall population with tinnitus. So, many, many people have tinnitus, see a physician. It gets explained to them that yes, they have whatever degree of hearing loss they have, and the tinnitus is likely a result of that. They're happy with that evaluation that there's nothing more serious wrong and go on with their lives, but there is this smaller group who aren't happy with that, and a significant chunk of the people who say, well, there's no treatment. There's nothing I can do about it, I'll go on with my life, who would really still benefit significantly in terms of quality of life by a treatment that actually reduced tinnitus. As someone who spent a big chunk of time trying to determine whether anything can actually reduce the tinnitus percept itself, I was pretty surprised to see the absence of any reference to the tinnitus percept in the report. I'd love to know why. The conclusions of all the studies I know show that none of these interventions have any impact on the tinnitus percept at all, whether we're talking CBT or any of the other ones, but when tinnitus retraining therapy was first introduced, it was advertised as a treatment that actually reduced tinnitus, the percept itself, and not just the distress. So, perhaps, Leila, can you comment on why tinnitus percept, tinnitus loudness, etc., is not addressed in the report at all?

Leila Kahwati: Sure. So, tinnitus . . . we did actually include measures of tinnitus loudness. They are categorized under the broader category of the tinnitus distress and disability measures. So, in some cases that saw

studies used a visual analog scale to ask people to self-report the level of loudness or severity. In other cases, many of the instruments that measure tinnitus disability and distress have items on them that assess loudness. So, loudness is, in fact, included, but it's loudness as self-reported, perceived, you know, by the individual. We did not include pure measures of I think you referred to them as psychoacoustic measures, because those are . . . we consider those to be sort of intermediate measures that may or may not be correlated with the person's perception and the level of distress associated with the perception. So, we thought that outcomes related to how the tinnitus is impacting the person's functioning or level of distress, those are the kinds of things that you would probably base treatment on versus just objective measures of loudness that may or may not correlate to bothersomeness. Does that help?

Jay Rubinstein: Yeah. I will agree, and I will disagree. So, across a large number of studies, tinnitus loudness and tinnitus distress are completely unlinked. There are people who have really loud tinnitus that doesn't bother them at all. There are people that have really soft tinnitus that drives them to distraction. So, yes, they are not linked to one another, but on the other hand, if we could actually reduce tinnitus loudness to zero, this problem would go . . . the distress would go away, because they would not have tinnitus. None of the tinnitus instruments that you're referring to are the same thing as a visual analog scale of tinnitus loudness. The questions that get to how much tinnitus bothers you are not the same thing as someone actually pointing out on a visual analog scale, you know, how loud their tinnitus is. It's really quite separate. None of the instruments that you have described, other than the VAS, really address loudness, per se.

Leila Kahwati: If the study reported VAS loudness, we captured that data, and it is in the report. It's just I didn't dive into all the details during this presentation, but we do have some studies that report VAS for loudness, and I can point to those sections.

Jay Rubinstein: The conclusions are that there is no effect on loudness. I think that's important to publicize. I think that should be a little more central in the presentation.

Sheila Rege: Thank you, Jay. That helps us understand your thoughts, and we'll keep that in mind, as we're debating things, but if it's OK with you, I'm going to move onto Seth, kind of his perspective, your gestalt on safety and effectiveness. Thank you.

Josh Morse: It looks like, Seth, you're muted.

Sheila Rege: I'll let you work with Seth to get unmuted. Otherwise, you can . . .

Seth Schwartz: Can you guys hear me now? This is Seth. Can you guys hear me now?

Josh Morse: Yes. We can.

Seth Schwartz: OK. Sorry. It wouldn't let me unmute. So, I like Dr. Rubinstein . . . I take care of a lot of these patients in my practice, and I'm familiar with a lot of this data. I think this was a very nice job done summarizing the complicated information that's here. Then, I think Dr. Rubinstein did a nice job of sort of pulling out the complicated nature of dealing with these patients, which it is a truly heterogeneous population. While tinnitus, itself, is very, very common, the many, many people that have it aren't that bothered by it, and the degree of distress that people experience is not necessarily very well correlated with the loudness. The same is true with hearing loss. So, there's a lot of people with very mild hearing loss that are tremendously bothered by it, and other people are nearly deaf and don't seem to care. So, that makes it very difficult to sort this population out. I think the other complication is how strong of a correlation there is between psychiatric comorbidities in this patient population. For that reason, I think it's really unsurprising that the CBT is most effective treatment that we're seeing. I think the data is pretty clear that there is very little harm in CBT and that there is some significant benefit to offering that. So, I think the data is strong in that, and I feel comfortable with that. For rTMS, I think there's really no data to support it. I think in clinical practice, it's not that popular of a therapy. So, I feel quite comfortable saying that's probably not something we need to be concerned about. I struggle a little bit with some of the way the tinnitus retraining therapy was handled, because I do think, for many of these patients that benefit from CBT, having something else is helpful. I think for the patients that do have some concurrent sensorineural hearing loss, the hearing aids are really effective and can be very helpful. I think that patient population was sort of pulled out from this report. Saying if they have hearing loss, we're not going to talk about that. So, it's hard to know exactly how to handle that, but I do think some of the tinnitus masking treatments, in conjunction with CBT, so some of the variations of tinnitus retraining therapy, do have a little bit of support here in the clinical practice and in some of the historical data we've looked at can be helpful for some patients. They are not going to be helpful for the patient with very little hearing loss and little tinnitus, but distress that's off the charts, but they may be helpful for some other patients. So, that's the one group that I'm struggling with a little bit, as

far as how to handle the uncertainty of the data that we've seen. So, I guess that's where I fall out on things.

Sheila Rege: Very helpful and good points for us to think about. Going on, Mika, we would love to hear your comments.

Mika Sinanan: Thank you. So, with regard to safety, first of all, I do appreciate the review. I think it was very helpful. So, it did sort of bounce at such a high level above the complexity and variability that the comments from Seth and from Jay are very helpful in that regard. It sounds like a miserable thing to have, and certainly the subset of people who are really bothered by it, and who have it despite hearing aids that appear to mitigate it, or who don't have any hearing loss seem to be the subject of what we're talking about. I don't see that there's a safety issue. I didn't really pick up on anything that was truly a safety issue. The effectiveness for the reasons we've talked about, it appears that the cognitive behavioral therapy is the one type of therapy in patients who don't have a concomitant hearing loss where there appears to be a benefit. The others do not appear to have any benefit. I wanted to ask whether, in fact, the comments from our outside speakers about acupuncture are incorporated in other tinnitus specific therapies. Would that be included there? Or is it completely out of scope. So, that's one question. Then, the other question I had was, are the hearing aids that are used in patients who have both a hearing loss and tinnitus, are they significantly more expensive? Or is there a compromise between augmenting the hearing and controlling the tinnitus that effects the quality of life or the quality of the effectiveness of the hearing aids. Is there a cost difference? Apart from that, it seems to me that the recommendation from Dr. Zerzan is a reasonable recommendation. Thank you.

Sheila Rege: And if Mika, if it's OK with you, we'll take those questions later. I've written down the three more questions, I think, for Jay. We'll take those kind of all at the end after everybody has kind of gone around the table, if that's OK with you.

Mika Sinanan: Sure. Fine. Thank you.

Kevin Walsh: I also want to compliment the quality of the presentation. I thought it was helpful. Thank you. In terms of safety, I did not see an issue with any of the therapies proposed. In terms of effectiveness, I agree with Dr. Zerzan that CBT was the only one that demonstrated benefit. To try to speak to the point that Seth brought up about possible benefit of tinnitus retraining therapy, I wondered if I can't remember, and maybe someone can help me, if any of those studies compared the combination of CBT

and sound therapy to sound therapy alone and to CBT alone. Can I ask for clarification on that? Beyond that, I was interested in the presentation of the acupuncturists and wondered also if the reviewers found any studies that looked at acupuncture, and if they could comment on why those were not included. In sum, I agree with Dr. Zerzan's recommendations.

Sheila Rege: OK. So, you have two questions. We'll come back. We'll give the experts kind of some time to [inaudible] on those. Tony, would you like to comment. We'd love to hear your comments.

Tony Yen: So, for number one, there doesn't appear to be much safety data, but also intuitively, it seems like all the options that are offered within the report are safe, except for maybe rTMS. I really don't know what the implications of using that for the longterm might be. For number two is that effective, at least my interpretation of the data, shows that the efficacy is probably really there only for CBT, although there may be some for the tinnitus specific interventions. I have to say that when I looked at the tinnitus specific interventions, it appears to be a bit of a combination of a lot of different sort of things. Sometimes involving also cognitive behavioral therapy. So, it's really difficult for me to tease out. For number three, does it provide value, I would also reference the same study that Kevin just spoke about regarding tinnitus retraining therapy. I think it's footnoted as reference number 76 that gives actually a QALY amount of about \$10,500 per QALY, which would, by most definitions, qualify as being cost-effective. That's really the only cost-effectiveness data or value data we should say that I can clearly see within the evidence that's provided.

Sheila Rege: I would agree. So, I don't have anything to add. I think all of you have put out kind of the limitations and the fact that this was an excellent review. Thank you. I learned a lot, and it was very helpful with a good summary. Now, what I would like to do is, I wrote down questions, and if I missed anybody, use the question box or speak up. There was a question, Jay, there were three questions. One was something along the biomechanical etiology and distress. I'll have whoever had those questions for Jay kind of come up with those if you'll ask those questions whoever you were asking them of.

John Bramhall: I think that was me, Sheila. So, Jay, it may not be in the scope of our discussion, to be honest, but I'm just intellectually curious whether this spectrum of disease that you see clinically, would it be fair to say hallucinatory? No. Probably not, but I'm just curious about the physical substrate of the sound that is perceived. Whether or not you can

objectify with things like frequency dependent auditory above potentials, or objective things like that. Is there a mechanism for taking the subjectivity away and objectifying the tinnitus in some way?

Jay Rubinstein: So, I heard two separate questions about can you measure tinnitus subjectively. What is the pathophysiology of tinnitus? I'll start with the second one. Pathophysiology of tinnitus is not known, but there is a lot that is known about the pathophysiology of tinnitus, because there are, in fact, animal models. Those animal models are very complex, and interpretation of the results is hence complex. Our current best explanation for what causes the majority of tinnitus is that it's a response of the central nervous system to the loss of afferent input from the ear. So, tinnitus does not arise from the cochlea in most cases, but it does arise from the brain's response to loss of input from the cochlea. Hence, it makes sense that restoring hearing, whether through hearing aids, cochlear implants, middle ear surgery, or what have you, is the best treatment for tinnitus. Now, I gave such a long explanation for pathophysiology, I had forgotten what the other question was.

Mika Sinanan: Jay, could I . . . just before you get off of that, could I just probe that a little bit? From what you said, I would take it that tinnitus is not a real sound. It is more a response of an amplification or a sensitivity level because of a lack of feedback, but it is not a real sound that is normally filtered out. Is that correct?

Jay Rubinstein: Yes. And you're actually more correct than you know, because there is evidence that the loss of input from the auditory periphery to the auditory brainstem actually causes a failure of feedback mechanisms and an increase in central auditory gain that results in the percept of tinnitus. What that actual percept is, is highly variable. It can be almost a pure tone. Typically people characterize it when compared to sounds that we give them, they compare it to a noise band that's generally in the vicinity of where their hearing starts to drop off. There are other variations on what people hear, obviously. If people hear anything more complicated than just a noise of a tone, generally, that's not tinnitus. That is, in fact, hallucinatory, and that's not what we're discussing here.

Mika Sinanan: And just to follow up on that, as a researcher in this field, is our ability to correct this simply a matter of more research time and technological innovation? Or is your perception that this is going to be mostly a management of a situation that will not be otherwise correctable?

Jay Rubinstein: My belief is, if we could correct minor degrees of hearing loss effectively, whether through cellular regeneration in the cochlea or some prosthetic

device, that we would have a very large impact on the perception of tinnitus.

Mika Sinanan: Thank you.

Jay Rubinstein: There was another question about can we measure it objectively. The best measurement of tinnitus is still subjective. Its loudness and pitch matching. So, it's possible to get very stable measures of tinnitus loudness and tinnitus pitch through the psychoacoustic techniques that I referred to earlier. We don't do that in a clinical domain, because it doesn't fundamentally impact any kind of treatment at this time, but from a research standpoint, it is possible to do that.

Mika Sinanan: Thank you. That's very helpful. I do appreciate that Jay. Thank you.

Sheila Rege: There were other questions. Did the answer, first, and we also had questions from Kevin about acupuncture and sound therapy? Maybe that's for the clinical expert. Dr. Sinanan had a question also that will go to . . . I forgot Dr. Sinanan's question. So, let's Kevin, let's go to your question first.

Kevin Walsh: I'm sorry, Sheila. Do you want me to refrain the questions?

Sheila Rege: Yes, please.

Kevin Walsh: So, both of my questions were to the reviewer. The first question was about just a clarification of the tinnitus retraining therapy studies and whether they compared the combination of sound therapy plus CBT to sound alone or CBT alone.

Leila Kahwati: No. The tinnitus specific therapies generally compared some kind of psychoeducational component plus or minus the sound therapy to a weightless control, or a delayed treatment, or an intention control. So, those were not looking at sort of incremental benefit of sound therapy. Now, the sound therapy studies, there were kind of four categories of those. One of them evaluated sound generators plus or minus a minor information or educational counseling, not CBT though, to the information counseling alone. Those studies were evaluating the incremental benefit of sound generators or sound maskers, but the tinnitus specific therapies were really comparing a package of interventions to basically weightless control.

- Kevin Walsh: I was asking because I wondered if the benefit seen in the studies that showed benefit to the tinnitus retraining therapies was the product of the CBT aspect of the therapy.
- Leila Kahwati: Yeah. It's hard to conclude it directly from the data. I think you sort of have to assume that, or you can propose that, but we don't actually have the direct data where we can tease that out if that makes sense.
- Jay Rubinstein: Leila, didn't Rich Tyler do a study like that where he compared directed counseling plus or minus sound therapy?
- Leila Kahwati: He may have. Was it just recently published? Because you did send me something . . .
- Jay Rubinstein: No. It was quite a long time ago.
- Leila Kahwati: OK. Yeah. I mean, we definitely screened . . . his studies did end up in our literature search, and we screened it. It may have not entered, because it might have reported the right kinds of outcomes. Or there may have been some other reason, or if it was an active comparator, it may not have made it in.
- Kevin Walsh: And then my second question was about whether acupuncture was even reviewed as a possible therapy in this literature review.
- Leila Kahwati: It was not. So, acupuncture fell under the complementary and alternative medicine interventions that were not in the scope of the review. I think we may have cataloged those studies in the report. I can't remember if we cataloged those or not, but we certainly did see some of those studies in the search that we did, but we did not include them in the report.
- Kevin Walsh: Thank you.
- Jay Rubinstein: I'll comment subjectively on the acupuncture question. I have an old colleague who was at the University of Nagoya in Japan at the time who in addition to being a fellowship trained neuro-otologist like Seth and I are, he is a fifth generation . . . he is of Chinese descent, even though he lives in Japan, fifth generation acupuncturist, as well, and he did a randomized trial of acupuncture for tinnitus. It was published in Japanese. So, it would not be in this review. The conclusion was that it helped with sort of general sense of well-being but had absolutely no impact on the tinnitus percept itself.

- Judy Zerzan: I'll just weigh in here that acupuncture was out of scope for this. So, that's why it's not mentioned. Acupuncture, as many of you know, is not a benefit on the Medicaid population. So, that would be . . . although I think some MCO do some coverage, but that is really a different topic. What you decide today wouldn't effect acupuncture in sort of any way if other carriers cover it.
- Sheila Rege: I think there were a couple more questions. Mika, you had a couple, if you want to refrain them?
- Mika Sinanan: Thank you. They actually have been covered. Tony had a question about slide 52 in Leila's report around TRT indicating cost-effectiveness.
- Sheila Rege: Tony, do you want to refrain your question on that. We can go back to that slide?
- Tony Yen: I don't think I have so much of a question, more of a comment that it actually had a QALY attached to it that was around \$10,500. It was referencing the report itself.
- Leila Kahwati: This is Leila. I can, yeah. The QALY from the healthcare payer perspective was \$10,000 and change, but we couldn't actually compute a confidence interval around that. The confidence interval, sorry. I just had it up right in front of me. The confidence interval from a . . . around the actual difference in costs actually crosses the null effect, which is one reason why we sort of didn't conclude there was cost-effectiveness, because the actual difference in costs and the difference in quality of life, those individual results crossed the null. So, when you put together the QALY, it's likely that the cost per QALY adjusted life year also crosses the null.
- Tony Yen: Thank you. Sounds reasonable to me.
- Sheila Rege: Yeah. Are there any other questions that we would like to kind of ask so the rest of us can hear and help us understand things better?
- Mika Sinanan: One other question, Sheila. Jay, maybe you could help answer this. Is there a cost difference between hearing aids that are in patients with both hearing loss and tinnitus versus just hearing loss? And would that be ever an issue in getting the patient a hearing aid that effected that?
- Jay Rubinstein: So, yes, a hearing aid that has a masking device incorporated into it costs more than a standard hearing aid. Typically, if you saw a patient who had very bothersome tinnitus associated with aidable sensorineural hearing

loss. I specifically say aidable sensorineural hearing loss, because there are many people who have sensorineural hearing loss and tinnitus who are not aidable. Their hearing loss is just not bad enough to warrant or justify a hearing aid, but if you have aidable hearing loss and tinnitus, typically, you will get a standard hearing aid first. The folks where you might recommend trialing a masker are folks who come back to you with their hearing aid. They say, look, my hearing aid is great. It's helping my hearing, but it's really not doing anything for my tinnitus. That's when you might trial what's called a tinnitus instrument, which is a hearing aid with an incorporated tinnitus mask. Yes. That does cost more.

Mika Sinanan: Thank you. Just to follow up that comment and your previous comment, if this is a gain issue that is commonly driven by some degree of hearing loss, do the majority of patients get better with hearing aids in terms of reduction of their tinnitus?

Jay Rubinstein: Yes. The statistics are variable, but it's anywhere from 50, depending on the study, anywhere from 50% to 80%.

Mika Sinanan: Does this coverage determination only allow, I mean for hearing, if the coverage determination only allowed treatment for hearing but not the masker, would that represent a clinical issue in practice?

Jay Rubinstein: Probably not, because the percentage of people who find the masker both suppressive . . . so back up a little bit. Not everybody's tinnitus is maskable. Most people's tinnitus is maskable, but not everybody, but if you take the people who have maskable tinnitus, a lot of them will find the masker to be just as annoying as their underlying tinnitus. So, excluding a masker from coverage would not have a substantial clinical impact. No.

Mika Sinanan: No. So, I'm very comfortable with that.

Sheila Rege: Now, have we missed any questions that were asked?

Conor Kleweno: I had a question for Jay just about etiology, assuming there are some components for genetic etiology versus environmental exposure, is there any difference in expected benefit of treatment or anything that we should be considering, in terms of etiology for our evaluation?

Jay Rubinstein: So, we know very little about the genetics of tinnitus, per se, because it's so intertwined with the genetics of hearing loss. And there is also a genetics of noise susceptibility. So, if you take 100 people and expose them to the same industrial noise, they'll have very different degrees of

hearing loss in response to that noise. That's been demonstrated in mice to have a genetic basis. Some mice and some people have tough ears. Some mice and some people have tender ears. Same goes for a head injury. There was a mention of L&I earlier. The L&I will typically involve either noise exposure or a head injury as a cause for hearing loss and tinnitus, but I know of no sort of systematic differences between these groups that would impact the efficacy of intervention or a lack thereof, or its cost-effectiveness.

Sheila Rege: Thank you. That was very helpful. If there are no more questions, and I'm going to look to Jay and Seth who have a lot of clinical experience with this on whether we are ready to kind of look for a straw vote. Maybe we should take the easiest, which is cognitive behavioral therapy for tinnitus where if we can pull up the agency medical director recommendations, the recommendation was cover. We can maybe go around like a straw vote of do we agree with that or do we want that with conditions, cover with conditions? Or not cover? Is there some . . . I would take a motion just on cognitive behavioral therapy or just discussion. Seth, please help me. Jay, please help me on this.

Mika Sinanan: On page 8 of this document that's up on the field, there's the safety, efficacy, and cost outcome questions that sometimes seem to be helpful in discussing this.

Sheila Rege: So, let's, yeah. That's helpful.

Mika Sinanan: Before we do the . . .

Sheila Rege: And should we . . . I'm looking for advice from Seth and Jay whether we should do it for everything or just do it for the cognitive behavioral, as separate from the others.

Seth Schwartz: I think it makes sense to separate out the CBT and then also to separate the rTMS, because I think those are going to be straightforward. Then, we can look at the tinnitus specific therapies. Although based on the data and everything we've heard, it's probably going to, I mean, we all know which direction it's likely to go, but I think we should do them separately.

Sheila Rege: So, we will do the cognitive behavioral therapy first on safety. This is, again, you know, a straw vote. We're not voting right away, but did we feel like it was safe. I'm opening it for discussion.

