Washington State Health Care Authority

Washington State Health Technology Clinical Committee Meeting

Transcranial Magnetic Stimulation for Treatment of Selected Conditions

March 17, 2023

DISCLAIMER

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Sheila Rege	Well, let me know when we have the committee members joined.
Val Hamann	We should have most here.
Josh Morse	Gosh, it looks like you have a quorum. I think I count at least seven committee members here. I think we're expecting 9 today.
Sheila Rege	OK, perfect. And while we're not talking if all the committee members could make sure we're on mute, just to avoid any distractions. Thank you for coming out and, umm, in the absence of any questions about procedure process. I'm gonna turn it over to Josh to begin a slide presentation.
Josh Morse	Great. And before we do that, I think we'll do a quick attendance and we can catch up if folks aren't here and if as we go through for attendance, if you could state whether you have any conflicts and this is attendance for the committee members today. If you have any conflict with the topic today or anything you wanted to disclose related to the topic. And Val, I think you have the list. So would you mind please just reading down the list alphabetically and we'll check off behind the scenes here who is present at this time and we can catch up with anybody who is coming in a few minutes late.
Val Hamann	Yeah, definitely. John Bramhall.
Val Hamann	Larry.
Josh Morse	I don't see John here quite yet.
Val Hamann	Larry Birger.
Val Hamann	Clinton Daniels.

Clinton Daniels	I am here are you wanting an intro as well Josh or or just whether or not, we have a conflict.
Josh Morse	Umm you could do an intro Clint if you wanna say a few words.
Clinton Daniels	Sure, I'm. I'm Clinton Daniels, I'm a chiropractor. I am the chief chiropractic at VA Puget Sound. I don't have any conflicts for this topic. I do see a number of patients with overlying or overlapping mental health disorders, but don't manage it myself. So this was a brand new topic for me. Thanks.
Josh Morse	Thank you.
Val Hamann	Janna Friedly.
Janna Friedly	Hi. Good morning. Uh, I'm Janet Fridley, physiatrist at the University of Washington. And I have no complex or new disclosures to report.
Val Hamann	Chris Hearne.
Josh Morse	You don't see Chris here yet.
Val Hamann	Conor Kleweno.
Conor Kleweno	Yeah. Uh, Conor Kleweno. I'm an orthopedic trauma surgeon at Harborview Medical Center in the University of Washington. I have no conflicts to this topic specifically.
Val Hamann	Christoph Lee.
Val Hamann	Laurie Mischley.
Laurie Mischley	Uh. Present. I'm a naturopathic physician in Seattle, WA and I do research at University of Washington and Bastyr University and I have no conflicts to disclose.
Val Hamann	Sheila Rege.
Sheila Rege	Good morning Sheila Rege readers, oncologist in the tri-cities, Washington. No conflicts to disclose on this topic. Thank you.
Val Hamann	Jonathan Sham.
Jonathan Sham	Good morning, Jonathan Sham surgical oncologist at the Prudential Cancer Center and have no conflicts.
Val Hamann	Tony Yen.
Tony Yen	Hi, I'm a hospitalist at Evergreen health. I have no conflicts or disclosures.
Josh Morse	OK. Thank you very much. So I believe that is 7 Members present, so we do have a

quorum so we can jump into this presentation. Bear with me for just a minute. OK, if you can confirm that you're seeing this first slide here, somebody.

Sheila Rege Yes.