- Seth Schwartz: I don't object to going through these one at a time, but I think we've heard pretty clearly the straw vote from everybody already.
- Sheila Rege: Right. So, I think we're, Mika do you, are you comfortable just with the cognitive behavioral, or just a straw on the agency medical director? Or would you like to go to the safety?
- Mika Sinanan: Sure, I mean, I would certainly be happy to, from a recordkeeping standpoint, just to ask for any exceptions to it being safe.
- Sheila Rege: That's a good idea. Anybody have an objection to us feeling it on the straw vote that this was safe? OK. Then moving on, can you go to the next page?
- Josh Morse: Dr. Rege, sorry. Are you addressing the sufficiency the evidence, the technology is safe. Is that what you were just discussing?
- Sheila Rege: Right. And this is just a straw poll. So, this is not the actual coverage yet.
- Josh Morse: OK. Thank you.
- Sheila Rege: So, we can now go to the next page. So, effective and cost-effectiveness is kind of the next thing with, are we comfortable with no exceptions if we go on a straw poll of looking at the agency medical directors' recommendation of coverage based on the evidence, just on cognitive behavior. Anybody think we need more data? Or any questions related to those two issues?
- Group: No questions.
- Sheila Rege: So, we don't have our little yellow cards, but assume we have our yellow cards, and we are now looking just at cognitive behavior therapy straw poll, I don't know how to do this. Are we kind of comfortable with CBT being . . . how many would say more in all for safety? Can we raise our hand? Can everybody raise their hands? Kevin couldn't raise his hand. Right?
- Mika Sinanan: Why don't we have a roll call? And then, each person can say what their vote would be for safety, efficacy, and cost.
- Sheila Rege: Are comfortable with this being a straw poll? Or should we move onto cognitive behavior to our final vote recognizing its 11:09, and we're supposed to break at 11:45?

- Mika Sinanan: I would suggest that we do the vote.
- Sheila Rege: So, everybody's comfortable with us going for a vote then?
- Group: Yes.
- Sheila Rege: OK. A little different in our process, because, but let's go further. So, this is on cognitive behavior. Go around the room. Josh, will you call it? You'll call on people?
- Josh Morse: Yes. I will. So, we're doing the voting questions for safety, efficacy, and cost-effectiveness. Is that correct?
- Sheila Rege: On cognitive behavior.
- Josh Morse: For CBT. Yes. OK. Dr. Bramhall for safety? Unproven, less?
- John Bramhall: So, I think I would hold up equivalent if I was in the room. I see it is as safe as a control or sham. So, I would equivalent.
- Josh Morse: Effectiveness?
- John Bramhall: For effectiveness, I think more in . . . for CBT, I think it's more in all. I think I'm convinced that the CBT is effective in all of the studies that were done at different levels of assurity to that, but I would say more in all. For cost outcomes, well it's effective, and it's relatively cheap on an individual basis. So, I would say more in all for that, as well>
- Josh Morse: OK. Thank you. Janna?
- Janna Friedly: For safety, I would say equivalent. For efficacy, I would say more in all. For cost, I'd say unproven.
- Josh Morse: Thank you. Chris?
- Chris Hearne: For safety, I will vote equivalent. For efficacy, I would vote more in some. For cost-effectiveness unproven.
- Josh Morse: Thank you. Conor?
- Conor Kleweno: Yes. For safety, I will vote equivalent. For efficacy, effectiveness, more in some. For cost outcomes, unproven.
- Josh Morse: Thank you. Laurie?

- Laurie Mischley: For safety, I vote equivalent. For efficacy, more in some. For cost outcomes unproven.
- Josh Morse: OK. Sheila?
- Sheila Rege: Safety, equivalent. Efficacy, more in some. Cost-effectiveness, unproven.
- Josh Morse: Seth?
- Seth Schwartz: Safety, equivalent. Effectiveness, more in some. Cost, unproven.
- Josh Morse: Thank you. Mika?
- Mika Sinanan: Same as Seth.
- Josh Morse: OK. And Kevin? Kevin, are you muted?
- Kevin Walsh: No. I'm sorry. Maybe I was. Can you hear me now?
- Josh Morse: yes.
- Kevin Walsh: Safety, equivalent. Effectiveness, more in all. Cost, unproven.
- Josh Morse: Thank you. Tony?
- Tony Yen: Safety, equivalent. Efficacy, more in some. Cost outcomes, unproven.
- Josh Morse: OK. Thank you. That's everybody.
- Sheila Rege: So, still doing CBT Seth and Jay, you know the process, help me out here. Shall we go to a vote just on that? Or shall we take the next one, which is, you were talking about the repetitive transcranial magnetic stimulation and do the safety and efficacy.
- Seth Schwartz: It would probably make sense to move onto a vote for CBT.
- Sheila Rege: That's what I'm hearing, too. So, Josh, for a vote, shall we just vote that if everybody says cover unconditionally and just . . . do you want to go through one by one, or can we just chime in? Let's go through this. Is there anybody in this group who would say not cover? Speak up now for CBT. Is there anybody who would say cover under conditions? So, it sounds like its unanimous, cover unconditionally for cognitive behavioral therapy.

John Bramhall: Yes. That's fair.

Sheila Rege: Yep.

Josh Morse: Should we do a roll call then?

Sheila Rege: So, now, I don't think we need to, but if you think you need to?

Josh Morse: Do you want me to record a vote to cover for each person?

Janna Friedly: Yes.

Sheila Rege: No. I think we, yes. We've all just voted.

Josh Morse: You have all just voted to cover?

Sheila Rege: We all said yes.

Josh Morse: OK. Bramhall is a cover. Friedly is a cover. Hearne is a cover. Kleweno is a cover. Mischley is a cover. Rege, Schwartz, Mika Sinanan, Walsh, and Yen I have recorded a cover vote for all ten members for CBT.

Sheila Rege: Correct.

Josh Morse: OK. Thank you.

Sheila Rege: So, now let's go . . . Seth, you had said to tease out the repetitive transcranial magnetic stimulation?

Seth Schwartz: Yeah. I think again, we're all probably in agreement on where we are with that. So, it makes sense to bang it out.

Sheila Rege: And now, we can just do a vote on what we would say on safety, efficacy, cost-effectiveness, whether we would consider that equivocal, more in some, more in all, less than. So, let's go back to that screen. This time, we'll have Tony go first. If you are voting on repetitive transcranial magnetic stimulation.

Tony Yen: Sure. I'm ready. Safety is I think unproven. Efficacy, unproven. Cost outcomes, unproven.

Josh Morse: OK. Thank you. And if you could just give me 30 seconds here, Dr. Rege. I need to update the form I'm working on.

Sheila Rege: OK. Kevin, you're up next. We're just going the other way so poor John doesn't get put on the spot all the time.

Kevin Walsh: Right. Do you want me to wait for Josh?

Sheila Rege: Yes. Wait for Josh.

Josh Morse: Yeah. Just give me ten seconds here. I'm just about there. OK. Ready to go.

Kevin Walsh: I would agree with Tony. I would say unproven for all three categories for rTMS.

Josh Morse: Thank you.

Mika Sinanan: Agreed, unproven for all three.

Sheila Rege: Seth?

Seth Schwartz: Yeah. I'd say less for safety, unproven for effectiveness, and unproven for costs.

Josh Morse: Thank you.

Sheila Rege: And I would vote the same as Seth, less, unproven, unproven.

Josh Morse: Thank you.

Sheila Rege: Laurie?

Laurie Mischley: I vote unproven for all three.

Josh Morse: OK. Thank you.

Sheila Rege: Conor?

Conor Kleweno: Unproven for all three.

Josh Morse: OK. Thank you.

Sheila Rege: Chris?

Chris Hearne: I will also vote unproven for all three.

Josh Morse: Thank you.

Sheila Rege: Janna?

Janna Friedly: Unproven for all three.

Josh Morse: OK. Thank you.

Sheila Rege: John?

John Bramhall: Yes. Exactly the same, unproven for all three elements.

Josh Morse: OK. Thank you. That's everyone.

Sheila Rege: Now, we're going to do the final vote on the rTMS. If you could move the screen that's projected. Based on that, I think we're ready. I would like to hear just on our vote, do we feel . . . we should . . . do we feel the evidence was sufficient to conclude for a vote? So, does anybody here want to cover unconditionally, rTMS? Anybody want to cover under certain conditions? And if you want it not covered, then say aye now. Aye.

Group: Aye.

Sheila Rege: Anybody outstanding? OK. So, I think you have, and Josh, if you want to repeat that for the record, we all say not cover.

Josh Morse: So, I have a no cover vote for all ten members.

Sheila Rege: Yes. Now, we have to shift gears. We'll take maybe sound therapy next. Or should we lump sound therapy and tinnitus specific therapies together? Seth, I'm relying on you, because you helped. I mean, you've seen this process.

Seth Schwartz: Yeah. I mean, it's a little bit challenging to know exactly how to handle this. I think if we do sound therapies alone, we could probably hold that out separately, but I wouldn't object to lumping them if that's what people want to do.

Sheila Rege: Let's do them separately. So, we'll go through the safety on sound therapy.

Mika Sinanan: Can I ask a quick question of Jay before we do that?

Sheila Rege: Yes. Yes.

Mika Sinanan: Thank you. Since L&I covers sound masking for sound therapy, is there something about tinnitus related to an L&I work environment that we should be thinking about in a coverage decision? As I understand it, if we say, for example, not covered, it means we're changing L&I's coverage decision.

Jay Rubinstein: I mean, I don't see a specific difference between tinnitus acquired from noise trauma or from head trauma, from tinnitus due to genetically determined progressive sensorineural hearing loss, but as I told you, indeed it does change the policy, but as I told you before, the number of people who actually use masking whether they're in an L&I circumstance or otherwise is a very, very small number. So, I don't see the impact of such a decision being large. Certainly, it will impact some individuals, but I don't see that as being a broad impact.

Mika Sinanan: Thank you.

Britt Reddick: I just wanted to just note that Dr. Gary Franklin from Labor and Industries just commented. Should I go ahead and unmute him? He can just comment directly.

Josh Morse: Sheila, that's a question for you.

Gary Franklin: I'm sorry. We're not concerned. Thanks for raising that.

Sheila Rege: OK. Well, thank you. So, looking at sound therapy, we're going to kind of go around the room about . . . do we think we need a straw poll? Or can we move to the safety, efficacy, and cost-effectiveness question on sound therapy?

Mika Sinanan: Move to a vote.

Sheila Rege: Let's go, OK. Let's do . . . is everybody comfortable individual votes on safety, cost-effectiveness, and efficacy? Are we comfortable with going there? Or do we have more discussion? This is on sound therapy. So, people who want to vote now say aye.

Group: Aye.

Sheila Rege: Are there people who . . . anybody who does not want to proceed, please say no now. Sounds like we're ready. John, I'm gonna put you on the

spot. We'll move the screen back to the safety. John, what would you say? This is for sound therapy.

John Bramhall: Yeah. So, my perception of the sound therapy data is that there was unproven safety. The efficacy was unproven by the data. Therefore, the cost outcomes are also unproven. So, I am voting unproven for all three categories.

Josh Morse: OK. Thank you.

Sheila Rege: Are you OK? Shall we continue?

Josh Morse: Yes, please.

Sheila Rege: Janna?

Janna Friedly: I am going to also say unproven for all three. Just as a note, I was waffling for safety between equivalent and unproven, but I think the data is just not very good overall.

Josh Morse: OK. Thank you.

Sheila Rege: Chris?

Chris Hearne: I will say unproven for all three, as well.

Josh Morse: Alright. Thank you.

Sheila Rege: Conor?

Conor Kleweno: Unproven for all.

Josh Morse: OK.

Sheila Rege: Laurie?

Laurie Mischley: Unproven for all three categories.

Josh Morse: OK. Thank you.

Sheila Rege: Sheila, same. Unproven for all three.

Josh Morse: OK. Thank you.

Sheila Rege: Seth?

Seth Schwartz: Yeah. Unproven for all three.

Josh Morse: Got it. Thank you.

Sheila Rege: Mika?

Mika Sinanan: Same. Unproven for all three.

Sheila Rege: Kevin?

Kevin Walsh: Yes. Unproven for all three.

Sheila Rege: Tony?

Tony Yen: Unproven for all three.

Josh Morse: OK. Thank you.

Sheila Rege: So, let us move onto a coverage decision for sound therapy. Anybody who says cover unconditionally, say aye now. Anybody who says covered under certain conditions, please say aye now. Anybody who says not covered, please say aye now. Aye.

Group: Aye.

Josh Morse: OK. I have ten no cover. Everybody has voted to not cover for sound therapies.

Sheila Rege: Any abstaining? No? OK. Let's go to tinnitus specific therapies. We'll do the safety data again.

Josh Morse: If you can just give me 30 seconds again.

Sheila Rege: Absolutely.

Josh Morse: Thank you.

Sheila Rege: This time, Tony, if you're OK. We'll start with you.

Tony Yen: OK. So, right now, we're voting on tinnitus specific therapies. Am I correct?

- Sheila Rege: Correct. Any discussion before . . . is everybody comfortable voting? Does somebody want questions or a discussion on tinnitus specific therapies?
- Seth Schwartz: I think there's not that much to say, given the data that we've seen here. I guess the only question would be for the tinnitus retraining therapy, which really is some combination of CBT with the sound therapy. So, I suppose I could see that being a specific condition, but it's hard to really call it out given the little data we're seeing.
- Sheila Rege: That was my, my issue, too, because the . . . so I wonder, I mean, if it's labeled cognitive behavioral therapy, it would be covered. So, I don't know if we need to add in under . . . if it's done with cognitive behavioral therapy. I'd be interested in discussing that. Seth, Jay, do you have any opinions on that?
- Jay Rubinstein: Sorry. I had to unmute myself. I have not seen, as in the report, I have seen no evidence that sound therapies of any sort added with directed counseling, whether or not you call that CBT, has an incremental impact. My own take on the data over all the years that people have been looking at this, is that the directed counseling is really the beneficial aspect of it. No one has been able to demonstrate any additive effect of any of the sound interventions.
- Seth Schwartz: I agree with Jay. I guess the only thing I think, it's already been called out, but I think we need to be very clear that this excludes hearing aids, because I think for the patients that do have associated hearing loss, then hearing aids are effective. That just needs to be very clear that we're not talking about hearing aids.
- Jay Rubinstein: Thank you for emphasizing that, Seth. That's really important.
- Sheila Rege: So, the agency medical director position that I think we were in agreement, noncoverage, but would cover hearing aids if hearing loss was present. That's what you're recommending. Correct?
- Seth Schwartz: Correct.
- John Bramhall: Excuse me, not to get into the weeds here, Sheila, but then there was a small discussion about more advanced more complicated hearing aids that did address the specific issue of tinnitus. So, we're not boxing ourselves into a corner here, I don't think. Hearing aids are, obviously, permitted. Are we making a comment on those more sophisticated hearing aids and the coverage for that second level of intervention?

Jay Rubinstein: Into that additional . . .

John Bramhall: In other words, what I'm asking really is, obviously, someone comes for assessment for hearing aids. They are given a hearing aid. That's obviously covered. Then, they return saying I am still troubled by the tinnitus. Apparently, there was a technical solution to that, that may or may not be effective. We don't have data on it here. I'm just hoping that we're not boxing ourselves into a corner or restricting. I think we may be restricting them the second level of hearing aid technology.

Jay Rubinstein: Yes. I would say we are if the decision is not to cover maskers, because that's what we're talking about here. A masking device as an option to a hearing aid.

Sheila Rege: Are we all still comfortable? We just voted on noncoverage with the agency medical director recommendation on sound therapy. Are we still all comfortable with that? Or do we want to look at that again? I'm hearing we're all comfortable, but.

Janna Friedly: I guess I'm getting a little bit turned around, as to why we need to . . . so, the suggestion is that we need to put specific language in that we would cover hearing aids if hearing loss is present, but that seems to be outside of the scope of what we're asked to do. Then, that implies that we've made a decision about hearing aids, which isn't part of the scope of this. So, I'm a little bit confused.

Sheila Rege: Maybe we could discuss that later, Seth, or Janna? We did say noncoverage but with a caveat that the scope of hearing aids was not in this.

Janna Friedly: OK. So, I just wanted to make sure I knew what we were voting on. That's all.

Sheila Rege: Seth?

Seth Schwartz: Yeah. It's my understanding that was already pulled out, but I just think that there is the potential for some confusion between what characterizes a sound device. I just want to make it clear that a hearing aid is not considered in this group of noncovered things. So, I know it gets complicated when you have a device that has multiple uses or multiple functionalities. So, I think that, at a granular level, might be challenging for an individual to look at, but I think we just have to be

clear that what we're talking about is hearing aids are OK. We're not saying . . . we're saying sound devices are not OK.

Sheila Rege: I would ask if there is somebody from the agency if that is clear enough based on our discussion.

Judy Zerzan: I think so. Yes. That's why I particularly called out a couple of times early on that this does not cover hearing aids for hearing loss.

Sheila Rege: OK. So, we just say that's outside of scope. OK. Everybody comfortable?

Group: Yes.

Sheila Rege: So, sound therapy is not covered. Now, we have to go to tinnitus specific therapies. Let's go around the room in terms of safety, related complications, adverse events, and efficacy, in terms of what the tinnitus symptoms, depression, anxiety, quality of life, and then cost-effectiveness. Where should we start? John, do you want to start? Oh, go ahead?

Tony Yen: Did you want me to start?

Sheila Rege: Yes. Tony. You're doing, yeah.

Tony Yen: OK. That's fine. So, for safety, I would say that's unproven. Efficacy, more in some, and specifically what I'm referring to is the combination of sound therapy with cognitive behavioral therapy. That appears to be within the tinnitus specific therapies. For cost outcomes, would be unproven.

Josh Morse: OK. Thank you.

Sheila Rege: Kevin?

Kevin Walsh: I agree with Tony's caveat regarding effectiveness and his other two criteria, as well.

Josh Morse: Unproven for safety. More in some for efficacy. Cost unproven?

Kevin Walsh: Right, with the condition that he described, and then unproven for cost-effectiveness.

Josh Morse: OK. Thank you.

Sheila Rege: Mika?

Mika Sinanan: Unproven in all three.

Josh Morse: OK.

Sheila Rege: Seth?

Seth Schwartz: Unproven for safety. Effectiveness, I would say exactly what Tony said. So, more in some with the caveat of combined CBT and possible sound therapy. For cost, unproven.

Josh Morse: I'm sorry. For cost-effectiveness, what?

Seth Schwartz: Unproven.

Josh Morse: Thank you.

Sheila Rege: I would say unproven for all three.

Josh Morse: OK. Thank you.

Sheila Rege: Laurie?

Laurie Mischley: Unproven for all three.

Sheila Rege: Conor?

Conor Kleweno: The same that Seth and Tony, the unproven, more in some when paired with cognitive behavioral therapy and unproven for outcome effectiveness.

Josh Morse: OK. Thank you.

Sheila Rege: Chris?

Chris Hearne: I would say unproven for safety. More in some for efficacy. [RD]

Josh Morse: I think you broke up there for cost-effectiveness. Was it . . . what was your vote there?

Chris Hearne: Oh, sorry. Unproven for cost-effectiveness.

Josh Morse: OK. Thank you.

Sheila Rege: Janna:

Janna Friedly: I'm gonna say unproven for all three.

Josh Morse: Thank you.

Sheila Rege: John?

John Bramhall: I'm gonna say unproven for safety. I'm going to say more in some. I agree with that logic. I don't want this to be excluded from combined therapy. So, more in some. Then, unproven cost outcome.

Josh Morse: OK. I think that's everybody.

Sheila Rege: I think we're ready to take a vote on coverage. This is related to tinnitus specific therapies. So, is there anybody who would say cover unconditionally? Anybody who would say cover under certain conditions?

John Bramhall: Yes.

Kevin Walsh: Yes.

Tony Yen: Yes.

Seth Schwartz: Yes.

Chris Hearne: Yes.

Laurie Mischley: Yes.

Sheila Rege: OK. Yes, for Sheila also. Anybody who says not cover? Say yes now.

Janna Friedly: Yes.

Mika Sinanan: Yes.

Conor Kleweno: Yes.

Sheila Rege: Did we get everybody? Did you count?

Josh Morse: I have cover with conditions for Bramhall, a no cover for Friedly. Chris Hearne, what is your vote?

- Chris Hearne: Yes. Cover with conditions.
- Josh Morse: Cover with conditions. For Conor, I have a no cover. For Laurie, what is your vote?
- Laurie Mischley: With conditions.
- Josh Morse: Thank you. And Sheila, you are with conditions. Seth, you are with conditions?
- Sheila Rege: Correct.
- Seth Schwartz: Yes.
- Josh Morse: I had a no cover.
- Mika Sinanan: Right.
- Josh Morse: Kevin, with conditions?
- Kevin Walsh: Correct.
- Josh Morse: Tony?
- Tony Yen: I wanted to have cover with conditions, with the condition being the combined CBT and sound therapy.
- Josh Morse: OK. So, the vote that I have for the committee is seven cover with conditions and three no cover.
- Sheila Rege: So, let's talk about what kind of conditions we are considering. I'm going to start with anybody who wants to speak up. Or otherwise, I'm going to call on Seth.
- Seth Schwartz: I think that everybody's talking about the same condition, which would be the coverage for sound therapy when done jointly with cognitive behavioral therapy.
- Sheila Rege: So, we're talking about, wait. We're talking about tinnitus specific therapy.
- Seth Schwartz: For tinnitus. So, this would be tinnitus, yes. The condition would be tinnitus retraining therapy. The challenge is, again, that that's somewhat

heterogeneous, but specifically, I think, what we're talking about is some form of combined therapy with CBT.

Sheila Rege: So, I, and this is me. I was looking at initially going not cover, but then I was looking at the data and thinking about some of the . . . with cognitive behavior, but why . . . wouldn't it be covered if cognitive behavioral is included? Won't that be covered anyway? Or is there a device that I'm missing? Is there something else I'm missing? I flipped on that. I was thinking one way.

Seth Schwartz: So, the challenge is that I think as they figured out doing these studies is that it's not clear . . . all these different therapies are heterogeneous. So, people aren't talking about exactly the same thing, which makes it challenging, but the ones . . . the tinnitus retraining therapy typically refers to some form of cognitive behavioral therapy with something else. The something else is usually some form of sound therapy. While the data was not great for that, at all, I think it was the one situation where we did see some potential benefit.

Conor Kleweno: I have a question along those lines for Seth. Give us a sense of the cost of the sound therapy that you had, that one would add with this CBT. My concern with the coverage is, people throw in a little bit of kind of CBT so they can add on a very expensive with potentially unproven sound therapy device or sound therapy session. I just wasn't clear on the cost addition for those additional treatments.

Seth Schwartz: Well, again, it's hard for me to speak specifically, because I think the reality is, we don't know. It's so variable depending on who is doing it and where it's being done, and what they even mean. It can be something as simple as a sound machine that you can pick up for \$20 or \$30. Or it can be a complicated combined hearing aid with some form of masking, which can be \$3000. So, the difference can be pretty dramatic. You're right, depending on who is doing it. Some people will say they are doing some form of cognitive therapy just to sell the device. Others are really trying to take care of the patients to their best ability. So, I think there's a real problem here. I'm really on the fence between no cover and cover with conditions, as well, but again, we are seeing some benefit in these situations where patients are getting CBT and some sound therapy. Again, the benefit is not dramatic, but I think there's some evidence for that. So, it's hard to say, because it's so different in every situation. I'm curious if Dr. Rubinstein has comments on that.

Sheila Rege: Hearing Conor, I worry, and Josh, I would like to actually change my vote to not cover, because I do worry that everything that comes up is going

to be called a tinnitus specific therapy device just to get coverage. There was no data on that.

Laurie Mischley: I would like to change my vote, as well, to noncover.

Josh Morse: OK. I have changed two votes from cover with conditions to not cover, one for Laurie Mischley and one for Sheila Rege.

Sheila Rege: Let's continue the discussion. Go ahead. Sorry, Kevin.

Seth Schwartz: I think Seth makes a compelling case about the difficulty in controlling this combined therapy. So, I would vote for no cover.

Josh Morse: I have changed your vote to no cover.

John Bramhall: I don't want to be a hold out. So, I don't feel . . . what I wanted was to be able to feel that we were still committing the full scope of cognitive therapy. It may be that some practitioners that want to incorporate sound therapy into that cognitive therapy. I'm not quite sure that I want to split those two out, but I think I probably would go . . . I'm persuaded by the majority opinion that we shouldn't cover it as an individual process. So, I will change my vote to uncover.

Josh Morse: OK. I have changed your vote.

Jay Rubinstein: My nonvoting contribution to this discussion is, I share Seth's concern for the practitioners who are just trying to do the best they can for their patients, but I would also be concerned about gaming the system, which is the other concern that was mentioned. I think that's a significant concern.

Seth Schwartz: Just to be clear, when we sort of did that vote, I wasn't actually . . . I didn't realize that was our binding vote. I was saying I think we need a little bit more discussion about what the condition would look like, because I think this would be the only condition that has any weight behind it, but I tend to agree with the group. I think it may not be compelling enough to offer coverage, but it's just something I think we needed to talk a little bit more about.

Sheila Rege: Right. We can consider our vote that we did a straw vote. Then, we can go around the room again for a final vote based on the discussion. I think this is a very important discussion. Is there any more discussion on tinnitus specific therapy conditions? I think right now, everybody, we'll

have Josh, just for the record, go through the votes. We can let them know if we're changing or not.

Mika Sinanan: From an evidence standpoint, the majority of the RCT's in that segment of the review showed no benefit. So, it's only two studies, and only one with significant numbers that show a potential benefit from an evidence standpoint. It seems to me that we really don't have the evidence. That's the reason I voted the way I did.

Sheila Rege: Any more discussion, or are we ready? We're going to, John, I'll start with you. What's your final vote on tinnitus specific therapy?

John Bramhall: I'm going to vote no coverage.

Sheila Rege: Janna?

Janna Friedly: No coverage.

Sheila Rege: Chris?

Chris Hearne: I'll vote no coverage.

Sheila Rege: Conor?

Conor Kleweno: No coverage.

Sheila Rege: Laurie?

Laurie Mischley: No coverage.

Sheila Rege: No coverage. Seth?

Seth Schwartz: No coverage.

Sheila Rege: Mika?

Mika Sinanan: No coverage.

Sheila Rege: Kevin?

Kevin Walsh: No coverage.

Sheila Rege: Tony?

- Tony Yen: Cover with conditions, with the condition that I mentioned before about combining CBT with sound therapy.
- Josh Morse: OK. I have nine no cover, and one cover with conditions.
- Sheila Rege: Correct. Tony, I hear you. Do you want to talk about it? Or are you good with the vote, and we'll move onto . . .
- Tony Yen: That's OK. I'm fine with the vote.
- Sheila Rege: . . . OK. Alright. We skipped a step. I just want to make sure we have nothing to add there. That was me. Was there any . . . on the one coverage, was there any safety issues we had missed? I mean, we have . . . I don't know. Josh, if you can go back, serious adverse events. It was device related complications, but cognitive behavioral therapy, there's nothing else in safety. We have that just . . . if there's anything we have to add to our list. The efficacy, I like what's already in our document, depression, anxiety, sleep, health related, quality of life, functional status, tinnitus symptoms, severity, and we already talked about cost-effectiveness. Is there any special population consideration we need to think about? We kind of touched on L&I. We discussed that, but it wasn't felt to be important. Are there any other considerations? On the PDF, I'm going to page 44. OK.
- Mika Sinanan: Children versus adults?
- Josh Morse: For the safety? Or for special populations?
- Mika Sinanan: For special populations. Does the coverage include children?
- Sheila Rege: I would think it would.
- Mika Sinanan: Jay, any comments about that?
- Jay Rubinstein: Yeah. So, tinnitus in children is a very different animal from tinnitus in adults. In my practice at Children's, I see a lot of kids with tinnitus. In children, it's much more common to find tinnitus with normal hearing. We know none of the studies that we've talked about, I believe, include a pediatric population. We know very little. On the other hand, my sense is that CBT is likely the best intervention we have for kids. I certainly would not want to exclude children from the CBT coverage decision, but I would acknowledge that we have minimal data in that population.

- Josh Morse: So, the scoping document makes clear that this was targeted to adults only.
- Mika Sinanan: Thank you.
- Josh Morse: Thanks for bringing that up. Let me make sure that I'm getting that from the document here. Adults with subjective tinnitus that is bothersome. That is how it's phrased.
- Sheila Rege: Thank you, Mika. That was good to bring it up. Now, we have to discussion item whether the determination is consistent with identified Medicare decisions or other expert guidelines. I think we've discussed that with the report. There was no Medicare national determination. We looked at commercial payers and also the NICE guidelines. Any other discussion about that?
- Josh Morse: So, from the report, there is not currently a national coverage determination in Medicare for masking devices. There was historically, according to the information on your screen. Then, you need to decide if your determination agrees or disagrees. If it disagrees, you're rational for not aligning with existing professional guidelines.
- Sheila Rege: When I looked at it, it looked like we agreed. Does anybody disagree?
- John Bramhall: No. It looks consistent.
- Sheila Rege: Yeah. It looks consistent. Josh, are we missing anything else?
- Josh Morse: No. I think that's it. Does this . . . I have the rough draft here. Does this look accurate to what you have . . . per your vote. We can clean up this language around hearing aids, but I wonder if this looks OK to you. This is what I've recorded.
- Mika Sinanan: Josh, we can . . .
- Sheila Rege: Secondary for adults . . . go ahead. That is bothersome. You're OK with that? That is bothersome, that descriptor, adjective?
- Mika Sinanan: . . . that was my question is, do we have to use that term, because subjective tinnitus is an oxymoron. It's always subjective.
- Judy Zerzan: It's actually not always subjective. There are anatomical conditions that make it objective. That was out of the scope of this review.

- Mika Sinanan: OK.
- Jay Rubinstein: That is correct. There are rare forms of tinnitus that other people can hear, other than the person who has it. That's a very different animal from what we've been discussing this morning. So, subjective tinnitus is the correct term.
- Sheila Rege: And you're OK with bothersome as a . . .
- Janna Friedly: Correct me if I'm wrong, but isn't that the language that was used to develop the report. So, to change it now doesn't make sense?
- Josh Morse: Or it could be said it warrants treatment is another way it's phrased in the population document, or the PICO.
- Sheila Rege: I'm fine with bothersome if we're OK with it, as a group.
- Jay Rubinstein: I like bothersome, because first of all, nobody whose tinnitus is not bothersome would even consider CBT. It indicates that it's not just somebody with tinnitus. It's somebody with tinnitus that they really want to address in some way, or feel they need to address in some way, because everybody who has tinnitus would like it to go away. So, you can argue that everybody's tinnitus is bothersome, but you have to add some word onto the sentence subjective tinnitus to indicate those who are, who would want to and are appropriate to undergo CBT.
- Tony Yen: Jay, is there any threshold, like, on the bothersome index, that we should include? I agree with you, nobody is going to go through CBT if they're not that bothered. I just don't know if we need language for a threshold level of bothersome or not.
- Jay Rubinstein: The term I use typically in my research is disabling, but I'm typically referring to people who would consider some sort of surgical intervention to eliminate their tinnitus, if such an intervention existed.
- John Bramhall: Jay, can I just ask you, if we used subjective, which seems appropriate, does that eliminate people who are suffering from auditory symptoms of hypertension, for example? Is that considered something different from subjective?
- Jay Rubinstein: No. That's a pulsatile tinnitus from hypertension or from carotid bruits. Those are all still subjective tinnitus if another person can't hear the noise coming out of their ear. Again, that's a very small group of people relative to what we're talking about.

- John Bramhall: OK. Thank you.
- Sheila Rege: So, if we were in person, we would walk away, stretch, to make sure this is a coverage determination. Is there anybody who wants to look at this again after our break? Or are we comfortable? I'm comfortable with this, but I'm giving people the option.
- Jay Rubinstein: Is the caveat with the hearing aids just adding confusion that we had before? We're clearly going to cover hearing aids for hearing loss, but we're not going to . . .
- Sheila Rege: . . . that language . . .
- Jay Rubinstein: . . . we're not going to cover masking devices. So, what I don't want is for people to see that statement and say, well, the patient has hearing loss. So, now they're going to get the fancy hearing aid with the masking device. It's a hearing aid. Whereas, we are considering that a masking device.
- Sheila Rege: Maybe just a noncoverage with a star that says hearing aids are outside the scope of this determination.
- Janna Friedly: I feel like that covers it well, the asterisk at the bottom.
- John Bramhall: I agree. It's quite clear in that note at the very bottom.
- Mika Sinanan: My only suggestion is to move the hearing aids for treatment of hearing loss are outside the scope of this determination just from a wordsmithy standpoint.
- Chris Hearne: I was going to suggest that, as well.
- Josh Morse: Sorry. Can you say that again? Hearing aids for treatment of . . .
- Mika Sinanan: For treatment of hearing loss.
- Josh Morse: . . . alright. Thank you.
- Seth Schwartz: Agree.
- Sheila Rege: OK. Any other discussion on this?
- Janna Friedly: No.

- Sheila Rege: OK. So, everybody likes this. I think we don't need another vote, Josh. We're good.
- Josh Morse: So, you have voted four times. Three noncoverage votes and one cover vote. You checked for Medicare national coverage determinations and professional guidelines.
- Sheila Rege: Well, thank you. For our first non in-person, I think we . . . thank you, to the team, the staff, and our experts for doing this. I think it went better than expected. Should we take a half hour break and then return? So, we'll be a little bit off schedule. So, we'll come back at 12:30. Will that be a problem for the open public comment, Josh?
- Josh Morse: No. I don't think being a little bit should be a problem for that.
- Sheila Rege: So, we'll come back . . . is everybody OK coming back at 12:30? Or does somebody want to come back at 12:15?
- Janna Friedly: 12:30.
- Sheila Rege: Everybody who wants to come back at 12:30 say aye.
- Group: Aye.
- Sheila Rege: Everybody who wants to come back at 12:15, say aye. OK. We got 12:30.
- Josh Morse: OK. We'll resume at 12:30.
- Josh Morse: We have 8 out of the 10.
- Sheila Rege: We have enough of a quorum. Dr. Novotny, thank you for joining us. If you wouldn't mind introducing yourself to the rest of the committee members.
- Edward Novotny: I'm Edward Novotny. I'm currently the director of the epilepsy program at Seattle Children's. I'm a professor of both neurology and pediatrics at University of Washington. I am also representing . . . I am also on the professional advisory board and the board of the epilepsy foundation of the State of Washington, as well as the National Epilepsy Foundation professional advisory board. I'm here as the clinical expert with regard to the use of vagal nerve stimulation in the form of neuromodulation that's been used for treatment of epilepsy, as an adjunctive therapy, of which I

have been involved for over 30 years. I'm looking forward to participation in this event.

Sheila Rege: Thank you. Welcome. Josh, I will turn it over to you to give you screen to the agency medical director.

Josh Morse: OK. And I am shifting my screen. Dr. Transue, are you there?

Emily Transue: I am.

Josh Morse: OK. I am giving you control for when you are ready.

Emily Transue: Alright. Are you seeing my screen now?

Josh Morse: Yes.

Emily Transue: Why is it at this moment you forget how to [inaudible].

Sheila Rege: While, we're waiting, John Bramhall, you're back. There was another person, I can't remember, but we're going to go ahead and start.

Emily Transue: Hi. I'm Emily Transue. I am the Associate Medical Director at the Healthcare Authority. I am here to talk today about vagal nerve stimulation for epilepsy and depression.

As everyone is aware, the vagal nerve is the 10th cranial nerve. It's the largest autonomic nerve in the body interfaced with parasympathetic control of multiple organs. Vagal nerve stimulation has been studied for the treatment of epilepsy and depression. It has also been considered for treatment of other conditions, including fibromyalgia and migraines. The nerve can be stimulated via transmitter implanted below the clavicle with electrodes wrapped around the left vagal nerve at the carotid sheath. Transcutaneous stimulation of the nerve at the ear, where it has sensory [inaudible] has also been studied. That's known as TVNS. The mechanism of action is somewhat poorly understood, but is presumed to involve neuromodulatory effects.

This panel has reviewed VNS previously. It was evaluated by the Health Technology Clinical Committee in 2009. The determination at that time was for coverage for management of epileptic seizures in patients 12 years old or older with a medically refractory seizure disorder. It was determined to be noncovered for management of depression. An updated literature search in 2013 did not indicate that there was new evidence with a need for rereview. However, in 2017, the FDA lowered

the age of coverage of VNS, which had previously been 12 for epilepsy down to 4. The 2009 Health Technology Clinical Committee review had not addressed younger children, and one of the reasons for returning to this topic today was the need to clarify coverage for that age group.

A policy question today, should vagal nerve stimulation be covered for epilepsy, and under which conditions, including age questions above. Should it be covered for depression? And if so, under what conditions? And should transcutaneous vagal nerve stimulation be covered, and if so when.

Current state agency policy reflects [inaudible] Health Technology Clinical Committee determination. For PEBB and SEBB and UMP, and Medicaid and L&I, it's covered for refractory epilepsy for patients 12 and older and noncovered for depression.

This is a look at utilization. So, this is looking at Medicaid, a combination of fee for service and managed care in 2017 to 2019. This looks at all VNS procedures [inaudible] implantation, but also subsequent procedures. In the light blue, we have the total number of patients. In the dark blue, we have that [inaudible] numbers. They seem fairly steady utilization over time, maybe going up a little. Cost per patient, again, for all procedures, not just for implantation, climbing a little bit over time to about \$3500 up to now around \$4000.

Here you see the same numbers looking at the UMP population. We have two years of data here, again, for all procedures. Light blue is total patients, quite a bit smaller than in Medicaid, but the number per 100,000 number shows it is fairly similar. Costs here are quite a bit higher, as we typically see in our commercial population. It's running around \$19,000, came down a little bit in the most recent year to \$17,000.

Looking specifically at the implantation procedures alone, here we only have the numbers to display this for Medicaid. Again, holding relatively steady over time, maybe up a little bit. The implantation cost is quite a bit higher. So, Medicaid here we're seeing around \$10,000 per patient for the implantation. To the right, we look at the number of patients aged 4 to 11 who have received implantations. This is just to show that despite the absence of a coverage policy for this age group, we have seen some utilization in this group, as well.

Here, we're looking at costs in the first year of implantation versus subsequent years with some procedures, such as spinal cord stimulation,

we see quite high ongoing costs. So, there was an interest in looking at how costs trended over time. So, this is just the patients who had an implantation in 2017. You will see their first year costs were around almost \$10,000. Then those dropped precipitously in subsequent years. So, really, the primary costs around this procedure is the initial implantation.

Looking at coverage comparisons, Medicare has a national coverage decision stating that VNS is reasonable and necessary for patients with medically refractory partial onset seizures for whom surgery is not recommended or has failed. It emphasized partial onset here, because one of the things that you'll see as we go on is that different recommendations and different studies include partial onset in some circumstances. At other times, they don't differentiate on that. So, I wanted to call that out. The national coverage decision does not consider it to be reasonable and necessary for other disorders. Depression is covered in Medicaid only in the setting of a clinical trial. There is no local coverage decision.

Aetna's policy is VNS is considered medically necessary for members with focal seizures refractory to optimal medication or surgical intervention, or with debilitating side effects. They also have coverage for Lennox-Gastaut, which is a rare childhood condition included here just for completeness. They consider tVNS experimental for epilepsy. Both modalities are considered experimental for depression.

Regence considered VNS medically necessary for those with refractory seizures not differentiating between partial or generalized onset who have tried and been unresponsive to at least two antiepileptic drugs. They consider VNS for other indications, including depression to be investigation, and the use of tVNS to be investigational.

CIGNA, somewhat similarly, considers VNS necessary for medically intractable seizures of any type when there is failure to suitable medical and pharmacologic management. Investigational for depression and tns [inaudible].

Moving on to look at guidelines here for VNS for epilepsy. The NICE guideline consider VNS indicated for adults, children, and young people. I'm curious about the distinction between young people and adults and children that they make. With epilepsy refractory to medication and unsuitable for surgery, this is for both focal and generalized seizures. This was a good quality guideline. The Scottish Intercollegiate Guidelines Network considers this appropriate for consideration in medically

refractory patients who are unsuitable for respective surgery, again good quality. There was one guideline on infantine epilepsy, which essentially concluded that there was not adequate evidence to make a decision, but that it could be considered under appropriate circumstances.

Guidelines around depression, working group out of Spain considers that VNS outside of research should be discouraged, because of its invasive nature and uncertainty about efficacy and adverse events. This was the one good quality guideline around depression. The Canadian Network for Mood and Anxiety Treatments considers this third line for refractory depression after repetitive transcranial magnetic stimulation and ECT. The Veterans Affairs Department recommends against VNS for depression outside of a research setting.

Agency medical director concerns around this topic are high for safety, efficacy, and cost.

Key questions for epilepsy, what is the evidence on efficacy and effectiveness for children and adults? What are the harms? Do these vary by patient characteristics and other features? What is the cost-effectiveness and other economic outcomes?

Key questions are the same for depression, but looking at treatment resistant depression rather than epilepsy.

Moving to the epilepsy evidence, these will be reviewed in detail by our evidence reviewers, but I wanted to call out some of the themes and variability in the evidence, maybe harkening back to Judy's theme of heterogeneity earlier. There are six RCT's that met inclusion criteria. Most of these compared high stimulation to low stimulation VNS with low stimulation essentially as a sham treatment. One compared VNS with best medical practice to best medical practice alone. There was one looking at high stimulation versus low stimulation tVNS. When you look at the ages included, they varied between studies. Some were adults only. Some included children down to age 12, and one down to age 4. With also a mix of studies, including partial onset only versus any type of seizure. Fifteen nonrandomized trials were also included. I will call out that nearly all of the trials identified have a moderate to high risk of bias and relatively low degree of confidence.

Again, you'll see all this data in more detail in the evidence review, but looking at some of the key results in the randomized controlled trials. For high stimulation versus low stimulation VNS, looking at rate of response, which was defined as 50% or greater reduction in seizure frequency,

which is significant improvement with high stimulation VNS with about a 1.6-fold greater response. For reduction in seizure frequency, there was a drop in frequency of around a third, which was also significant.