Josh Morse Great. OK, so this is our health technology assessment meeting for today, March 17th. The topic is transcranial magnetic stimulation for selected conditions. I'm Josh Morse. I am the program director here, Val Hamann, who you've heard is our program specialist. So we have started the meeting is being recorded. Uh, we will create a transcript from this. And today we are using Teams, so if you're not familiar with Teams, here is a a brief bit of information. So committee members we will be using the raised hand function for, umm for voting, we're gonna try that today, at the start, we may shift around if that becomes unwieldy for some of the votes. But that's where we will begin asking you to raise and then unraise your hand when we get to some of the voting. We're gonna practice that here in just a minute for non committee members who are on the call. You may not have full control for voice and camera at this time. We can change that if you wish to make a public comment and we're going to chat. We'll have a slide here on that in a moment. So if you're hoping to make a public comment during the public comment period, please let us know that through the chat function and indicate that when you're ready to do that or now actually so that we know that you're there and you wish to comment. So on today's agenda, so the first thing we're going to do is a clinical committee decision to conduct a fully remote meeting. After that we will do previous meeting business and then we will move into today's technology review, again, the TMS for treatment of selected conditions. All of today's meeting materials are available at this link. I'm going to leave this slide up here for a moment. If you don't have access yet, you can look at this link and you can follow this link to the meeting materials for today. But first, what we're going to do is go back to item one and do this right now. So committee members, we did discuss this in your public meeting in January. About conducting a acknowledging that we're conducting fully remote meetings for this meeting and future decision meetings which will buy OPMA requirements likely be what are called hybrid meetings where people we will have a room reserved for access for the public, but the committee will be meeting remotely. So today what I would like to do and Val will be recording this is, Do you ask you now? Do you agree that today we will be conducting in future action meetings will will be conducting fully remote meetings? And we can do a voice vote. So all in favor of a fully remote meeting, please say aye, I'm contradicting myself on the raised hand function because I cannot see that right now. So let's do that. So if you all agree to do a fully remote meeting today, please say Aye committee members.

Janna Friedly Aye.

Sheila Rege Aye.

Clinton Daniels Aye.

Tony Yen Aye.

Conor Kleweno Aye.

Laurie Mischley Aye.

Jonathan Sham Aye.

Josh Morse Anybody opposed to doing a fully remote meeting today or in the future for these action meetings? OK, so I think we have full agreement. And Tony has tested his hand. Do you have a question? Dr. Yen.

Tony Yen No, no, I I put my hand back down because I thought we supposed to raise our hands. Sorry about that.

Josh Morse Yeah, I'm good. Yeah. Sorry about that. I'm. I'm myself in conflicted on this. So. All right. So we have acknowledged and recorded on the record that we're gonna do fully remote meetings. That was what one of the things we were required to do today. So we'll move on into this into the presentation.

Sheila Rege Josh as a, as a procedure while we do fully remote meetings, can you just for our, our public or for recording state what the procedure would be or you planning to cover that on anybody who wants to make a comment? Thank you.

Josh Morse We will cover that. Yes, thank you. But thank you for asking the question. Great question and again at this link on the slide that I'm showing right now, this is on this page or actually, this page takes you to our main site and on that page if you Scroll down a bit, you will see a meetings and materials link, at that link we have the access link published. For this meeting, and it will be there for future meetings, so you can join this meeting from that link by teams or whatever technology we're using on the meeting day right now. We're using teams. There's also a phone number and there will be more procedure information for future meetings when we exit the public health emergency in early May, the procedure will change a bit. The remote meeting access will remain the same, but there will be other options for attending, having access to the meetings if you don't have the ability to join on your own virtually so. So again, I can't say this enough the meeting is being recorded. We will create a transcript. The transcript is available from another page from the meeting materials page as I just described. So when you're speaking, if you could please state your name and use your microphone. Thank you. So now some background on the program for folks who may not be familiar with this. So the Health Technology Assessment program is administered by the Washington State Health Care Authority. The program brings evidence reports to the Health Technology Clinical Committee this group to make coverage decisions for certain medical procedures and tests based on the evidence for safety, efficacy or effectiveness, and cost effectiveness. So multiple state agencies are participating and they participate to identify topics and to implement the