For VNS versus treatment as usual, the rate of response was somewhat similar but was not significant. We did have somewhat low numbers here.

Looking at benefits for transcutaneous VNS, looking at rate of response, we essentially see no difference between high stimulation versus no stimulation VNS.

Turning to harms, these are a number of the harms, which are typically associated with this treatment, including hoarseness, cough, and dyspnea, pain, typically at the insertion site, paresthesias, nausea, and headache. We see that a few of these were statistically significant in these studies, which are highlighted in orange. Others may be suggestive, but do not reach the [inaudible].

One additional policy questions that we wanted to call out around epilepsy is the question of the definition of medically refractory. These definitions vary between different studies, guidelines, and policies. Typically, this involves an adequate therapeutic trial of two to four medications. Notably, the likelihood of response diminishes with each additional drug that is tried. The international league against epilepsy had a taskforce on this topic, which proposed a definition of failure of adequate trials of two tolerated appropriately chosen and administered antiseizure drugs, either monotherapy or in combination to achieve seizure freedom. Notably, however, a followup study cited here noted that particularly in children around a quarter of those classified as intractable by this definition would achieve a sustained response to additional medications. They suggested using a threshold of three rather than two medication trials to define medically refractory.

Looking at the evidence around depression, there were five studies included resulting in nine publications. Two were randomized control trials. One randomized study both with moderate risk of bias and two nonrandomized studies with high risk of bias.

Looking similarly at the results here for high versus low stimulation VNS, looking at a 50% reduction in the Montgomery Asberg Depression Rating Scale. We see significant improvement around two-fold. Suicide death was about the same. Suicide attempt slightly but not significantly lower.

Looking at VNS versus sham with 50% reduction in depression score, again slightly better, but this time nonsignificant. Suicide death was actually slightly higher in the high treatment group here, but all collective deaths was just a single incident.

Harms of depression, again . . . sorry, harms of treatment in the depression studies, again, the same list. Again, a few that came out statistically significant. The others not, although numbers were limited.

One additional risk that we felt it was important for this group to be aware of, this comes from the FDA MAUDE database, this is postapproval data identifying adverse events. It may be too rare to show up in clinical trials but did emerge with tracking over time. There are multiple reports of bradycardia. Some were preceded with asystole up to 15 seconds. Some of those resulting in drop episodes that were often initially confused with seizure. Most of these patients had a normal baseline EKG. The reported episodes resolved with turning off or removing the VNS device. This is believed to be rare but potentially serious. We felt that it was important for the committee to be aware.

Differential impact by patient characteristics. Again, the evidence reviewers will go through this in detail, but essentially, no major distinctions were identified by patient subgroups or other characteristics for either depression or epilepsy.

Cost-effectiveness, for epilepsy, there was very limited data. In children specifically with tuberous sclerosis who had failed two medications, there was a cost per QALY adjusted life year that was below the willingness to pay threshold at \$13,000/QALY, but it was less cost-effective than other interventions, such as additional medications or a ketogenic diet. Another study looking at children age 12 and older with drug resistant partial onset seizures found a five-year net cost savings of about 21% of cost relative to medication alone. This was primarily driven by a decrease in seizure related hospitalizations. The placement costs were off that 1.7 years after placement.

For depression and for tVNS for either indication, there was no data available on cost-effectiveness.

Final recommendations are that vagal nerve stimulation for epilepsy be covered with conditions. We recommend that it be considered medically necessary when the following are met, seizure disorder refractory to medical treatment, defining that as at least three adequate trials of anti-epileptic medication. They based at three on the study I mentioned

earlier. Where surgical treatment is not recommended or has failed. We considered the question of whether this should be only for partial onset seizures, but a combination of factors, including the evidence was mixed, including trials of both kinds of seizure, as well as partial onset only. Also, that the existing recommendation covers all kinds of seizures. The one trial in younger kids included both types.

Our recommendation for vagal nerve stimulation for depression is that it be noncovered. Our rationale here is the compelling evidence for the effectiveness and safety is lacking. Also, that there are multiple other effective modalities for management of treatment resistant depression that exists and are covered. There is a large clinical trial, which is finishing in 2022. Depending on those results, it is possible that a rereview would be indicated.

Our recommendation for transcutaneous vagal nerve stimulation is that it not be covered. Again, this is based on the lack of [inaudible]. Any questions?

Sheila Rege: Thank you. That was very helpful. If there are no questions for Emily, we could move onto the public comment.

John Bramhall: Sorry to be late. Could I just possibly ask Emily one question about the conditions for coverage? Emily, you put up . . . seizures refractory to medical treatment with three adequate trials. I just wanted to ask maybe semantic. If the medical treatment ‘cures or treats’ effectively the seizure, the epilepsy, is there a space for people who don’t tolerate the medications well, even though they are suppressing the epileptic seizures?

Emily Transue: That’s a great question. I think it would be appropriate to have coverage for those who are intolerant of medications, as well. I think that would be a very reasonable addition.

John Bramhall: OK. Thank you.

Emily Transue: Yeah. Refractory to or intolerant of . . . go ahead.

Edward Novotny: I think that’s . . . failure also includes intolerance. That’s a very common reason why drug failure works. Side effects or intolerance to treatment or to the medication.

John Bramhall: OK.

- Laurie Mischley: I had a quick question. You showed really nice data on the cost of VNS but didn't mention any costs associated with the transcutaneous VNS. Can you just speak to that?
- Emily Transue: We don't cover it currently. So, we have not. We don't have any cost data to present around it, in terms of our experience. I don't have information immediately available on typical charges. I don't know if that's something that our expert could speak to at all.
- Sheila Rege: Are you muted, Edward?
- Edward Novotny: I'm not an expert on tVNS. That's something I don't prescribe either.
- Sheila Rege: OK. Any more questions? Thank you. That was very informative. Should we go to public comment? Again, this would be three minutes each, name, conflicts, and disclose if anybody has paid for your travel or time here.
- Josh Morse: Dr. Rege, we have four separate groups that have signed up. We've made arrangements for pooled time. The first commenters are Dr. Gwinn Ryder and Cathy Hill, and Dr. Gwinn has five minutes. I will time this, Dr. Gwinn, and if we get to five minutes, I will let you know that your time has been used. Some commenters have slots. Let me just grab this slide. If you can let me know when you'd like me to advance your slides, I will do that. Let's just make sure I can find the present button.
- Britt Reddick: Dr. Gwinn, I am going to unmute you now so you are able to speak.
- Ryder Gwinn: Great. Thank you, very much. I'm Ryder Gwinn. I am a neurosurgeon working at Swedish Medical Center. I've been treating patients with epilepsy and depression using neuromodulation for 16 years now. I've been asked to represent organized neurosurgery today for this meeting. We really have nothing to say about the epilepsy recommendation and want to focus on depression. If you could advance two slides, I would love it. This is the summary I've taken from the final evidence report from OHSU and that's being used today. Here, it says there is a lack of robust evidence on the effectiveness of VNS for treatment resistant depression in adults. We wanted to kind of give a little bit of feedback about that conclusion. If you could go back one slide then now. A lot of this is taken from the final evidence report here, as you had mentioned before. There are two randomized trials looking at treatment resistant depression with the use of the VNS. There is a high versus low stimulation with Aaronson in 2013 and on VNS versus sham in 2005. I just wanted to note that the high versus low did show a higher rate of

response with the MADRES compared to the low stimulation, but not associated with reduced depression severity. Then, the sham . . . the other study did not show a difference between the groups sham versus VNS. However, with both of those studies, if you look at the response versus baseline, they are significant. So, the real question here is why have the sham groups responded, or the low stimulation groups responded, as well? There is another very good five-year open label study by Aaronson in 2017 looking at VNS with treatment as usual showing that it is more treatment . . . excuse me. VNS with treatment as usual is more effective in reducing depression symptoms and had higher response rates than treatment as usual alone and may be associated with lower mortality rates. If you could go forward two slides now. I just kind of wanted to go through . . . sorry, back one. I wanted to go through some of the highlights from the final evidence report that were positive for VNS in treatment resistant depression. There was an increased response rate when compared with low stimulation, as I've talked about. VNS with treatment as usual reduced depressive symptoms more than treatment as usual alone. VNS with treatment as usual also resulted in higher rates of response compared to treatment, as usual alone. There were guidelines that did recommend vagal nerve stimulation as you had mentioned earlier by the Canadian Network for Mood and Anxiety Treatments. They recommended it as a third line treatment after transcranial magnetic stimulation and ECT. In fact, CMS has issued a national coverage decision that covers VNS when it is associated with the CMS approved double blind placebo controlled trial that is underway. So, if you could go to the next slide. I want to go back to the issue of the problems that we've had with the randomized studies. Here, this again, is from the final evidence report, the Aaronson study D21 from 2013 showed that at week 22, remission was not significantly different between the treatment groups. However, it was significantly different from baseline. They also say at week 50, response was numerically higher than it was at week 22. So, an improving response over time, but there was no difference between treatment groups, but this is an open label phase where both groups would be receiving whatever treatment was desired at that point in time. So, there really was no comparison group anymore at week 50. So, you wouldn't expect to see a difference between the groups. If you could go to the next slide there.

Josh Morse: OK. And 30 seconds.

Ryder Gwinn: Other neuromodulation, you can see here on the left that VNS, both the low, medium, and high doses in the D21 group had a response that lasted for a good 18 weeks. With the low dose group, you do see a little bit of a return to the norm in their IDS scores, but not in the medium or high

groups. Then, it goes into the open label phase. So, you really lose your ability to look at how that low treatment group might have gone back further towards their baseline. This looks very similar to other neuromodulation that we have studied. On the right, you see the RNS trial for treatment in epilepsy. You see that the sham and treatment groups both got much better right after implantation, but over time, slowly, the sham group got more back towards its baseline so that we were able to see a difference, a statistical difference.

Josh Morse: That's time.

Ryder Gwinn: Well, let me just summarize by saying that significant . . . you can go to the last slide. Significant improvement in depression scores were seen with VNS stimulation. It's been recommended, as a third line treatment with fair guidelines. It has clear improvement and remission response rates and mortality. It behaves like many other neuromodulation therapies with an increasing responder rate over time. Randomized control trials that don't last for years will not reflect this well. We need definitely better options for patients with treatment resistant depression. We would ask that the HCA cover it, but if they are unable to do that, then we would please request that Washington State patients would be able to participate in the coverage with evidence CMS trial. Thank you, very much.

Josh Morse: OK. Thank you. The next speakers are Dr. Allen and Bess. I do not have slides for you. Is that correct?

Dr. Allen: That's correct.

Josh Morse: If you could please state if you have any conflicts of interest. I'll remind everybody that for scheduled public comments, the information about the speakers and their conflict of interest forms are available on the meeting materials.

Dr. Allen: We have one conflict of interest in that our clinic is participating as a site in the RECOVER CMS trial on VNS efficacy. So, we have no financial interest in that. We are a site for the study.

Josh Morse: OK. Same as the previous, I'm going to start the time for five minutes. Thank you.

Dr. Allen: OK. So, we are physicians who work at a treatment resistant depression center. So, we are in a unique position to address this sort of multiple other effective modalities arguments that Dr. Transue made about why

VNS isn't worth covering. We offer, esketamine and medications and ECT. In fact, our ECT program is the largest in this quadrant of the country. We have a handful of patients who have had VNS implanted for depression. So, we can speak to, clinically, how we actually use this tool. We would never implant VNS for mild or moderate depression. We have only used it in people who have had ECT, which is much, much worse in terms of every aspect of side effects or risk that you guys have mentioned so far with VNS, who have had a partial response to ECT but not a durable response. The 2017 study by Anderson et.al that had that five-year followup, there was a subgroup in that study where patients that had a history of response to ECT had a significantly higher five-year accumulative response rate of 71.3%, which is just very, very high. A five-year followup is showing that the VNS had increasing effectiveness over time, which is what we see clinically. Dr. Bess?

Joshua Bess: I 100% agree with what Dr. Allen has already said. I can just tell you from personal experience and individual patients that these are the people who can maybe get to a point where they're coming to ECT every other week, still suffering side effects, keeping the depression at bay, but they don't have any kind of quality of life at that point. We have been able to use VNS in that situation to further taper ECT and stop ECT. Two people who I have worked with recently who have VNS have both gotten their lives back on track after multiple years of disability and poor ability to function, not to mention severe depression, suicidal ideation, and attempts.

Dr. Allen: What we're saying really is, the risk versus benefit considerations of VNS change depending upon what patients you're talking about. So, everything you've said about VNS not having enough evidence to support makes sense, if you're talking about mild or moderate patients with depression, or even severe depression where they haven't tried very many medicines, haven't tried esketamine, haven't tried TMS, haven't tried ECT, but who actually wants these implanted devices? And who would we, as clinicians, give these implanted devices to? It's the worst of the worst of patients who have really failed everything else. The risk versus benefit considerations, I mean, what is hoarseness? What is a one-hour procedure with a low risk of infection compared to the damage that depression does to their lives and to the people around them. And when you're thinking about a person who is undergoing ECT over and over and over with the cognitive side effects with the repeated anesthesia with cost to the system of that, VNS really does make sense in some people with depression. It would be a shame to not have that option. We agree with the Canadian Network 2016 recommendations that VNS would make sense as a third line treatment for refractory

depression after trying the other effective modalities, but the reality is, those effected modalities are not effective in everybody. So, TMS, transcranial magnetic stimulation, works in five or six out of every ten people with depression. Esketamine works in five to seven out of every ten people with depression. ECT works in about eight out of every ten people with depression. So, you're left with people who really don't respond to any of those options or who have a response to ECT, but it's too temporary, and we can't taper them. VNS in those cases really can make a difference. We have seen it make a huge difference. There is evidence to support that from this five-year observational study.

Josh Morse: You have about 30 seconds.

Dr. Allen: Dr. Bess, is there anything?

Joshua Bess: I think putting on the other hat of WSPA president and Dr. Allen as president elect, I mean, a big part of our mission is to advocate for the people who are overlooked and left behind. I make it my mission statement to never tell someone that I don't have anything to offer them. So, this is a very important tool in the toolbox.

Josh Morse: OK. That's time. Thank you. So, our next scheduled public commenter is Dr. Dunner. I have your slides.

David Dunner: Thank you. Can you hear me?

Josh Morse: Yes. We can hear you.

David Dunner: Thank you.

Josh Morse: So, you have three minutes. If you could please state if you have any conflicts. I will let you know, as time goes.

David Dunner: Thank you. Our conflicts are on the next slide. The most pertinent one is that I'm also an investigative site for the RECOVER study, but we haven't received \$10,000, as of this morning. I have spent my academic and clinical career involved in evaluating and treating patients with treatment resistant depression and also doing research on these patients. This was begun at NIMH and then Columbia University and a long stint at the University of Washington, and currently at the Center for Anxiety and Depression on Mercer Island. We were the first in the Northwest to treat patients with vagal nerve stimulation for treatment resistant depression and to treat patients with TMS and also to provide patients with esketamine nasal spray for treatment resistant depression. Considering

definitions of treatment resistant depression, I think I agree with our previous presenters that VNS is really for patients with severe treatment resistant depression. That's defined as patients who fail four or more treatments. They are not likely to respond to the next treatment trial. In contrast to one of Dr. Transue's slides, there aren't good options for these patients. They are actually very few that might be effective. They are esketamine nasal spray, TMS, ECT, and VNS. As a clinician who deals with these patients on a daily basis offering treatment opportunities for patients is important. Some of the patients don't opt for these treatments, because of cost or convenience issues. VNS for depression is not experimental. Its FDA approved. It's an effective treatment for patients with treatment resistant depression. The efficacy is slow but increases over time. It's safe. It's well tolerated. There are comparator studies that I think were ignored, particularly the Aaronson 2017 study, which really wasn't brought up in the database, because it wasn't a randomized control study, but I think it undervalues the clinical effect of VNS. That study and other reports suggest that VNS reduces suicidal behavior and also reduces medical costs. The statement from Dr. Transue's presentation that there was no cost reduction data I think is not consistent with the Aaronson study and also a study that I authored several years ago.

Josh Morse: That's time.

David Dunner: Thank you. Last slide, please. In summary, I think this is an important treatment for a severe treatment group who don't have good treatment options. I would hope that you would approve its use for this population. Thank you.

Josh Morse: Thank you, Dr. Dunner. We have a final group of individuals. They have each agreed to three minutes. We will start with Dr. Dicarlo. It'll take me a moment here to get the slides up.

Britt Reddick: Hi, Dr. Dicarlo. I just unmuted you. Are you able to speak? Check your audio? Dr. Dicarlo, will you be presenting today? I've unmuted you.

Josh Morse: We can come back to Dr. Dicarlo. Is Dr. Aaronson unmuted?

Britt Reddick: Yes. Just one moment.

Josh Morse: Thank you.

Britt Reddick: Dr. Aaronson, you should be unmuted now. Are you able to speak?

Scott Aaronson: Can you hear me?

Britt Reddick: Yes. Thank you.

Scott Aaronson: OK. Terrific. So, I'm Dr. Scott Aaronson. I do have a conflict of interest in that I have been a consultant to LivaNova, the manufacturers of the vagus nerve stimulator. You've heard my name come up a whole bunch of times, because I'm the author of papers that came out in 2013, as well as 2017 looking at vagus nerve stimulation for treatment resistant depression. I do think that some of the introductory comments were really, as previous speakers have said, have really not grasped who our patient population is. When you look at a treatment-resistant depression population, and you look at drugs that have been approved for treatment-resistant depression, we're looking at folks who have failed one to three treatments. We're really looking at people who have failed a minimum of four treatments. The average number of treatments that people have failed, particularly in my five-year observational study, was eight. You would really need to demonstrate to me that you have any evidence that anything that's currently approved by you is able to have any efficacy whatsoever in people who have failed eight and more treatments. This is a patient population that is severely impaired, chronically ill, and most often disabled by their depression. The morbidity expenses account for 40% of the 100 billion dollar annual expense of depression in the U.S. We've got very little to offer these folks. Let's just skip over this, move onto the next slide. This is just data about the observational study. I do want to mention that when you report that there is inadequate randomized clinical trial evidence, please bear in mind that the original study that was done in 2002 that didn't separate the primary endpoint of that study was eight weeks after the device was implanted and turned on, which wound up being an inadequate amount of time to show separation. The problem with my study that came out in 2013, which was a dose finding study, what we did not realize when we assigned people to low, medium, and high dose, we assumed low dose stimulation would be inadequate to relieve symptoms of depression. However, when you look at six months of even low dose stimulation, you can have a meaningful benefit. It wasn't as durable as the folks who had high . . .

Josh Morse: 30 seconds.

Scott Aaronson: . . . stimulation, but that was the problem with that study. We've got long-term study where people are randomized to either getting treatment as usual, or VNS plus treatment, as usual. These are results

from the paper. There's a paper that was published 2017. It was actually the lead article in the American Journal of Psychiatry and I had a . . .

Josh Morse: That's time.

Scott Aaronson: . . . editorial. You can see that there is a pretty profound separation between the treatments as usual group, as well as the VNS plus treatment, as usual with P-values of less than 0.001.

Josh Morse: OK. Thank you, Dr. Aaronson. We have exceeded the time.

Scott Aaronson: OK. Please do consider your decision about making something available for a patient population for which there are no approved treatments.

Josh Morse: Thank you. Is Dr. Dicarlo available? OK. Our final scheduled speaker is Dr. Conway. Is Dr. Conway unmuted?

Charles Conway: Yes. Can you hear me?

Josh Morse: Yes.

Charles Conway: OK.

Josh Morse: Bear with me for just a second. I'll have your slides up. Dr. Conway, if you can state any conflicts of interest and you also have three minutes.

Charles Conway: Yeah. The only conflict I have is, I am the lead investigator in the national randomized clinical trial that is currently underway. Medicare sponsored coverage with evidence trial. LivaNova does cover some of my research at Washington University. I'm a professor of psychiatry at Washington University. The main focus of my three minutes is going to be on there is some interesting data that emerged from the study that Dr. Aaronson just spoke about, the five-year registry data. In addition to demonstrating increased efficacy in terms of remission and response with clear separations in both areas, it also demonstrated significant improvements in quality of life. There has been an emphasis in psychiatry that measuring simply depression in a population as impaired as this is not adequate. So, there's been a focus on measuring functional outcomes, in particular for quality of life. This particular study, which was published in the Journal of Clinical Psychiatry in 2019 demonstrated that using what's called a minimally clinically important difference, using a well-established quality of life and enjoyment satisfaction scale, we were able to demonstrate patients receiving VNS and TRV experienced markedly improved quality of life improvements that were even superior

to the advantage that VNS experienced with depression improvement. This is the . . . in addition, there's another scale that most of those who have psychiatric backgrounds are familiar with is CGI. This also demonstrated improvement. This is the proven quality of life experienced in the five-year TRD VNS registry. The red bar, or the red line, represents treatment, as usual. Blue is VNS plus treatment as usual, as you can see. The shaded areas are the 95% confidence intervals over the course of five years. VNS from six months, or from four months on, demonstrated improved quality of life. I would argue very strongly, one of the other speakers indicated or tried to allude to the possibility of a placebo effect. I would argue the placebo effects generally, in this population, are rare. They certainly don't extend over five years.

Josh Morse: You have about 30 seconds.

Charles Conway: This slide is a comparison of when patients were experiencing quality of life improvement. The X-axis here has dropped in the MADRS scale. The Y-axis is the improvement quality of life. The base finding of this trial, probably the biggest finding, was that patients who experienced a 34% reduction in depressive symptoms experienced a clinically improved quality of life. So, long story short, VNS demonstrates improvement in quality of life, even when the patient's depressive symptoms are not what we classically believe to be responding to treatment. So . . .

Josh Morse: And that's time.

Charles Conway: . . . OK.

Josh Morse: Thank you, very much.

Charles Conway: Thank you.

Sheila Rege: Thank you. Is there anybody on the phones that would like to do a public comment?

Josh Morse: There is one hand raised. Carla Monticelli, it looks like.

Carla Monticelli: There we go. Two things. Dr. Dicarolo is having technical difficulties. So, he has been present. I don't know if there's anything that can be done to get him to speak, number one. I'm with LivaNova, vice president of government affairs and market access. Number two, the only other comment I wanted to make was that you mentioned the Medicare coverage with evidence CED, the NCD, and one point of clarification I wanted to make is that outside of a clinical trial, Medicare, as part of a

national coverage decision, is covering battery replacements for all patients previously implanted with VNS for depression. So, they don't need to be in the clinical trial. It is coverage outside of the trial for battery replacements. I just wanted to make sure that the committee had that for consideration as well.

Josh Morse: Thank you, Carla. So, I am not seeing Dr. Dicarlo on the attendees list.

Britt Reddick: I have sent him the call in information. So, maybe we can just give him one minute and see if that works.

Carla Monticelli: Thank you. And if he can't, we do have Ryan Verner on the line from LivaNova, would be an option potentially to take Dr. Dicarlo's place if we can't get it. That's one other option. Thank you.

Sheila Rege: So, it's 1:28. By 1:30, I think I would like to start the evidence report. So, it's up to you whether you want to bring somebody else in.

Carla Monticelli: Would you try to unmute Ryan Verner?

Britt Reddick: Yes. I will do that.

Carla Monticelli: Thank you.

Britt Reddick: Ryan, you should be unmuted now.

Ryan Verner: Hello, everybody. So, I will step in briefly for Larry. My name is Ryan Verner. I work within the clinical strategy group at LivaNova. I've been working for a number of different responses to your report, so far. So, I just want to start by saying we really appreciate your recognition for the need for additional treatment options. People living with treatment-resistant depression, this is a relatively underserved population of patients who still experience symptoms after four or more interventions. As Dr. Aaronson mentioned, a lot of the work that we've done so far has been in patients that exceed even that number of four. The consequences of nonresponsiveness to different treatment options can be fatal, as CRD is highly associated with suicidal ideation and suicidal attempts. That's something that we've been hoping to impress upon the committee in the evidence report, thus far. So, despite this, there are still very few treatment options available to these patients who struggle with daily living, and as other callers have mentioned, so far, VNS therapy is an FDA approved therapy from 2005. It's really no longer an experimental therapy. It should be considered as such. Since approval, we've done a number of different postmarket studies. The most recent

one, and one that Dr. Aaronson called very close attention to, along with other callers, was his 2017 study, which was a five-year followup study that showed a wide range of benefits related to VNS therapy in the treatment group; 67% of the patients achieved clinical response; 43% of those achieved remission; and there were 50% less suicides in the treatment group, as well. It's our understanding that no other therapy has a history of treatment of depression that shows such long-lasting durable treatment effects. There have been two APA documents published since 2007 that support the use of VNS therapy. We urge you to please consider the broadest available set of evidence and APA guidelines to provide patients living with treatment-resistant depression access to VNS, as a potentially lifesaving therapy. As a consideration of the committee's time, we're past 3:30. So, I would like to just yield the rest of the time, please.

Josh Morse: Thank you.

Sheila Rege: Great. Any, anybody else on the phone not related to whoever has presented? OK. In that case, we will move onto the evidence report. Did I hear somebody?

Josh Morse: I see Gary Franklin has his hand raised. Dr. Franklin, do you wish to make a comment?

Gary Franklin: I didn't have my hand raised.

Josh Morse: I see no other hands. Sheila?

Sheila Rege: OK. In that case, we'll go to the evidence report. Is that Beth?

Beth Shaw: Yes. Hello.

Sheila Rege: Thank you.

Beth Shaw: I'm just gonna show my screen. Can you see that now? Is that a . . .

Josh Morse: Yes. We can.

Beth Shaw: Great.

Sheila Rege: Thank you for the public comments. Thank you for taking the time. That's very, very helpful and informative. So, I appreciate it. Thank you, Beth.

Beth Shaw: No problem. Thank you. So, my name is Beth Shaw. I'm a senior research associate at the Center for Evidence Based Policy at Oregon Health and Science University. I am going to be presenting you today the evidence report that was commissioned on VNS for epilepsy and depression. So, this slide just gives you an overview of the contents we're going to cover today. So, I'll go through the background and the policy context, our methods and search results. We'll go through some summary findings and conclusions. So, in terms of the findings, we're going to be looking at the evidence, some of which has already been discussed. We'll be talking about the relevant guidelines, as well as relevant coverage policies. In that summary of findings, we're really going to focus on the headlines with the opportunity for you to delve deeper into issues. Perhaps at the end of the session with some questions.

In terms of the background and policy context, VNS is a stimulation technique that sends electric signals to the specific brain structures by the vagal nerve. Sorry. I've just realized I've got the . . . I've still got the little thing there. There we go. Is that better? I'm just trying to minimize something I think is in your screen. Can you see? Oh, there we go. Let's live with that. So, VNS is a stimulation technique that sends these signals by the vagus nerve. It's a small device called a pulse generator that's implanted in the left hand side of the chest. It produces these repeating low level pulses of electrical current transmitted via leads along that nerve to the brainstem. This is an invasive procedure, but transcutaneous VNS is a noninvasive alternative that targets the cutaneous receptor filled at the auricular branch of the vagus nerve at the outer ear. As we've heard, mechanism of action is unknown, but it's assumed to involve the neuromodulator reaction of the vagus nerve resulting in antiseizure effects, changes in mood, behavior, and cognition. So, hence the interest in the use of VNS for epilepsy and depression.

So, where does VNS fit in the care pathway for people with epilepsy? VNS is an option for people whose epilepsy is not adequately controlled with other treatments, primarily pharmacological management or surgery, or for people for whom surgery is not suitable or possible. We know the [inaudible] epileptic [inaudible] are effected, but there is a subgroup of people whose epilepsy doesn't respond to two trials of antiepileptic drugs. In these cases, those people are very unlikely to respond to further trials. We know also that people whose epilepsy is not adequately controlled with other treatments are at increased risk of sudden, unexpected death and epilepsy or SUDEP. So, where does VNS fit for people with treatment resistant depression? Well, VNS, again, as we've heard, can be an option for people with treatment resistant

depression. However, there is no clear consensus on that definition, but it's commonly defined as a failure of treatment [inaudible] response, or remission for patients after two or more treatment attempts of adequate dose and duration. As we've heard, the FDA approval for this is for people who have not had any response after four inadequate antidepressant treatments. Again, we know that after two treatment steps, around 50% of patients will achieve remission if they stay in treatment. After failing those two trials, the chances of remission with further trials of antidepressant medications are much lower and around a third of people will not achieve remission after four treatment trials. So, other options for treatment-resistant depression include behavioral health therapies, such as CBT, or the stimulation technique, such as ECT, and more novel treatments, like, esketamine.

So, in terms of the policy context for epilepsy, in 1997, the U.S. FDA approved the use of VNS through the 510[k] premarket approval process. That's a specific process that the FDA used to evaluate the safety and effectiveness of class 3 medical devices. These are devices that support or sustain human life or a substantial importance in preventing impairment of human health, or which present a potential of reasonable risk of illness or injury. They approved VNS for adjunctive therapy, reducing the frequency of seizures and adolescents older than 12 with partial onset seizures that are refractory to medication. In 2017, the FDA lowered the age of use in children from 12 to 4 years. In the next slide, we'll look at the evidence that they gathered and used to support that change in age. Currently, tVNS is not FDA approved for use in epilepsy. So, in 2017, the FDA considered new evidence for the expanded use of VNS for epilepsy in that younger group of children aged 4 and older. They considered evidence in children and young adults from a child's use to the initial approval. They also took information from a Japanese registry and the postmarket surveillance database owned by Cyberonics. Based on the evidence, the FDA concluded that VNS is an effective and safe treatment for the reduction of partial onset seizures in younger children aged 4 to 11 with refractory epilepsy. Based on the Bayesian hierarchical model that was developed for this approval, the 12-month responder rate for pediatric patients in the Japanese postapproval study was 39% with a credible interval, 28% to 52%. So, they concluded that VNS is effective in this younger age group.

Safety was obviously a key consideration again for this younger age group. What they saw from the data, there were no unanticipated adverse device effects seen in this younger group of children. However, they did see a higher incidence of infection and lead extrusion for wound infection when compared to those older children, as well as adults. So,

the FDA emphasized a need to monitor site infection, as well as avoiding manipulating the surgical site post-implant in children. Overall, they found that treatment emergent adverse events in patient's age 4 to 11 were consistent with patients who were 12 years and older treated with the VNS, and they didn't identify any new risks in this patient population.

So, in terms of the policy context, for depression, as we have heard, VNS is FDA approved for adjunctive long-term treatment of chronic or recurrent depression for adults who are experiencing a major depressive episode and who have not had an adequate response to four or more antidepressant treatments. Again, tVNS is not currently FDA approved for use in depression. In terms of the policy context in Washington. Again, we've heard that VNS is covered for the management of seizures in people aged 12 years and older, but this isn't covered for the treatment of depression. In terms of why this report was selected at this time, it was because of high concerns about safety, medium concerns about efficacy and costs. And that change in the FDA approval for epilepsy, that is, lowering the age.

So, let's start looking at the methods. In terms of our PICO, for epilepsy, we were looking at adults and children aged 4 and older with epilepsy. We were looking at VNS or tVNS, either used alone or in combination with other treatments. The treatment as usual, primarily antiepileptic drugs. We compared it with a wide range of comparators. So, you're looking at medication, surgery, or other types of brain stimulation either invasive or noninvasive, sham VNS, other VNS device isn't planted, but it isn't turned on. All we were looking at that VNS [inaudible] therapeutic level or no treatment. In terms of outcomes, we were looking at the primary outcomes of seizure frequency or the secondary outcomes, such as seizure cessation, seizure severity, measures using validated scales, seizure duration, etc., as well as things like quality of life. In terms of safety, we were looking for direct harms, for example, infection or hoarseness, but we were also looking for reimplantation rates or failure rates. We also looked for economic evidence so that's things like cost-effectiveness outcomes, perhaps cost of procedure avoided, or cost utility outcomes. So, incremental cost-effectiveness ratios, or cost per quality adjusted life year gained. We limited our evidence to settings that were in countries categorized as very high on the United Nations Human Development Index to maximize the applicability to the U.S.

You've seen these key questions. We're basically focusing on our efficacy and effectiveness. We were also looking at direct harms, as well as how these effectiveness and harms outcomes differed by patient

characteristics, type of seizure, duration or intensity of treatment. We were also looking for that cost-effectiveness and economic information.

For depression, we limited this to adults, aged 18 and older, with treatment-resistant depression. Again, we were looking for VNS or tVNS alone or in combination with treatments, as usual. That could have been medication or nonpharmacological therapies. We were looking at VNS or tVNS compared with medication, those nonpharmacological treatments, such as CBT, other types of brain stimulation, and again, sham VNS and VNS at a subtherapeutic level, as well as no treatment. For depression, our primary outcome was depression severity measured using a validated tool, but we were also looking for information on mortality, suicidal ideation, as well as response and remission and compliance with other treatments, anxiety, etc. In terms of safety, again, we were looking direct harms, such as infection or hoarseness, as well as reimplantation and failure rates. We were also looking for the same economic outcomes. Again, limited to those countries categorized as very high.

The key questions are very similar. We were looking efficacy, effectiveness, and harms, and whether these varied by patient characteristics, in particular the duration or type of depression, as well as the duration and intensity of treatment. Again, those cost-effectiveness and economic outcomes. In terms of types of studies we included, for the key questions of one to four, we were looking for randomized control trials, but we also included nonrandomized comparative studies with ten or more participants in each group. For those key questions two and three on harms and subgroups, we also included large multisite registries with 100 or more participants. We also looked at databases containing reports of procedure related harms or device recalls. So, that's the FDA MAUDE database or the FDA Medical Device Recall database. In terms of the key question four on the economic outcomes, we were also looking for cost-effectiveness studies and other formal comparative economic evaluations. We also identified systemic reviews and sources to check that we hadn't missed any trials that would have been eligible for our report.

We searched a range of evidence sources, which you can see here on the slide. We limited our searches to those published, since the original report in 2009. Our searches were conducted in October 2019. We also reassessed the studies that were included in the original report. Studies that were identified in the evidence lit 2013 against our inclusion criteria agreed for this review.

Here, you can see the PRISMA Study Flow diagram. I just wanted to highlight a few key points. First of all, we conducted a dual independent review of the studies for inclusion, both at the title and abstract stage, and then at the full text level. We screened 1151 records. We then looked at 369 full text studies. We ended up with 20 studies reported in 23 publications. You can see the details down at the bottom left hand side of this diagram. So, overall in this report, we included nine randomized control trials, 20 nonrandomized studies, and two economic studies.

Just a reminder about the overall certainty of evidence that we assign to outcomes using the grade approach. So, for each outcome, we assigned this overall certainty of evidence. So, if we assign a high certainty of evidence, we're very confident that the estimates of the effect, of the intervention on that outcome really does lie close to the true effect. What that means is really that future research is very unlikely to change our understanding of that estimate of effect. Conversely, if we assign a quality of evidence of very low, it means that we're really uncertain about that estimate of effect. Really, we need more research to give us much more confidence in that estimate.

So, moving into the evidence review. As I have said, I am going to present a summary of the main findings. Then, we do have a few additional slides at the end if there are questions. Hopefully, they'll answer your questions.

So, this presentation will start with epilepsy. So, we'll go through the effectiveness and harms, then the cost-effectiveness, then the same for depression.

So, overall, we found five randomized control trials in eight publications. Four of these compared high and low stimulation VNS. As we've heard, that low dose is generally assumed to be a sort of therapeutic level. The reason this is done is because it's difficult to blind patients and providers and assessors in the trials, because this is an invasive implantable technology. So, this design of comparing therapeutic levels of stimulation so that high stimulation with subtherapeutic levels low is a common approach to help maintain blinding during those trials. We also found 50 nonrandomized studies. Sorry. There was also one randomized control trial that compared VNS plus best medical practice with best medical practice alone. We found 15 nonrandomized studies. These included varied comparators including surgery, no treatment, as well as other types of stimulation. Finally, we found one randomized control trial comparing high versus low stimulation transcutaneous VNS. All of these

trials were assessed as being moderate or high risk of bias, and particularly, there was nonrandomized studies recessed as being at high risk of bias. The randomized control trial in the tVNS group, again, was assessed at being high risk of bias.

So, we'll start with the first comparison of high versus low stimulation. I'll just orient you to the table, because you'll be seeing lots of these tables in the next few slides. On the left hand side, you can see the number of participants and the number of studies. Then, we have the findings in that next column. Then, we have the certainty of evidence, which I think is really important. We've seen a lot of information provided about significant effect, but actually, we need to think about how confident we are in some of those estimates of effect. Then, we have the rationale on the left hand side for why we downgraded in certain instances. So, we'll start with the first outcome, which is a reduction of 50% or more in seizure frequency. So, you can see that high stimulation was associated with more people, significantly more people having a 50% or more reduction in seizure frequency when compared with the low stimulation VNS group. However, there is some uncertainty around this. We graded this as being low quality evidence from three randomized control trials. This was downgraded each for risk of bias. If you remember, all the studies had some risk of bias, as well as imprecision. So, that would indicate wide confidence intervals really meaning that we're not entirely sure of that estimate of effect. So, there is some uncertainty around that. You can also see that high stimulation VNS was more effective in reducing mean seizure frequency than low stimulation VNS. However, we're really uncertain about that. It was downgraded two levels for risk of bias and done level for imprecision. In terms of seizure freedom, you can see these very low numbers here. One participant in high stimulation VNS group and no participants in the low stimulation group became seizure free. However, it's really not possible to do any . . . because of those low number. Again, lots of uncertainty around that downgraded for risk of bias and imprecision.

Moving onto the next slide, again, this is the same comparison of high versus low stimulation. You can see that there were similar numbers of withdrawals in both those groups. However, lots of uncertainty around that estimate. In terms of some of the harms, you can see that we have significantly higher levels of voice alteration or hoarseness. We're actually relatively certain about that. So, it's moderate certainty of evidence. We also see that there were similar rates of cough in those two groups. However, there were higher rates of dyspnea or shortness of breath. However, some uncertainty around that increased oxidation.

Moving onto the next slide, again, we're still on high versus low stimulation for epilepsy. You can see that between those two groups, we have similar rates of pain, paresthesias, some numbness or tingling, nausea, and headache. However, each of these outcomes are assessed as being very low certainty of evidence. Again, because of risk of bias and impression.

So, this is just a slide that kind of puts those tables into text really. So, I'll just leave it up for a couple of seconds.

So, moving onto our next comparison. So, this is a comparison of VNS versus treatment as usual. You can see the reduction of 50% or more in seizure frequency. We don't see any difference between those two groups. However, lots of uncertainty around that estimate of effect. When we look at seizure frequency and seizure freedom, now we're starting to look at some nonrandomized studies. Unless we see that VNS is associated with greater improvement than seizure free [inaudible] treatment as usual or ongoing medication. We're really uncertain about that. Similarly, for seizure frequency, VNS doesn't appear to be associated with higher rates of seizure freedom than treatment as usual or ongoing medication. However, we're really uncertain about the estimate of effect. Moving onto treatment withdrawals, again, you can see similar number of withdrawals in these two groups, VNS versus treatment as usual. Some uncertainty around that with a low sensitivity of evidence. Similar levels of voice alteration or hoarseness with treatment as usual. Lots of uncertainty around that. In this instance, we didn't have any data on either cough or dyspnea.

Just looking at the harms pain, paresthesias, headache, there were similar levels between these two groups. However, we had very low certainty around that. Nausea wasn't reported. I think what's interesting about this slide, the risk ratios and confidence intervals are absolutely identical, because each of these outcomes, three patients in the VNS group experienced these . . . three different patients had pain. Three different patients had headache, etc., but no patients in the treatment as usual group reported those adverse events.

Again, this is just a summary slide, but it's probably just worth looking at that final point on the slide, because we also found one registry study that was noncomparative but fails they found that these laryngeal symptoms, such as hoarseness and coughing and local paresthesias related to that VNS use tended to decrease over time while rates of high lead impedance tended to increase over time. Other adverse events, such as cardiac or respiratory complications and local infections were low

at all time points in that particular study. So, now we're looking at VNS versus surgery. I think it's worth noting here that there were no randomized control trials for this comparison. So, we're really . . . all of this data is based on nonrandomized studies. What we see is that VNS is similarly effective as surgery in reducing seizure frequency, but this wasn't consistent across those four nonrandomized studies. So, we assessed the certainty of evidence here as being very low quality. That was downgraded both for risk of bias and imprecision, but also those differences between studies, so inconsistency. We also found that VNS may be less effective in reducing seizure freedom than surgery, but again, this wasn't consistent across studies leading us to a very low certainty of evidence.

Again, just a text kind of summary of that, but again, I think it's worthwhile noting here, again, that final bullet point, we didn't find any evidence on comparative harms from the eligible evidence for this particular comparison.

So, moving onto the next comparison, our final comparison here. This is VNS versus other stimulation techniques. So, this was specifically VNS versus responsive neurostimulation. Again, we didn't find any randomized control trials for this comparison. VNS was similarly effective in reducing seizure frequency than the responsive neurostimulation, but again, these results weren't consistent across studies leading us to a very low certainty of evidence. In terms of seizure freedom, again, VNS and responsive neurostimulation appeared to be similarly affected, but again, those results weren't consistent between those studies.

Again, interesting from here, we didn't find any comparative evidence from those two nonrandomized studies on harms.

So, now moving to high versus low stimulation transcutaneous VNS, we found one randomized control here, that if you remember, we assessed at being high risk of bias. You can see already the number again is small, 76. So, in terms of seizure frequency between high and low stimulation transcutaneous VNS, there was no difference in rates of response. However, we assessed the certainty of evidence as being very low. In terms of seizure freedom, again, no difference between those two groups. In the seizure severity, similar rates, similar seizure severity caused. However, both of those outcomes we graded as being as low certainty of evidence.

In terms of treatment withdrawals, again, no difference between those groups. I think what is interesting here is that no participants in either

group reported coughing or hoarseness. If you remember, those are relatively common side effects that are known to be associated with the invasive form of VNS. You can see dyspnea wasn't reported. In terms of pain, nausea, and headaches, we see similar rates between the high and low stimulation group. Paresthesias weren't reported in this one randomized control trial. All of those outcomes are assessed as being very low certainty of evidence.