policy decisions that come from this process. These agencies include the Health Care Authority that administers the uniformed medical plan, as well as the Apple Health Medicaid plan for the state of Washington, the Department of Labor and Industries, and the Department of Corrections. State agencies implement the work and the determinations from the program and from the Health Technology Clinical Committee within their existing statutory frameworks. The purpose of this process 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. The process develops scientific evidence-based reports on medical devices, procedures, and tests for the clinical committee to review, and we support the HTC the Clinical Committee to make these determinations for the selected medical devices, procedures, and tests based on the available evidence. There are multiple ways to participate. As I've said a few times now, there is a the website is the main place to gain information about the program. Individuals can sign up from that website to receive program notifications by e-mail. And anybody may provide comment on topics when they're proposed, when they're selected on draft key questions on draft and final reports and on draft decisions, as well as anybody may attend these HTCC public meetings and present comments directly, including today. Additionally, anyone may nominate a topic for review or for rereview. So public comment today, attendees will be allowed to unmute and turn on their cameras if they desire to give a public comment, and if they wish to use their camera. Uh, please, uh comments will be limited to 4 minutes. We will uh time anybody who is requesting to make a comment today and we will ask you to stop if you exceed 4 minutes. If not signed up in advance, please indicate your interest by providing to provide a comment using the chat function before the comment period. The volume of signups will determine the available time for each person. I believe we have 40 minutes on the agenda, so if we exceed 10 people who wish to give comments today, we will need to limit the time to less than 4 minutes. So if you can please at when you are asked to, when you do provide public comment, please disclose any conflicts of interest prior to making your comment. We will present this slide during that period and we will ask you to clearly state your name again stating the comments any conflicts and this again we will have this up during that part of the. So this is a more detail on the agenda. So first we're going to cover the minutes from the previous meeting and then we will move into the topic for today. It'll start with the agency medical directors presentation. We'll then have the public comment period followed by the evidence report presentation. The committee question and answer session with the evidence report and then committee discussion and decision. There are breaks also outlined on the agenda. So upcoming health technology clinical committee meetings. On May 19th we are scheduled to review stereotactic body radiation therapy, so at this time there is a public comment period open for the draft evidence report. So if you wish to review the draft evidence report, that's, uh, that reports out there now for review and and comments may be taken. In July, we are scheduled to review hyaluronic acid and platelet rich plasma. In one report, the status is in progress. The final key questions have been posted. The next step in that process

	will be publication of the draft key questions. There are approximate dates for each topic available on the website. And then scheduled for November 17th is the topic spinal cord stimulators. This is in progress. The next step is the publication of draft key questions. Those have not been published yet. So after today's meeting on transcranial magnetic stimulation, the program will publish any draft decision that's developed today. That determination will be available for a public comment period for two weeks. If there are any questions about this at this time. Community members, please let me know. Otherwise, I think we are ready to move on to previous meeting business.
Sheila Rege	That was an excellent summary and a guideline. Any questions from the committee members? If not. We are ready for the next item, which I believe is approval of the minutes from the previous meeting. January 27th. Am I correct Josh?
Josh Morse	That is correct. I can get those minutes up here on the screen. Umm Val will be recording the vote and why don't we do it by a hand vote this time. How's that sound? I will share my screen so you can see the minutes. They are again available in the. In the packet as well.
Sheila Rege	I will take a verbal motion to or approve. And the second and then I'm trying to figure out how to raise my hand myself. On my iPad I have, so, I have reactions but I don't have a raise my hand. Josh, how. I'll take a a motion to approve and this was the January 27th. There was no decision made at that meeting.
John Bramhall	I'll so, I'll move approval cause I can do it at my voice without my hands. So move approval.
Sheila Rege	Great. Thank you, John.
Josh Morse	We'll stick to a voice vote and UM. What we'll do is we'll do an alphabetic roster in this. I'm glad we're finding out the the technology tweaks here, so we've previously used zoom. It's a Teams is a little different and just as a side note, we're exploring other software options that will allow electronic voting that is. Doesn't use.
Sheila Rege	And the other the other option, Josh, we can do voice vote for this meeting. The other option is what we've done for other meetings on Teams is just a up and down like a chat function. Thumbs up. But no, we kill or approve with the writing and approve.
Josh Morse	OK.
Sheila Rege	But let's do a voice vote. Go ahead. We gotta. We got a motion a second.
Josh Morse	We have one motion to approve.