So, just thinking about some of the more serious outcomes, we asked the question about SUDEP. So, that's the sudden and unexpected death in epilepsy. Mortality wasn't a key outcome for this particular part of the report for the epilepsy part. So, I did look back through the evidence to just look through those case series adverse events from the evidence we reviewed. So, in one randomized control trial comparing the high and low stimulation VNS, we saw that one patient in the high stimulation group experienced a nonfatal MI, which resulted in the generator being deactivated, and the device removed. In the other study comparing high and low stimulation, transcutaneous VNS, we saw that one patient in the low stimulation group died of seizure. However, this death wasn't rated as being related to treatment. One patient in this trial also had palpitations. This was assessed as being possibly or probably related to VNS treatment, transcutaneous VNS. Apologies.

In terms of effectiveness and harms by subgroup, we found two studies, both of those assessed as high risk of bias. One of those studies reported that people who have had prior cranial surgery may have lower rates of response to VNS at 12 months compared with people who haven't had prior surgery, but the longer term outcomes appear to be similar. In terms of early versus late treatment with VNS, people who are treated earlier with VNS may have better outcomes. As I said, both of these studies were assessed at being at high risk of bias. So, the evidence is very uncertain and probably more hypothesis generating rather than evidence to guide clinical practice or coverage decisions.

In terms of cost-effectiveness, we found two studies. One was a hypothetical cohort. So, this is an economic modeling study. They found that VNS was more costly and less effective than other strategies, but it was in a very specific group. So, this was children with tuberous sclerosis complex who had not responded to two or three antiepileptic medications. We assessed this as being very low certainty of evidence. We also found one budget impact study where they found that VNS was associated with a reduction in costs over five years compared with medication alone. So, this budget impact study considered the cost for VNS in children aged 12 and older with drug resistant epilepsy with

partial onset seizures specifically from the perspective of managed care organization. They included costs on VNS implantation. So, this was around \$40,000. So, that included programming and maintenance, which included battery replacement costs of around \$2200 per year. They looked at adverse events in this budget impact model, and they included cough and voice alteration with an assumed incidence of around 40% and infection with an assumed instance of around 3%. They also included drug costs of around \$6,500 per year, assuming that two antiepileptic medications were used per day.

Moving now onto the evidence for effectiveness and harms in depression. We found two randomized control trials in three publications. One comparing high versus low stimulation VNS. One comparing VNS versus sham VNS. Sham VNS is where they implant the device, but the device wasn't turned on. We found three nonrandomized studies in six publications. All of them were comparing VNS versus treatment as usual. We found one randomized control trial comparing high versus low stimulation transcutaneous VNS. Both of the randomized control trials on the left hand side were assessed as being moderate risk of bias. Two of three nonrandomized studies were assessed as being at high risk of bias. The transcutaneous VNS RCT was also at high risk of bias.

So, moving into the detailed results, this is the comparison for high versus low VNS. As you can see, there was no difference between those three VNS stimulation protocols when measured on the inventory of depressive symptomatology clinician version. However, low certainty of evidence around the estimated effect. There were similar levels of depression severity. Similar rates of suicide or attempted suicide. There was no difference between those two groups. However, there was a higher response rate defined as that 50% reduction or more measured on the MADRS score. However, there is some uncertainty around that. We downgraded that both for risk of bias and imprecision. Again, that wide confidence interval. So, looking at treatment withdrawals, there were similar numbers of withdrawals between these two groups. However, a lot of uncertainty around that. For the outcomes of voice alteration or hoarseness, cough, and dyspnea, you can see there was no difference between these two groups. We assessed the evidence as being low or very low certainty.

Looking at pain, paresthesias, nausea, and headache, you can see we have similar rates between those two groups across the board. Again, we assessed this evidence as being low to very low quality.

Looking at the comparison of VNS versus sham VNS, again, where the device was turned off, you can see similar levels of depression severity, both as measured on two scales. So, we have the Hamilton Rating Scale for depression, and the Inventory of Depressive Symptomatology self-report version. No difference between those two groups. We're relatively certain, we've actually got moderate certainty in this evidence. Again, we see no difference between the two groups in terms of suicide. However, lots of uncertainty around that. There is no difference between the two groups in terms of response, as measured on the MADRS score. Again, very low certainty around that.

Looking in terms of treatment withdrawals, again no differences between the groups. However, a lot of uncertainty around that estimate. Certainly, for voice alteration or cough, we actually see higher levels of these two adverse events. We're relatively certain about those increases in voice alteration and cough. However, similarly, there is no difference between groups for the dyspnea.

Looking at pain, paresthesias, nausea, again you can see similar levels of both pain, paresthesias, and nausea. However, in this trial, headache wasn't reported.

So, now looking at a comparison of VNS versus treatment as usual, again, this comparison is purely based on nonrandomized studies. So, there wasn't any randomized control trial evidence with this comparison. What we did find is that VNS was more effective in reducing depression symptoms than treatment as usual alone. However, this is assigned a very low certainty of evidence. In the grade scheme, nonrandomized studies start out with being low certainty. However, you cannot grade . . . we didn't upgrade in this instance, but we did downgrade both for risk of bias and imprecision. You can also see that VNS was associated with a higher rate of response than treatment as usual, but again, very low certainty of evidence for the outcome. We also saw that VNS may be associated with higher rates of attempted suicide or self-inflicted injury, but again, the evidence is very uncertain about this outcome. It actually may reflect greater severity of depression in the VNS group rather than the VNS causing this increase. However, we also saw that VNS may be associated with lower mortality rates, but the study results weren't consistent. Hence, the certainty of evidence being very low certainty here.

Looking at treatment completion rates, we see higher treatment completion rates in the VNS group when compared with treatment as usual group. However, lots of uncertainty around that.

So, moving into the comparison of transcutaneous VNS versus sham transcutaneous VNS, we did see the tVNS may be associated with a clinically meaningful change in depression. So, this is using the Beck depression index, which you can see on the second row. However, when using the Hamilton Rating Scale, there was no difference between transcutaneous VNS and sham VNS. Both of these outcomes were assessed as being low certainty of evidence.

In terms of adverse events, no adverse events were reported in this small randomized control trial. So, actually, I think we remain really uncertain about what adverse events may be associated with transcutaneous VNS.

In terms of effectiveness and harms by subgroup for depression, we found information on these four subgroups. As we have already heard, patients who have been treated with ECT, regardless of response, had higher response rates than patients in the treatments as usual group. We also found information that the presence of anxiety didn't appear to be associated with reduced effect of VNS. So, people with comorbid anxiety had similar rates of response to VNS to those who didn't have comorbid anxiety. We also found that the effectiveness of VNS did not appear to differ by type of depression. So, that's specifically unipolar versus bipolar. In terms of age, as we've just heard, mortality rates were significantly lower in the VNS group than the treatment resistant depression managed depression groups overall, but this wasn't the case for that subgroup of people aged under 40 years.

In terms of cost-effectiveness for depression, we didn't identify any eligible studies reporting economic outcomes of VNS or tVNS for depression.

We also looked at the MAUDE database and the FDA medical device recall database. So, the MAUDE database is a voluntary user facility distributor and manufacturer report about adverse events. We specifically limited this to VNS use in the last five years. There were many entries for this. You can see already, we have 397 entries from the MAUDE database. Both of this type of data, so the MAUDE and the medical device database, doesn't really allow us to analyze the data by condition, but what we saw from the MAUDE database is that we saw very similar types of adverse events to those reported and are eligible studies for epilepsy and depression. We found 26 recalls documented in the medical device recall database. As you can see here, they kind of grouped into five buckets. They tended to be errors in impedance measures, some unintended warning messages, miscalculations resulting

in inappropriate stimulation levels both high and lower levels of stimulation than expected, reductions in device and battery longevity, and also lead fractures. Again, it's difficult to draw robust conclusions on the rates of adverse events, but it does give us an indication on the types of adverse events and device failures that may be experienced by patients with VNS.

We were also asked about specific adverse events, such as bradycardia. So, again, I'll look back through the evidence that we had. We found that in one randomized control trial containing VNS and sham VNS, one patient experienced bradycardia during surgery in the VNS group. From the MAUDE database records, we saw nine cases of bradycardia postsurgery and three cases during surgery. Some cases were assessed as being linked to VNS while other cases were not thought to be related. So, for example, they had prior history of bradycardia, or the symptoms remained unchanged after VNS removal. So, again, overall, we're not really able to determine a rate or any estimate of incidence, or whether this is really a direct harm of VNS at all.

I just wanted to touch on the FDA medical device recall. So, this was in December 2019, the FDA issued a Class 1 recall for the VNS SenTiva Generator System. The Class 1 recall is the most serious type of recall where problems with the recalled devices may cause serious injuries or deaths. LivaNova specifically recalled this system because of unintended reset errors that caused the system to stop delivering VNS therapy. The FDA, alongside with the manufacturer, issued guidance to patients and providers and encouraged increased monitoring of VNS effectiveness and level of stimulation, also increased review of programming, as well as providing information to patients on alternative treatments that might be available to them.

So, on April 17TH, 2020, we just went back to check the status. These are just the class of recall that we found on the FDA medical device recall database. You can see most of them, four or five, at that level 2 class of recall. Then, at bottom in the bold, you can see some of the detail on that Class 1 recall for the VNS SenTiva Generator Model1000.

So, now we're moving to clinical practice guidelines and payer coverage policies. For epilepsy, we found six relevant guidelines, two assessed as being good methodological quality from NICE and from SIGN. One fair methodological quality from the ILAE, specifically with their commission of pediatrics. Then, three poor-methodological quality guidelines, one from the Australian government, MSAC, the epilepsy implementation

taskforce, and one published by Wirrel et.al on behalf of a North American Consensus Panel.

You can see here that NICE and SIGN both recommended VNS as adjunctive therapy for adults with drug resistant epilepsy who are not suitable candidates for surgery. NICE also recommended VNS as an adjunctive therapy for children and young people who are refractory to medication but who aren't suitable candidates for surgery. NICE stated that VNS is an option for adults and children whose epileptic disorder is dominated by focal seizures with or without secondary generalization or generalized seizures. I just wanted to interpret a detail on the evidence for some of these recommendations. So, in terms of the NICE guidance, the recommendation on VNS was made in the original of 2004 guideline. However, while that's a [inaudible] guideline, it's assessed regularly for currency in the standards today, surveillance schedule undertaken by NICE. So, it does remain a current recommendation. So, in 2004, NICE published interventional procedure guidance on VNS. That's a type of guidance that really focuses on the safety rather than the effectiveness. The IP guidance was based on the 2002 Cochran review that included two studies, both of which are included in this report. So, because there was that interventional procedure guidance in place, the guideline committee would have simply incorporated the wording for children. The committee also reviewed the evidence for adults and found the same two trials reviewed in systematic reviews and health technology assessments. That's what the recommendation is based on. As we heard, the taskforce report for the international league against epilepsy, the commission of pediatrics, recommended that infants with medically refractory seizures who are not suitable candidates may be considered for VNS. However, they did note that there were insufficient data to really conclude that there was a benefit for intervention. So, they really based that recommendation on the experts' opinion and standard practice, including receiving optimal level of care at specialist facilities. Recommendations from other guidelines also supported the use of VNS for adults and children whose seizures didn't respond to other therapies, such as changes in medication, surgery, and specifically the ketogenic diet for children.

For depression, we found five relevant guidelines, one assessed as being of good methodological quality. That's the working group at the clinical practice guideline on the management of depression in adults. Three fair methodological qualities, including the Canadian Network for Mood and Anxiety Treatments, which we've talked a little bit about today. Then, one poor methodological quality.

You can see here that the good methodological quality guideline recommended VNS outside the scope of research should be discouraged, due to the invasive nature of the procedure and uncertainty about efficacy and adverse events. As we've heard, the Department for VA and Department of Defense recommended against offering VNS for patients with MDD outside of that research setting. The Canadian Network for Mood and Anxiety Treatments, this is an interesting guideline, in that this specific guideline really only focuses on your stimulation. So, it's actually not entirely clear where they're intending VNS to sit in that care pathway. Certainly, they define people should have access to neurostimulation treatments. They have to be people with unipolar depression who have failed one antidepressant medication. So, that's a very different population, certainly that its FDA approved for, but also some of the populations that we've heard from the public comments. The Royal Australian and New Zealand College of Psychiatrists make no explicit recommendations. Then that poor quality guideline that didn't support public funding for chronic major depression episodes, again, noting concerns about safety, evidence of effectiveness, and then the impact on the uncertainty around cost-effectiveness.

In terms of payer policies, epilepsy and depression, overall, there is a high level of agreement across the coverage determinations. So, Medicare and the three commercial payers we looked at cover VNS for the management of seizures but not for depression. They also cover revision or replacement of the implantable battery. None of the reviewed policies we looked at specified any age restrictions. On February 15, 2019, CMS issued a national coverage determination that covers FDA approved VNS devices for treatment resistant depression, coverage with evidence development. This requires patients to be entered into a CMS approved double blind randomized placebo controlled trial with a followup duration of at least one year, and CMS will cover the use of VNS for use of treatment resistant depression if a patient is registered in that approved study. All of the commercial payers we reviewed consider the use of transcutaneous VNS as being experimental and investigational only.

We also looked for ongoing studies. So, we found one study for epilepsy. This is the CORE-VNS study. It's a prospective registry of adults and children with drug-resistant epilepsy. They are only looking at VNS. It's a noncomparative study, but they're looking at outcomes that we would be interested in, such as seizure frequency, severity, quality of life, etc. They estimate enrollment was around 2000 participants. It's estimated to complete in December 2026.

We found two ongoing studies for depression. One is the RESTORE-LIFE prospective registry. This is in adults with difficult to treat depression. Again, it's noncomparative. Its VNS only, but it's looking at relevant outcomes and around 500 participants estimated to complete in December of 2023. On the second row, you can see the RECOVER trial. So, this is the CMS approved randomized control trial specified in the coverage with evidence decision. As you can see, it's a large randomized control trial. This is 6800 participants, and it's estimated to complete in August of 2022.

So, in conclusion, VNS is an effective treatment option for people with drug-resistant epilepsy who are not eligible for surgery. However, there is a lack of evidence on the cost-effectiveness of VNS for epilepsy. There is a lack of evidence on the use of transcutaneous VNS for epilepsy. Guidelines and commercial coverage policies are generally supported VNS for epilepsy. So, policymakers will need to consider whether the current coverage policy should align the lower age of VNS use with that policy of the FDA, so lowering that age to 4 years.

In terms of depression, VNS may be an effective treatment option for people with treatment resistant depression who have not responded to other treatments. We didn't find any evidence on the cost-effectiveness of VNS for treatment resistant depression. Again, there's a lack of evidence on transcutaneous VNS in this population. Generally, guidelines and commercial coverage policies aren't supportive of VNS for treatment resistant depression. So, policymakers will need to consider whether the current coverage policy should be changed in light of the evidence from this report. Thank you.

Sheila Rege: Thank you, very much. Do we have some time for questions for Beth? I had a question on the epilepsy was for adults and children within this scope. Depression was only in adults. Is that true, Beth?

Beth Shaw: Yes. So, we did that because of the FDA approval. So, yeah, for epilepsy we adverse events looking for children aged 4 and older and adults for depression, adults aged 18 and over.

Sheila Rege: OK.

Mika Sinanan: The takeaway I see in this is that it's ongoing therapy. Once you start it, you change the batteries and keep going. That may be something that Dr. Novotny could answer us as well, but is this sort of without an end or indefinite?

Beth Shaw: People do have them removed for various reasons, but yeah. I think the intention and obviously the clinical expert will be much more reliable than me, but yeah. I think the intent is to . . . as long as people are continuing to receive benefit, that outweighs any harms that they may experience, I think the intention would be to keep it.

Mika Sinanan: OK. Follow up to that before Dr. Novotny answers, does it change the sensitivity or response to other medical therapy? In other words, make drugs more effective or make them more feasible as an adjunct?

Beth Shaw: I don't know the answer to that. So, I'll leave that for Dr. Novotny, but what I do know is that in that budget impact model, when they considered the cost of drugs, they considered that the cost of drugs would remain similar, wouldn't change actually, the people in that VNS group. So, they didn't take back any reduction in drug costs.

Mika Sinanan: Thank you.

Edward Novotny: Those are excellent questions that I can address. In terms of the longevity of treatment, it is often expected that this will be a more prolonged treatment. In one of the initial presentations, there is some beginning data that having the device in for long periods of time actually improves . . . leads to more efficacy over time. So, we sometimes see that in certain subpopulations. We often maintain the device for longer periods of time. On the other side of the coin, there are certainly many patients where they feel they do not get any benefit. Or they have adverse reactions. We often may discontinue or remove the device, as well. The other aspect of the treatment, because of the need for battery replacement, that's an important period of time to assess the efficacy and reevaluate the need for continuation of therapy, as well. That's commonly done in clinical practice of making that assessment again, in terms of looking at efficacy. An important aspect of when it . . . looking at the overall treatment of epilepsy. In clinical practice, we often use it in patients who are obviously treatment resistant to antiseizure medications. There is no good study looking at is there any synergy or increased benefit from the use of the device, but in clinical practice, we often have patients who are in three, four, or sometimes more medications and often using the device as an adjunct allows either discontinuation or reduction in the medications that they're taking. So, that's why some of the cost-effectiveness analysis makes the assumption that they are staying on the same amount of medications, but in clinical practice, that often does not happen.

- Mika Sinanan: I just want to follow up. I assume from what I've read that this is not doing any sensing. It's not like a responsive pacemaker that's measuring anything and then initiating a signal in response to something. It's just continuously activated. Is that right?
- Edward Novotny: So, there are two ways that the device is used. One is that it is programmed. You're correct, it's not doing any sensing. The second way the device is used is often either the patient or the caretaker may manually activate the device that may lead to aborting a seizure or aborting a cluster of seizures. So, there are two ways that therapy is provided. One was from the programming standpoint. It was the amount of stimulation at regular intervals. Second, by manual activation, either by the individual with the device, or by caretakers who sometimes can abort the device. So, you are correct in the fact there is no sensing. However, the new device, which has been recalled, the SenTiva, is a device that actually uses cardiac sensing as a way to deliver therapy. That is a relatively new implementation of the device where when the device senses a rapid onset of heart, or a tachycardia, it actually provides a stimulation. There have been studies that have shown with certain seizures, you get a very rapid increase in heart rate, from which you can adjust your therapy to be in response to a heart rate change, as well. So, that's actually a new way of therapy that's relatively recent in the last few years or so.
- Mika Sinanan: But there is no comparable type of reactive activation in depression. I mean, if you feel worse one day, you don't activate it and not activate it the next day. That's not the way it works.
- Edward Novotny: Correct.
- Mika Sinanan: OK. Thank you.
- Janna Friedly: I'm struggling with your conclusion slide for the depression studies. I want to make sure that I haven't completely misunderstood something, but your conclusion . . . I'm sorry. I just lost it. I had it in front of me. So, your main conclusion here is that VNS may be an effective treatment option for people with treatment resistant depression who have not responded to other treatments. Was that based on the one study that was compared to VNS to usual care that did show a difference versus the other ones that were looking at VNS versus sham, the one from 2005, and the other . . . the high versus low stimulation. It just seems a little bit at odds with the data that I'm looking at. So, I'm just a little bit confused.

Beth Shaw: OK. So, here's the high versus low stimulation. You can see there was no difference in depression severity. No difference in rates of suicide or attempted suicide. There was a higher rate of response defined as at 50% reduction. Similar numbers of withdrawals and adverse events. That was based on randomized control trials. Here, when we're comparing it with sham VNS, again, there is no difference in depression severity not associated with any lower rates of suicide, similar rates of response compared with sham VNS. However, higher levels of voice alteration and hoarseness. And when we look at treatment as usual, this is that big study that we've heard a lot about. There were some positives, but it's a nonrandomized study. So, that brings questions about causation versus association. We've got actually, I think, I'm just gonna move this, very low certainty about that. So, I think that's where some of these nuances come in about how confident we . . . does VNS truly improve reduced depression?

Janna Friedly: Yeah. It does, it . . . thank you. I mean, I think I understood the data as you presented it. I just . . . that conclusion didn't quite seem to summarize it in a way that made sense to me.

Beth Shaw: I apologize.

Janna Friedly: I understand. No, it's an interpretation. So, I just wanted to make sure I wasn't missing something important, as we're discussing.

Sheila Rege: Any other questions for Beth? If not, we can take a ten minute break and then come back and go around the room commenting on our personal kind of perspective on the quality of the evidence and the data related to safety, effectiveness, cost, and then we'll move on. So, it's 2:31. Oh, go ahead, Mika?

Mika Sinanan: Yeah. Just a quick question to Beth. The speakers from outside who presented data from a series of studies, were all the studies that they referenced included in your analysis? I haven't gone back and made sure that you captured all of the studies that they had presented in your survey of available data. Have you done that? Did you have a sense of that?

Beth Shaw: It's almost like you could see my screen. Yes. I think all of those studies appeared recognizable. Certainly, when we went for both the payer review comments and public comments, people did suggest studies that they felt we'd missed, but they wouldn't have met our eligibility criteria. So, certainly, that Aaronson study that was talked about, that five-year observational study, is absolutely included.

- Mika Sinanan: Thank you.
- Sheila Rege: Any more questions? If not, if there's any way we can just take a seven-minute break and come back at 2:40? We will try and catch up some time. OK. Break until 2:40.
- Josh Morse: OK. Thank you.
- Sheila Rege: Can everybody hear me?
- Josh Morse: Yes. I can hear you Sheila.
- Britt Reddick: I just want to do a quick audio check for Dr. Seth Schwartz. I'm going to unmute you. Then, you can mute yourself and have the ability to speak. Great. Thank you.
- Sheila Rege: Shall we go down alphabetically and give our gestalt about the evidence. And we could split it into epilepsy versus depression in terms of safety, effectiveness, and cost-effectiveness. John, do you want to take a stab at going first? Or we can move to Janna. Janna, are you ready to just lead? Just around the room. If there are any questions we can ask before we start using our decision aid tools, kind of the strength of the evidence and how comfortable you feel with what's been presented so far. This is a tougher one.
- Mika Sinanan: I'll take a stab to start off if that's OK. There are . . . so the implantable device . . . the difference is between implantable versus transcutaneous. I would say that transcutaneous has very little evidence for effectiveness and value and would discount that as being any covered benefit at this point with regard for any indications. With regard to the implantable device for epilepsy, it clearly has some safety issues, infection and side effects. Some of them are quite serious, like bradycardia, prolonged asystolic periods, that kind of thing, but it seems that those are manageable and anticipatable. With regard to its effectiveness, and that applies to both groups actually, with regards to effectiveness, my sense from the data is that there is a preponderance of evidence that is moderately good that it is effective in epilepsy. I think that the recommendation from the agency about broadening it from one kind of epilepsy and leaving that up to a clinical decision is a reasonable accommodation. Does it provide value? Well, it appears to provide value in people who have a very difficult and refractory disease that is certainly life altering and health altering with some information that it improves value in terms of cost-effectiveness. With regard to the depression

effects for efficacy, there are observational studies, which seemed to show that it's effective, but they have significant methodologic problems, and they are largely observational. For that reason, even though the impression is that they appear to be effective, it's not hard data. There is a randomized trial that is going to be coming out in 2022. It seems to me that it would be better to wait for that result than to approve something now that, in fact, may have very limited effectiveness. For the same reason with low effectiveness, it's very hard to measure value. I say that understanding that people with severe refractory depression have a very difficult problem that is certainly life altering and have very few options, but that is not an argument to offer treatment for which we don't have evidence. So, that's my assessment.

Sheila Rege: Thank you. Very helpful. Does anybody want to volunteer to go next?

Janna Friedly: I'll go next, because it's easy to follow Mika, because I echo everything that he has said. For me, the evidence is more clear for epilepsy and broadening the type of epilepsy for which it is covered. The evidence for depression, I think, is very limited. I think it is fraught with issues and some controversy. I think that the fact that there is a very large clinical trial and a Medicare national coverage decision that only approves it with participation in this trial, to me, is very reflective of the fact that we don't have the answers yet. I think we will have . . . this trial is, I think, going to answer a lot of these questions. So, I agree that it seems prudent to wait to make a coverage decision and not cover it at this point, but to reconsider it once the results of the trial come out.

John Bramhall: I completely agree with Janna and Mika. I think you both encapsulated my thoughts perfectly. There doesn't seem to be a big divide with the epilepsy issues. I, personally, would follow the expert guidance and assume the age level of 4 was an appropriate level to start initiating this kind of therapy if it's needed. The depression . . . the depression side of it is, yes. It's uncertain. Yes. It's a deadly disease. Yes. There's a group of patients who failed four, maybe eight sets of other therapies, but it seems . . . I'm really pleased to hear about the escape route that some patients will have into a trial rather than supporting ad hoc relatively unproved and probably very poor collection of data following from that. I think it's absolutely the best thing that could be done is to channel vulnerable patients who have got no other options, no financial options to support the payment for the therapy themselves, to put them into a Medicaid group that is going to have clear collection of data that will lead to information that can fuel further decision down the line. So, I'm really pleased about that. I think it is an escape chute. The administration of the medication is going to be done, is being done, under controlled

circumstances with the collection of data. That's what we consistently miss in nearly all of the things we look at. I mentioned that at the beginning of the morning. All these studies that lead to low quality information that doesn't help guide committees like ours very well. So, yes. I'm in favor of supporting the epilepsy route and to decreasing the age limit. I'm not persuaded that we should be expanding into the realm of depression.

Laurie Mischley: I largely agree with what you just said. The only thing that I would add is that I actually have a little more respect for the five-year observational data than I feel the discussion has suggested so far. I think that's actually really valuable data, especially in a condition where everything else has failed. We have something that looks like it does improve options for some people. It is sustainable. For a therapeutic that has manageable side effects and reasonable safety profile, I do tend to not be so dismissive of observational data, but otherwise, I agree with everything else that has been said so far.

Conor Kleweno: I agree with the comments on the treatment for epilepsy, including the generalization of the definition. That allowing clinicians to determine the appropriateness for inclusion on epilepsy, as opposed to restricting the definition of what kinds of epilepsy, I agree with that. I also agree, I think it was Mika, that commented that just because you have no options doesn't mean you should offer somebody a poor or a useless option. That said, of the public comments that were provided, the one that was most meaningful to me were the comments from the Washington State Psychiatry Association, I believe. It seemed that was somewhat level 5 evidence and supported. So, my question would be, and I don't know if there's anybody can answer is, per John's comment, the eligibility to be involved within the trial, is that something where these people that they mentioned who are sort of out of all options, the worst of the worst as they said, is that something that they would be eligible? Or is the eligibility of this study strict enough that they would not be able to be enrolled and thus would not have that sort of parachute that John had mentioned.

Sheila Rege: Anybody want to answer that.

Conor Kleweno: A parachute would be a 50% chance anyway of true treatment versus placebo.

Seth Schwartz: I'm not certain of the specifics, but this has come up a number of times before with this concept of approval with evidence generation. What that . . . the way that really works is, all the agencies have the authority

to pay for something that they want to pay for and paying for it in the setting of a study is something that they can choose to do, even if we deny coverage. Whether or not the patient would be eligible for the studies, however, is a totally separate issue that we have no purview over. So, I think that the answer is kind of yes and maybe.

Edward Novotny: I just didn't know if there was a content expert that could comment on that.

Britt Reddick: I see that Dr. David Dunner has his hand raised. Dr. Rege, is this a good time to receive comment or feedback?

Sheila Rege: Sure. Josh, is that good for the process? Hello?

Britt Reddick: Are we waiting for Josh's . . .

Josh Morse: I was muted. Sorry.

Britt Reddick: OK.

Josh Morse: Yes, if Dr. Dunner has information specific to that trial, if that's what you're asking for. I was also trying to say that Dr. Transue may have some information about how the agency considers IRB approved trial access for people.

David Dunner: This is Dr. Dunner. The RECOVER study is limited to patients who have Medicare insurance.

Sheila Rege: Let's hear from the agency where that is something that you can provide outside of our coverage decision.

Emily Transue: I actually have to check on that. I haven't encountered this specific question. Typically, our trial coverage is that we would cover the standard components within the setting of a trial that would be otherwise covered, but that the key experimental components would be covered by the trial, itself. That's our standard. In terms of [inaudible] discretion, I don't know if there's anyone else on the line who has more information than I do on that, although it sounds like in this case, if it's Medicare only, it wouldn't be relevant.

Josh Morse: Yeah. And I can speak to the HTA framework, or the Health Technology Clinical Committee framework. It says in the Health Technology Clinical Committee law that if the committee decides to not cover something that the agencies still have the authority to make that decision about

covering something in the context of a clinical trial. I think that's what we, in the past, have talked about when the committee has considered coverage of the evidence development and the complexities of decisions like that. It is clear that the agencies still have discretion beyond a noncoverage decision to make a decision about covering things in the context of a trial.

Sheila Rege: OK. Good to know. Chris, do you want to opine? Or Dr. Novotny? Kevin or Tony?

Chris Hearne: I agree with what's been said about the epilepsy treatment. I think with regards to treatment for depression, I think for a lot of these technologies, sometimes I find myself wishing that the authors that had done the sham comparison, and we often don't have that. So, in this situation when we do have that, and it doesn't seem to show any good effect, it seems hard to recommend an approval for it.

Tony Yen: I agree with what's been said about the epilepsy, as well as with the depression. I think because of the reference that we have with a nice randomized trial, at least we have a randomized trial about comparison between VNS versus sham VNS for depression and showing that there is no significant difference. I think that's compelling. That would actually influence how I would vote.

Seth Schwartz: I don't have a lot to add. I was just curious about one thing related to the broadening, the inclusion for this for epilepsy and allowing the clinicians to decide for themselves, because the only thing that comes up here is that we did see some data on the tuberous sclerosis in children. It looked like it was not effective in that situation. So, I don't know if we need to call that out specifically. Or if anybody has any thoughts about how to handle that, but that's my only concern that we see some data in a specific situation where it's not helpful. Then, we decide to broaden the clinician's opportunity to use this more instrumentally.

Edward Novotny: I can comment on the tuberous sclerosis study, I think it's a small population. It's a very . . . children with tuberous sclerosis have a very . . . and adults with tuberous sclerosis, have a very intractable epilepsy that often is not remediable to medical treatment. Other approaches, such as surgery or neuromodulation with VNS and other procedures are commonly used. Even with the other treatments, they often fail, whether surgery or some of these other treatments, as well. I think it's a specific rare or difficult patient population to deal with. I think this study is small. It's not surprising.

- Beth Shaw: The other thing I would say is that it was a cost-effectiveness modeling study. So, it showed that it wasn't cost-effective, but I wouldn't necessarily take that as evidence about effectiveness.
- Emily Transue: It was cost-effective to a point, but it was less cost-effective than a couple of other options. I agree. I wouldn't take that as evidence for lack of effectiveness.
- Seth Schwartz: Thank you for clarifying.
- Sheila Rege: Kevin, anything to add?
- Kevin Walsh: No, only that I think that there needs to be a decision about the number of drug trials, as it pertains to children before VNS is covered. There was data about two drugs, three drugs, four drugs, and we should probably take a minute to make a decision about that, but I agree with Dr. Sinanan said initially for both epilepsy and depression.
- Sheila Rege: Dr. Novotny, anything more to add?
- Edward Novotny: I agree with sort of the NICE recommendation that probably three drugs is reasonable. I am glad to hear that people are positive about its approval in children, realizing that children with epilepsy, and adults with epilepsy, 30% of patients don't respond to antiseizure medications. So, having alternatives, such as VNS and these kind of stimulations is very important and an important adjunct to their treatment. In the State of Washington, that's roughly around 3600 children who would be recalcitrant to medical therapy. So, it's good to have VNS as an alternative treatment.
- Sheila Rege: Thank you. If we could just review before we go to the decision aid. We could review what's been listed and on the PDF page 131, the safety outcomes. If there's anything more we want to add there. We've got infection, hoarseness, reimplantation, failure rate on safety. Does anybody want to add anything more we need to think about?
- Edward Novotny: I'd like to comment on those. So, the hoarseness and cough and some of those side effects are again common, but they're easily remediable by making adjustments in the therapy. The infection rate is no different than a lot of other surgical procedures and can be easily monitored closely to minimize that risk.

- Sheila Rege: Anything we've ignored though? Anything we need? For safety, I heard some device recalls. Did we put that in there? Is that common? Is that unusual?
- Edward Novotny: The device recall is with that new device was one of the recalls. Then also there were some issues regarding the software that's used for programming, which are unfortunately not uncommon technology issues, but I think the company has quickly identified that and have been able to make quick responses.
- John Bramhall: The bradycardia that we heard about, it sounded like it was low frequency and methodic. I'm wondering if you know whether or not that's treatable in the sense that changing the characteristics of the stimulator decrease the incidence of bradycardia in people who have already experienced it. Is that something that's true sort of thought? Or is the bradycardia completely random?
- Edward Novotny: That's a good question. I think there are sometimes where it is modifiable by adjusting the parameters of the device, but again, it's often very difficult to identify, is it directly related to the device? Or are there other factors that are contributing to the bradycardia, as well?
- John Bramhall: I see. OK.
- Sheila Rege: I think we should add bradycardia in addition to device recalls. I think we should add bradycardia just so we know we discussed it, even though it's very rare.
- Mika Sinanan: I agree with that.
- Sheila Rege: Anybody object to adding bradycardia to the safety outcome on the list there?
- Group: No.
- Sheila Rege: Anything else we've neglected? I think we've got the safety pretty well discussed. We could move to whether we're comfortable with what the efficacy, the effectiveness, primary outcome being seizure frequency reduction. Then, the secondary outcome.
- Josh Morse: Sheila, there are two hands raised. One is a public commenter, and one is Gary Franklin, the medical director. Would you like to hear from them at this point?

- Sheila Rege: Yeah. That's a good idea. Josh, I'll defer to you on what order you want. We'll go with Carla.
- Gary Franklin: This is Gary. I didn't raise my hand.
- Josh Morse: Gary did not raise his hand. OK. We will unraise your hand. Carla Monticelli wants to make a comment, I think. I will unmute you now. Carla, are you there?
- Carla Monticelli: Hi, Josh. Thank you. This is just in reference to the discussion around the coverage with evidence development. I wanted to make sure everybody was clear. Medicare, obviously, started the trial. They're approving it. They are allowing any patients from other payers to be enrolled in the trial. So, to your point, Josh, if Washington Medicaid will approve and pay, a patient would be allowed to enroll in the trial. The criteria for enrollment is very much tied to our label. So, four more failures, you need to be in a major depressive episode. All subjects are enrolled. They are randomized. Everybody receives the implant. At 12 months, if you were in the non-random, or the turned off section, you would be turned on. So, at 12 months, all patients, all subjects are turned on. They are followed for five years. So, I just wanted to make sure everybody understood that part of it. There's a lot more inclusion/exclusion, but it's based on our label's indication.
- Josh Morse: OK.
- Carla Monticelli: And if you allowed it, Medicare would allow Washington Medicaid patients to be enrolled in the trial.
- Josh Morse: Thank you, very much.
- Sheila Rege: So, moving onto efficacy on epilepsy, I think we've got it all covered there. Anybody want to add or have an objection to what's listed on the screen? Then, we can move onto depression. That goes onto the next page, too, on depression. Then, cost outcomes I don't have anything to add. Chime in if you do. Then, special populations, I heard children. Do you want to . . . Dr. Novotny, do you want to also differentiate . . . you had said something about children with a certain thing, or even adults? Was it tubular . . . for depression? Do you want to make that? Or is that just too much in the weeds?
- Edward Novotny: No. I think that's too specific.

- Sheila Rege: OK. So, we just leave it at that? And now if we . . . any more discussion? Or shall we use the decision aid on how we feel? And let's first take . . . I'm open to suggestions. Do we first want to take depression? Or do you first want to take epilepsy? Somebody, give us advice? Mika? I'm going to pick on you. Which one do you want to go first?
- Mika Sinanan: OK. Epilepsy.
- Sheila Rege: OK. Go ahead for epilepsy?
- Mika Sinanan: Yeah. For safety, I would say more in some. Efficacy, more in some. Cost-effectiveness, more in some.
- Josh Morse: Thank you.
- Sheila Rege: Tony, would you like to go next?
- Tony Yen: Sure. So, for epilepsy, safety would be more in some. Efficacy would be more in some. Cost outcomes would be unproven.
- Josh Morse: Thank you, Tony.
- Sheila Rege: Kevin?
- Kevin Walsh: I agree with Tony's three.
- Josh Morse: More in some.
- Sheila Rege: More in some. More in some. Unproven.
- Kevin Walsh: Yes. Thank you.
- Josh Morse: Thank you.
- Sheila Rege: Seth?
- Seth Schwartz: Just to be clear, when we're talking about safety, are we saying that it's safer, if we say more in some, are we saying it's safer in some conditions to do it?
- Sheila Rege: Yeah. Good point.
- Seth Schwartz: I guess what I'm struggling with is that, I mean, this is a surgical intervention. So, it seems like it's gonna be less safe than not doing

anything, unless you take the opposite view of risk of suicide and things like that. So, I'm not exactly sure how to grade it for safety. So, my inclination is to say less, but I don't . . . I'm not sure exactly how we're weighting that.

Laurie Mischley: Can we hear from Mika and how you interpreted this when you answered this more in some?

Mika Sinanan: Thank you. I was struggling with that, as I thought about it. I said more in some relative to the consequences of untreated, uncontrolled epilepsy, because these are seizures [inaudible] other therapy.

Seth Schwartz: I still think I would say less for safety, more in some for efficacy, and unproven for cost-effectiveness.

Josh Morse: OK. Thank you.

Sheila Rege: I would agree with Seth. I'm going to go with what Seth said.

Josh Morse: OK.

Sheila Rege: If I'm next. Laurie?

Laurie Mischley: I would say for safety more in some. For efficacy, more in some. Unproven for cost-effectiveness.

Josh Morse: Thank you.

Sheila Rege: Thank you. Conor?

Conor Kleweno: Yes. For safety, if we're considering compared to untreated, then I would say more in some. Efficacy more in some. With respect to the comments about decrease in medication cost, depending on those costs, I would say more in some for cost-effectiveness.

Josh Morse: OK. Thank you.

Sheila Rege: Chris?

Chris Hearne: I would say for safety more in some. For efficacy more in some. Unproven cost-effectiveness.

Josh Morse: Thank you.

- Sheila Rege: Janna?
- Janna Friedly: I am going to say more in some for safety, even though I'm not quite sure that captures it. More in some for effectiveness. Unproven for cost.
- Josh Morse: Thank you.
- Sheila Rege: John?
- John Bramhall: I'm passing it the same way that Mika elaborated. I think that the some, in my mind, is the group that's responsive to the therapy. So, I think that it's safer for some people to be treated in this way than to leave them relatively untreated, or unsuccessfully treated. So, more in some for safety. For efficacy, more in some. Not everyone responds, but some do. And those that do are going to benefit. For cost outcomes, I agree with Conor. I think again using the same logic, there's a group of people that are going to have decreased medication cost if this therapy is successful for them. So, I think that's a group that would have cost outcomes that are more in some, more effective in some.
- Josh Morse: OK. Thank you.
- Sheila Rege: I think we got everybody? Did we?
- Josh Morse: Yes. I think that's everybody. I have a record of everybody.
- Sheila Rege: OK. Good.
- Mika Sinanan: Sheila, quick question. In terms of the cost-effectiveness, there was a comment in one of the presentations about reduction in hospitalizations. I suppose that applies both to depression and to epilepsy, but if you include hospital costs, there was some data about reduction in hospital costs. Beth, can you comment on that?
- Beth Shaw: Yes. We didn't include [inaudible] use or hospital costs. Sorry. No. That's not true. We were looking for economic outcomes. We wouldn't have found any hospital costs. It was only those two economic models. There were some studies that I think included kind of hospital use, but we didn't include that.
- Mika Sinanan: OK. Thank you.

- Edward Novotny: I can comment. So, there have been those looking at Emergency Room visits and hospital admissions. Those are, again, low quality studies but have shown some benefit.
- Sheila Rege: Any more discussion? Any more questions? We're just now talking about epilepsy. I don't see a lot of differences of opinions on this. So, I would take a motion that we vote on coverage. We can start with a straw vote and discuss.
- Mika Sinanan: I so move.
- Sheila Rege: So, let's talk about . . . would anybody not cover this for epilepsy? If there is somebody, let's have you speak up and talk about why. Is there anybody that would cover this unconditionally for epilepsy? And then we're going to cover under conditions. Let us . . . could we pull up the agency medical director wording and just discuss that. It sounds like everybody wants to cover with conditions?
- Group: Yes.
- Sheila Rege: Should we go around the room? Is that true? Everybody who wants to cover with conditions, please say aye.
- Group: Aye.
- Sheila Rege: So, here's what the agency medical directors have said. Cover with conditions. When all of the conditions are met, seizure disorder refractory to medical treatment defined as at least three adequate trials of antiepileptic medications and surgical treatment is not recommended or has failed.
- Janna Friedly: I have a little bit of confusion about the defined as at least three adequate trials of antiepileptic medication. Usually, I think of it as you have tried at least three different medications. This makes it seem like it could be three trials of the same medication, which doesn't clinically make sense to me. So, it feels like the wording needs to be a little bit modified.
- Sheila Rege: Do you have a suggestion on how to modify that?
- Emily Transue: It was not our intent that it be the same medication three times over.
- Janna Friedly: Right. That's why I think it needs to be modified. Defined as . . .