Laurie Mischley	This is Laurie I second.
John Bramhall	And this is John, I approve.
Josh Morse	The roster and.
Sheila Rege	Josh, do you wanna do it alphabetically or something in the chat chat function?
Josh Morse	Yeah, Val, Val has the the checklist and uh, I'm gonna turn to Val for for these to run down these lists.
Val Hamann	John Bramhall.
John Bramhall	Yes, I approve.
Clinton Daniels	I Approve.
Val Hamann	Janna Friedly.
Janna Friedly	I approve.
Val Hamann	Conor Kleweno.
Conor Kleweno	Approve.
Val Hamann	Laurie Mischley.
Laurie Mischley	Approve.
Val Hamann	Sheila Rege.
Sheila Rege	Approve.
Val Hamann	Jonathan Sham.
Jonathan Sham	Approve.
Val Hamann	Tony Yen.
Tony Yen	Approve.
Josh Morse	Did we get everyone?
Val Hamann	Yes.
Josh Morse	Great. Thank you. OK. So thank you very much. We have completed the previous meeting business. We've completed the future meeting discussion and the vote on the remote meetings that we needed to decide today. I think we are ready to

move into the transcranial magnetic stimulation topic. So we will get the agency, I will get the agency medical director slides up.

Sheila Rege Josh, before that one thing. I, uh, and I cannot, um, remember if we've done it and the introductions or in the conflicts and introductions, do we have the, our expert uh committee member, did we introduce? Him or her?

Josh Morse We have not. Doctor Burns has joined us. I see we have Doctor Bramhall here as well. I think, yeah.

Sheila Rege So let's go with anybody who wasn't here when we did that to just introduction and conflicts with this topic, please. Thank you. I'll let you the roll call Val.

Val Hamann Sorry, were you wanting the?

Sheila Rege On the new on the new members, new people joining.

Val Hamann I believe we just have a Chris Hearne right now.

Josh Morse Who has not joined?

Val Hamann Ohh and John Bramhall also joined after so.

Josh Morse Doctor Bramhall, would you like to introduce yourself and state if you have any conflicts onto these topic?

John Bramhall Sure. I don't think I have any conflicts at all with this topic. John Bramhall, I'm practicing anesthesiologist at the university here in Seattle. I work at Harborview, and I'm also one of their medical directors and I'm delighted to be here. Thank you.

Josh Morse Thank you and welcome Doctor Burns. Thank you so much for being here today. If you wouldn't mind taking a moment and introducing yourself.

Tuesday Burns Sure. Hi. Thank you so much for having me. I'm doctor Tuesday Burns. I am a psychiatry attending at the University of Washington and the outpatient center. I've been using TMS in my practice off and on for many years, since 2010, right after FDA approval. And I'm just excited to be a part of this. Thanks for having me. I don't have any disclosures.

Josh Morse Thank you very much. So Doctor Burns is appointed to the committee today as the expert and non-voting member. And.

Val Hamann And then we also have Chris Hearne here.

Josh Morse Ohh did Chris join? See.

Sheila Rege Chris. Thank you.

Rache Mureau-Haines	Hi this is this is Chris. I am I realized that I appear as a different name on accident. I'll I'll try to fix that, but I am here.
Josh Morse	Thank you. Apologies. What name are we seeing on the screen, Chris? Thank you.
Rache Mureau-Haines	You're seeing a Rache. RACHE. That's my wife's name. But that automatically logs me into team under, under her name. I didn't realize that when I first opened it up.
Josh Morse	Sorry for the confusion about that.
Rache Mureau-Haines	No, that's OK.
Sheila Rege	And any. Umm, would you tell us what you do in any conflicts with this topic please?
Rache Mureau-Haines	Sure. Uh. I'm Chris Hearne. I'm a nurse practitioner. I work with uh for hospital medicine at Swedish Medical Center and I have no conflicts.
Sheila Rege	Welcome. Thank you.
Josh Morse	OK. And so we're moving into the agency medical director presentation. We have a number of agency medical directors here and it's probably an opportune time to do introductions there, so. Doctors, there's an. Would you like to start? Judy may have stepped away. Gary. Gary, you're on mute.
Gary Franklin	Gary Franklin, medical director at Labor and Industries and Co-chair of the agency medical directors group with Judy.
Josh Morse	And Doctor Fotinos.
Charissa Fotinos	Good morning. Charissa Fotinos Medicaid and Behavior Health, medical director at the Health Care Authority.
Josh Morse	Doctor Farokhi.
Azadeh Farokhi	Good morning. I'm, I'm Azadeh Farokhi, one of the associate medical directors at LNI.
Josh Morse	And Doctor Miller?
Sophie Miller	Hi, I'm Doctor Miller. I'm. I'm a medical officer supporting the Medicaid program.
Josh Morse	OK. Did I miss any medical directors from the agencies?