- Sheila Rege: Trial of three different medications?
- Mika Sinanan: Three adequate trials of appropriate but different antiepileptic medications?
- Janna Friedly: Sure. To me that is specific enough but vague enough to allow for clinical judgment as to what an adequate trial is and what those medications are, but it gets across the gist that you need to have at least tried three things.
- Mika Sinanan: Dr. Novotny, is that broad enough or specific enough for clinical practice?
- Edward Novotny: Yes. It fits with several of the guidelines from the ILEA, a well. So, again, it's different trials. They can either be sequential or in combination.
- Sheila Rege: We had talked about children. You were OK with three drugs in children also?
- Edward Novotny: Yes. Correct.
- Sheila Rege: Does anybody have an objection to this language for epilepsy?
- Mika Sinanan: Just so the wordsmith defined as adequate trials, move the adequate trials to right after the as. Defined as adequate trials of at least, and then take this out here. Three appropriate but different antiepileptic medications. It just sounds better.
- Sheila Rege: That flows better. Yeah. That flows better. Anybody want to add anything to these conditions? So, based on our discussion, maybe we could do a vote of covered under these conditions. Everybody, let's not go to aye anymore. Let's just yes, approved on this. Josh can then take it as unanimous. So, everybody in favor of this language for epilepsy, covered with conditions under those conditions for adults and children age 4 and older, say yes.
- Group: Yes.
- Josh Morse: OK. I have ten cover with conditions.
- Sheila Rege: Any more discussion on epilepsy? Let's go back to depression now. Let's go . . . John we'll start with you on safety using these five unproven, less, equal, and more in some, more in all, effectiveness or efficacy and cost-effectiveness. This is on depression.

- John Bramhall: Yeah. I have a little bit of a dilemma. Depression is a fateful disease. By the time you get to the point to which you'd be considering this therapy modality, it's a very dangerous disease. So, I think I'm going to say that this therapy is more safe in some cases. So, more in some for safety. For effectiveness, we're not convinced by the data that we've been presented with, but I am . . . it's certainly not equivalent. I think it's unproven. I think I have to say it's unproven, even though you know that I actually want to have people be able to be enrolled into the trials that are ongoing. For cost outcomes and cost-effectiveness, no knowledge at all. So, unproven. So, back again, more in some. Unproven. Unproven.
- Josh Morse: OK. Thank you.
- Sheila Rege: Jenna, are you prepared to go and give us your thoughts on it?
- Janna Friedly: Yes. I agree. I'm going to say unproven in all three. Again, for safety, I think you can only make the argument that it's safer in some people if you can demonstrate that it's more effective than the other treatments at improving the condition. So, to me, you can't say that we have any safety data that shows that it's safer, because we don't have the data that it's more effective. So, I'm going to say unproven for all three.
- Josh Morse: Got it. Thank you.
- Sheila Rege: Chris?
- Chris Hearne: I agree. I would say unproven in all three categories.
- Josh Morse: OK. Thank you.
- Sheila Rege: Tony?
- Conor Kleweno: Yeah. So, I will say unproven for safety. I did put a little bit of stock in the observational trial, as well as the level 5 evidence presented. So, I will say more in some for efficacy. Cost I will say unproven.
- Josh Morse: Thank you.
- Sheila Rege: Laurie?
- Laurie Mischley: For safety, I'm going to say more in some. For efficacy, more in some. For cost-effectiveness unproven.
- Josh Morse: Thank you.

- Sheila Rege: I would say unproven in all three.
- Josh Morse: Alright. Got it.
- Sheila Rege: Seth?
- Seth Schwartz: Same troubles with safety. I guess I would say less for safety. Unproven for . . . or I guess I would say more in some for the efficacy. Unproven for cost.
- Josh Morse: OK. Thank you.
- Sheila Rege: Mika?
- Mika Sinanan: Less, because an operation in these people is even harder for them to tolerate and risk here. Unproven. Unproven.
- Josh Morse: Thank you.
- Sheila Rege: Kevin?
- Kevin Walsh: I think that Seth and Mika make a compelling argument for less regarding safety. So, less. Unproven. Unproven.
- Josh Morse: Got it. Thank you.
- Sheila Rege: Tony?
- Tony Yen: Unproven in all three.
- Josh Morse: OK. Thank you. That is everybody.
- Sheila Rege: OK. Before we go on to a coverage decision, I think Josh, if you would [inaudible] regardless of our coverage decision, you say the agency medical directors can then decide on exceptions or enrolling into trial. Correct? Can you restate that for the committee?
- Josh Morse: Yes. Let me . . . right. So, here's what it says in the State law for this program. The participating agencies shall comply with the determination of the committee unless, and here is the unless part, reimbursement is provided under an agency policy regarding experimental or investigational treatment, services under a clinical investigation approved by an institutional review board, or health technologies that have a

humanitarian device exemption from the federal Food and Drug Administration. So, that's what gives the agencies the authority to do something other than follow your noncoverage decision in a situation like this. Did that answer your question?

Sheila Rege: Yes. Any questions for Josh on that? We as a committee have to make a recommendation based on the evidence. Then, the agency medical directors have an additional authority. Then, let's talk about . . . we'll start with, would anybody in this group want to cover this unconditionally? Any takers on that? Anybody want to cover under certain conditions?

Laurie Mischley: I would vote to cover in treatment resistant depression that had failed drugs and procedures. I know I'm going to be outvoted on this, but I just want to . . .

Sheila Rege: No, that's . . . you may not be. So, we have one and let's . . . I'm going to write that down. So, treatment-resistant depression failed the same thing, failed three drugs?

Laurie Mischley: Yeah. I'm open to discussing that, but.

Sheila Rege: Anybody else inclined to cover under certain conditions?

John Bramhall: Well, yes. I mean, I'm sorry, I'm being inconsistent intellectually. I know, but I agree with Laurie's sentiments really. I think what I would like to see . . . well, you know what I'd like to see. I'd like to see that people who have failed everything and they have got intractable depression have an access route when the economically [inaudible] an access route into the study. In other words, the therapy is offered and monitored carefully, and it contributes to the literature and all the rest of it. So, we can ultimately get a straight story at some point. That's what I would like to see. I'm not sure that my verbose language fits with everything, unless I simply say, cover with conditions. The conditions that I would put in would be the conditions required for entry into the Medicare supported study.

Laurie Mischley: Are we able to make that recommendation in a coverage decision? Or is that something that we need to leave up to the agency to decide?

Kevin Walsh: Historically, we have not been able to do that. We have had to leave it up to the agency to decide.

- Sheila Rege: Right, because I think we are supposed to vote on the evidence. Then, the agency has the authority.
- Laurie Mischley: Otherwise, I would probably make that recommendation for almost everything that we don't have evidence for that they could . . .
- Sheila Rege: Any more discussion? I'm going to go down the list. So, we've got two. John, actually, if you wouldn't mind, would you say not cover knowing what Josh said? Or would you take another approach? So, go ahead.
- Laurie Mischley: Not cover.
- Sheila Rege: Not cover. Chris?
- Chris Hearne: Not cover.
- Sheila Rege: Conor?
- Conor Kleweno: I would cover based on the modifications that the, I think it was the Canadian Organization had.
- Sheila Rege: Can you elaborate?
- Conor Kleweno: So, there was a number of different organizations that had their recommendations. I believe it was the Canadian one that the Washington State Psychiatry Associated referenced in their recommendations. It was definitely, you know, resistant depression having failed multiple different drugs. I just don't remember the wording on it. We could potentially bring it up, and we could review.
- Sheila Rege: Yes. Let's pull, let's have you pull that up. I'm going to go on. Sheila, I would say not cover. Seth?
- Seth Schwartz: Not cover.
- Sheila Rege: Mika?
- Mika Sinanan: Not cover with a recommendation for rereview after pending the results of the upcoming large RCT.
- Josh Morse: That's a great point, Mika. That was a question of mine. Can the committee make a recommendation at this point when this would be rereviewed?

- Kevin Walsh: I don't think we have to. I think the whole foundation is that when the medical directors feel that there is compelling evidence regarding a technology that they will ask for a rereview.
- Josh Morse: I will add, anybody, should a study be published, who identifies it, can ask for a suggested rereview.
- Sheila Rege: So, no coverage at this time is what I'm hearing from Mika.
- Mika Sinanan: Correct.
- Sheila Rege: Kevin?
- Kevin Walsh: No coverage.
- Sheila Rege: Tony?
- Tony Yen: No coverage.
- Sheila Rege: OK. I think we pulled up, and I'd like to spend some time for Laurie or John or Conor to help us understand your position knowing that the agency medical directors can enroll people on the study if needed. So, we've all voted. Correct? So, Josh, do you want to summarize?
- Josh Morse: Dr. Bramhall, what was your vote? That's the one blank that I have?
- John Bramhall: Well, yes. I was voting to cover with conditions. The conditions were as just described.
- Josh Morse: OK. And Seth?
- Seth Schwartz: I voted no cover.
- Josh Morse: No cover. Thank you. I'm sorry I missed that. So, I have three with draft coverage with conditions and seven no cover.
- Sheila Rege: That was kind of . . . I presumed it was a straw vote, just because of the topic. Laurie or John or Conor, anything more to add? Conor, you had said the Canadian, and I think Josh is trying to pull that up.
- Conor Kleweno: That just specified the conditions that were mentioned. Third line treatment after failure of ECT and transcranial magnetic stimulation. I'm assuming that it would also add in after medication, refractory to multiple medications, as well.

- Sheila Rege: Do we know if the Canadians cover this? Or I see that the recommendation by organization, and that was 2017.
- Josh Morse: I don't think we know about the coverage. We typically don't go looking for that coverage. We do look for the guidelines, which is what this is from.
- Sheila Rege: Alright, any more discussion?
- Mika Sinanan: It says the Network of Academic and Clinical Experts. So, you're right. It's a professional organization, not a government organization.
- Sheila Rege: Right. I see this is a chance, you know . . . I like it when we're all unanimous and close in voting, but I see this as a chance to kind of flush out. I think people know that there are studies coming. I'm comfortable, personally, knowing that the agency medical directors have an option for severe cases, if need be, and I do see evidence about having enough evidence for efficacy to be covered. That was my vote. If others want to speak about it or change their minds before we move on.
- John Bramhall: Again, so if the agency has the capability of putting someone onto the study, is that correct, Sheila? So, if the agency reviews a specific clinical case, they can come to a determination that this is a case that should be entered into a trial and not simply be offered the same therapy as is being offered within the trial. They would want the patient to actually be enrolled in the trial. Is that true?
- Sheila Rege: That's what I got from what Josh was saying.
- John Bramhall: So, on the one hand, if we're hardnosed and say, well, there's no good evidence that this therapy is of any value whatsoever for depression, which is one sentiment that could be elaborated, then I'm assuming that the agency would be thinking that they wanted to contribute to the information from the trial, just as much as they would be wanting to give someone a shot at therapy that may or may not be effected. So, again, I'm sorry. I always struggle this way. It seems like there's a group of patients. We heard from the nonexpert lay testimony from educated people that there's a group of patients who do seem to benefit clinically. It's not demonstrated wholesomely in the literature. So, we really have difficulty dealing with this other information, but there certainly is a group of people who get to the end of the line that failed everything, and they have this devastating disease. I would like to just . . . I just would like to have reassurance that that kind of case presented on perhaps

Medicaid basis, would be viewed with some level of favor by the agency. That's all I'm sort of searching for. I don't think I can do it within the constraints of the committee any other way than voting for cover with conditions, but that's what I'm rooting for.

Emily Transue: Maybe I can speak to that a little bit. I think within . . . there's a process within Medicaid called exception to rule where almost anything can be overwritten under really extraordinary circumstances. So, there is always a little bit of an out on Medicaid's side. With that so, under the managed care companies, it wouldn't be something that would be being reviewed by the medical directors in house at the HCA. It would be on those [inaudible] at the MCO's to make a determination. That's not true on the PEBB and Uniform Medical Plan. We really don't have an ability to make exceptions when you've stated a determination. Again, in the setting of an actual clinical trial could be different.

Sheila Rege: Anybody else want to discuss, or I'll take a motion to do our final vote? Any other discussion?

Laurie Mischley: I'll just chime in and say, I'm trying to make my decision separate from any trial that's happening. Of course, I want the trial to happen. I look forward to seeing those results, but they're very separate issues. Things happen. It might be that a study loses its funding. It might be that someone who would be otherwise eligible can't meet the study schedule. They can't get to the location at a certain time to be able to participate in the trial. So, I'm trying to make my decision independent of an ongoing trial, although like everybody else, I look forward to that. The way I am seeing this is, there is not as high of quality of evidence as what we would all like, but we do have evidence in an observational study that one, it is better than standard care alone, and it's sustainable over five years, in a group that is at high risk and has a devastating disease, both personally and economically. We're talking about a medicine, or a therapy that seems to offer some benefit when nothing else is. Even in the head-to-head comparison between low dose, high dose, we heard a very good explanation for why we don't see a difference, and that's because we actually see an improvement in both groups. What we thought was a sham actually ends up looking like even it offers some help. So, the reason we're looking forward to this double blind placebo controlled trial is to kind of get to is it placebo, or is it the stimulation that's actually helping. I would actually argue that's getting into the mechanism a little bit. What we're seeing here are a couple studies that suggest that by using this intervention, we do offer a population of people that is not being otherwise helped some opportunity for help. We have already agreed, it's reasonably safe. So, that's kind of where I'm coming from.

The data is not as good as I want, but this is a population of people who needs help. We do . . . the limited evidence we have suggests it might be able to help some of them.

Sheila Rege: I see where you're coming from. I still wasn't convinced with the data personally, but anybody else want to talk about it?

Conor Kleweno: One other comment based on Laurie's line of reasoning that if we're going to rereview it after this trial, either that means we guessed right or we guessed wrong on either side of it. So, we decide to cover. The trial suggests that it's not effective, we stop covering it. Or we decide not to cover it, and then we cross over, but either way are I think valid depending on how you interpret the entirety of the data.

Sheila Rege: Right. Anymore discussion? Or I'll take a motion to do our final vote.

Tony Yen: I'll move for a final vote.

Kevin Walsh: Second.

Sheila Rege: All in favor?

Group: Aye.

Sheila Rege: Alright. We'll go down the list. John, your vote?

John Bramhall: I vote to cover with conditions.

Sheila Rege: Janna?

Janna Friedly: Not cover.

Sheila Rege: Chris?

Chris Hearne: Not cover.

Sheila Rege: Conor?

Conor Kleweno: Cover with conditions.

Sheila Rege: Laurie?

Laurie Mischley: Cover with conditions.

Sheila Rege: Not cover. Seth?

Seth Schwartz: Not cover.

Sheila Rege: Mika?

Mika Sinanan: Not cover.

Sheila Rege: Kevin?

Kevin Walsh: Not cover.

Sheila Rege: Tony?

Tony Yen: Not cover.

Josh Morse: Thank you. I have seven not cover, three cover with conditions.

Sheila Rege: OK. Going onto identify Medicare decisions and expert guidelines. Were we consistent with that? I'm open to discussion on that. I'd like to take a minute. Then, we'll come back to our exact language, just taking a break from. We'll do one final look at our language before we adjourn, but I think it was consistent. Medicare coverage guidelines.

Josh Morse: Dr. Rege, we also need to address the transcutaneous VNS.

Sheila Rege: I was on mute. I'm sorry. Yes. We do need to go back for that. On this, OK. Let's go back to transcutaneous. Let's pull up the agency medical director recommendations, not to cover, but let's go through safety, efficacy, and cost-effectiveness. Anybody want to take a stab at that?

Mika Sinanan: Unproven for all of them.

Conor Kleweno: Unproven for all of them.

Laurie Mischley: Unproven for all three.

John Bramhall: Unproven for all of them.

Janna Friedly: Unproven for all three.

Seth Schwartz: Unproven for all three.

Chris Hearne: Unproven.

- Kevin Walsh: Unproven for all three.
- Tony Yen: Unproven for all three.
- Josh Morse: OK. That's everybody.
- Sheila Rege: I'm unproven. Yes. So, now let's . . . if we're all in agreement, this will be the final vote. If we're not, we'll consider this a straw vote. Anybody want to cover unconditionally? Anybody want to cover under certain conditions? Everybody who says not cover, I was going to say raise your hands. Say yes or aye.
- Group: Aye.
- Sheila Rege: Anybody want to abstain? No. OK. So, Josh, do you want to review what we just?
- Josh Morse: So, I have everybody voted unproven for safety, efficacy, and cost. I have ten votes to not cover vagal nerve stimulation transcutaneous device.
- Sheila Rege: Now, we'll go to the expert guidelines. Do we still need to review that for the transcutaneous?
- Josh Morse: I think for everything. The Medicare coverage is here. You've talked quite a bit about the Medicare coverage and the fact that it's a coverage with evidence development.
- Sheila Rege: Any discussion, but I think we've been pretty consistent with that.
- Josh Morse: And if you could make a short statement about the evidence and your concerns related to coverage right now. You were waiting for future publications is what I heard you say?
- Sheila Rege: We're waiting for future studies to mature and be published.
- Josh Morse: Alright. Thank you.
- Sheila Rege: This is, again, going down depression. Then, we've already reviewed some of the other guidelines. I think we're consistent.
- Josh Morse: OK. Thank you.

- Sheila Rege: So, at the next meeting, we will review these findings, but now I'd like to go back and one last set of eyes on what we came up with so we can review that document. This is our conclusion. Vagal nerve stimulation for epilepsy adults and children covered with conditions. Conditions being seizure disorder being refractory to medical treatment, defined as adequate trials of at least three appropriate but different antiepileptic medications. Thank you, Dr. [inaudible] for that wordsmith. Surgical treatment not recommended or has failed. Not cover on depression or the transcutaneous vagal nerve stimulation.
- Josh Morse: I'd like to check, I think is the depression coverage only for adults. I think I need to clarify that before . . .
- Sheila Rege: Yes. Depression was only for adults. Yes. The expert could clarify that. Beth, would you like to?
- Beth Shaw: Certainly. We just looked at adults.
- Sheila Rege: Anymore discussion on this? OK. Then, I think everybody is comfortable with this document. Everybody who is comfortable, please say yes, aye.
- Group: Aye.
- Sheila Rege: OK. Josh, anything else that we need to do?
- Josh Morse: No. That concludes the action items on today's agenda. Thank you all very much.
- Sheila Rege: I would like to say, Dr. Novotny, thank you, so much. I know it's tough when we're all on a telephone, and you haven't met us. So, thank you for just helping with sharing your expertise. Josh and Britt, I think Kevin and I did a little session trying to learn this, but you guys just made it happen like magic. I mean, sharing your screen and everything, which I know is difficult. Thank you. Thank you to all the panelists, Beth and Emily and Erica and Valerie, thank you, very much. The agency medical directors, thank you for all the input. Any recommendations from the committee on how this went that we would differently, please email Josh or me or we can say something now. We have eight minutes to 4:00. We're actually ahead of time.
- Josh Morse: Yes. Please let us know if you have any recommendations. We do plan to do this again on June 12th. I do not anticipate that that meeting will happen in person. We'll be here, but it won't be a full day like today was.

Thank you all, very much, for your participation. I'm so glad this worked out the way it did, so far, technically.

John Bramhall: Is there any way that we go to meeting format permits webcams?

Janna Friedly: I see Valerie right now.

John Bramhall: Yeah. It just popped up. I didn't see that option when I was logging on. We do zoom day in and day out. And it's just automatic there that you can select yes or no. I just wonder, a, is it possible. Yes, it is. B, is it desirable? Do we want to see each other?

Britt Reddick: I think another option would be, I think Dr. Rege had brought this up, but when we met, but maybe even just putting up a picture in case the webcams become a bandwidth issue. So, thankfully, we've got some options. Yeah.

Sheila Rege: I actually like seeing people. I'm enjoying seeing Valerie right now.

Josh Morse: I think you're on mute, Valerie.

Valerie: It only means that I hit the wrong button by mistake, but it proved that it could do it.

Sheila Rege: Is there anybody in this group who would object to being on a webcam?

Conor Kleweno: I think one option would be putting up your picture for times where you don't want to be on the camera.

Valerie: Could I just say one thing? One thing we've noticed, because we've been doing a ton of webinars, has been that for some people, their internet doesn't support the video and the data very well. So, they get better data support if they turn off their video. So, that's just one potential downside.

Josh Morse: Yeah. That's the guidance that Britt received from our technical folks here is that going without the video was a safer bet if there were any bandwidth issues.

Sheila Rege: so, the next meeting, I'm hearing the recommendation that we do it without video from the experts?

Mika Sinanan: It seemed to work quite well today. I think we got a lot of engagement. So, thank you.

Sheila Rege: We'll do the same, Mika. Then, we can see. We can experiment. One or two of us can turn it on by accident.

Josh Morse: I think that's fine. This is Josh. I would support that. I think if things slow down or get choppy, we can turn the cameras off.

Mika Sinanan: I will say that if we ever review transcranial magnetic whatever, if it looks like that colander in Back to the Future, I'm definitely going to vote for it.

Josh Morse: Well, you did review . . . the committee has reviewed transcutaneous magnetic stimulation for treatment-resistant depression along with ECT. They are both covered.

Mika Sinanan: Well, there you go.

Josh Morse: Similar to the Canadian guideline for treatment-resistant depression that is resisting drug treatment.

Mika Sinanan: Nice job today, Sheila.

Janna Friedly: I agree. Thanks, Sheila.

Conor Kleweno: Thanks everyone for welcoming me on my first session. It was great working with you all. A very collegiate experience. Very professional, and I very much appreciate it.

Group: Welcome.

Josh Morse: Alright. Well, thank you everyone. I think we'll wrap up, and we'll see you in a few weeks.

Group: Thank you.