Gary Franklin Doctor Nam.

Ji Young Nam Good morning. My name.

Josh Morse Ohh. Doctor Nam, thank you.

Ji Young Nam My name is Ji Young Nam associate medical director at LNI. I thank you.

Josh Morse Excellent. Thanks very much. OK.

Gary Franklin And Ian Zhao. Ian Zhao is also on.

Josh Morse Doctor Zhao. Ian.

Ian Zhao Hello. Ian Zhao. A research specialist at L and I, thank you.

Josh Morse OK. I think we're ready to move on. Umm. Dr. Franklin. If you'd like to. I I can advance your slides when you're ready.

Gary Franklin OK, great. Thank you all and. We'll get started here. So the next slide. So this is about transcranial magnetic stimulation for a a number of behavioral health conditions. It goes without saying that behavioral health disorders are extremely common and caused a great burden and among our citizens, and our also very expensive L and I is actually seeing a lot of PTSD now that we have presumptive coverage for first responders and we may be seeing more of that type of stuff in the future. But the topic today is really major depression, treatment resistant, depression on people with treatment resistant depression are much more likely to be hospitalized than those with major depressive disorder and the cost and quality of life are higher and worse. And then these other conditions like substance use, uh, are also of course, extremely common, so it's obviously be great to find some other kinds of treatments that work for these things. Next slide. So today, uh, TMS for his treatment of selected behavioral disorders. The major one that we covered previously and that is currently covered, uh, for TMS, major depressive disorder, treatment resistant depression and then these other conditions are were reviewed for today's, uh rereview also. The next slide. So current treatments for behavioral disorders of course, include pharmacotherapy and psychotherapy, ECT for major depression. TMS is a noninvasive neuromodulation technique that's been cleared only by the 510K approval, which is means that it was approved based on substantial equivalence to another technology prior to 1976. And when it the FDA clears it, that means it's a cleared for marketing. It doesn't necessarily mean that they have proven that it is effective. If the FDA has cleared a TMS for major depressive disorder for OCD, for smoking cessation, and anxiety in those with depression and acute and prophylactic treatment of migraine with aura. TMS is not currently cleared by the FDA for treating anxiety disorder, PTSD or substance use disorder. The next slide. And I'm sure we'll hear much more

about this as we move along here from Doctor Burns. I'm looking forward to that because I don't really understand it myself. TMS is an electromagnetic device that noninvasively delivers a rapidly pulsed magnetic field focally to the cerebral cortex. It it's presumed to activate neurons. There are several types of TMS device and those are all reviewed today of the most common one is repetitive TMS, but then also there's a few studies on Theta Burst and deep TMS. The treatment protocols vary both within and across. These types of TMS. Which makes things slightly confusing. The next slide. The 2014 HTCC review was on nonpharmacologic treatments in general for treatment resistant depression, and it was determined that both electroconvulsive therapy and repetitive TMS were covered benefits for the treatment of treatment resistant depression. The next slide. So why the TMS topic is selected for rereview was because there's been a growing evidence based on TMS, which has led to growing interest in a possibly applying TMS to a broader set of conditions, such as the others that are being looked at today including OCD. The next slide. When the agency medical directors chose this topic, our concerns at that time were low to medium for safety, but medium to high for efficacy and medium to high on cost. The next slide. Currently, because of the prior HTCC determination, all the state agencies cover this for treatment resistant depression. The next slide. But all of these other things have been considered investigational, they are not currently covered for the other behavior, health disorders. The next slide. The costs are starting to go up, uh, you can see here the amount paid from 2018 to 2021. It's going up very substantially. The next slide. It combined the agency cost is about 3 1/2 million dollars at this point, and the number of encounters has been going up as well. The next slide. So the payment per individual so the issue is that you know 20 to 30 treatments are done for each individual for each set of treatments so that adds up to around, uh, 5 to $15,000 per person for some reason, L and I has been quite a bit higher and we've got people looking into that. I'm not really sure why that is. The next slide. So you'll hear much more about the evidence report from our evidence vendor, but this is the summary on a forest plot of the, uh remission rate, or the opportunity for remission of for treatment of major depressive disorder. You can see the upper part of the forest plot is for RTMS repetitive TMS. You can also see on that that the overall analysis is that effectiveness about 1.86 overall, but that is coming from approximately 4 studies, that only four of these studies were, were, uh, significantly benefit positive and beneficial. The evidence is mixed on on Theta and on deep TMS. The next slide. So in summary, on major depressive disorder overall these are relatively small sample sample sizes. Short follow up time, so there's a question of durability of the treatment effect. Varying degrees of evidence on the various technologies which I think will be difficult to sort out, differentiating these types of these different types. And there are different protocols as I mentioned earlier and we're seeing new ones, you know every few months. I mentioned before that 11 of the 15 RTMS RCT showed no difference compared to Sham. A lot of these were funded by

industry, which you'll probably hear more about. And the risk of bias was. High or of concern and a lot of the studies. There are varying degrees of response from mission and treatment resistance. Is it unclear, in fact of the underlying or the impact of underlying comorbid psychiatric conditions, since they are not really fully called out in a lot of the studies. And perhaps Doctor Burns could say a word about that when we get to it. There are very few studies, including special populations or subgroups. The next slide. So the overall evidence on obsessive compulsive disorder is not significant. And the two major studies in here that are positive had a a lot of potential conflict and high risk of bias. The next slide. Again, small sample sizes short follow up times and all of these studies, by the way, the outcomes are only posthoc, not the outcomes and all these studies are not like pre and post, it's just both the treatment and the Sham post. And there's also some confusion here about the definition of treatment resistance. Five of the seven RCT's on OCD showed no difference compared to Sham. That pulled result is not significant the next slide. This is an example of one of the positive studies of the Carmi study from 2019. Doctor Carmi has received research and travel support from BRAINSWAY. Dr. Tendler serves as the chief medical officer of and has a financial interest in Brainsway and other things. This is just an example. The next slide. So the evidence considerations on the other behavioral health conditions you'll hear more about, but it's much more mixed than it is for effectiveness and treatment resistant depression. There's limited data with insufficient to low strength of evidence. I'm not gonna go into that in more detail. You'll hear more about that from the evidence vendor. The next slide. Safety is kind of an issue. Long term, safety evidence is lacking, uh, and the quality of the evidence on short term safety is low or very low. The common adverse effect events are a headache, scalp pain, treatment site discomfort, facial twitching. Very rarely, some of these other things, but the most important thing that people have been concerned about, but it's not common are seizures. A few of these uh seizures are relatively rare, but serious, of course, and safety protocols include, including offering some protection but also having antiepileptics and oxygen or hands are recommended by the FDA, but they're not mandatory. So it's really unclear as to how often these things actually are in place in regular psychiatric offices, so also a little bit unclear as to who is supposed to apply the treatment and who actually gives the treatment because it seems somewhat clear from our experience that it's other folks in the office that may be applying it once it's once it treatment begins. The next slide. There is a a fair amount written on the seizure risk and TMS. It it's again quite low risk somewhere between probably .02% and .09%, which is fairly low. Almost all of the seizures occur around the time of treatment, usually during the first treatment or two or three. It doesn't usually if it's if it's going to occur, it's gonna occur early. The next slide. The FDA has has been concerned about all of this and they have special, uh, instructions for psychiatrists and others who use this. These are some examples of the special controls guidance that the FDA has put out. One of the things that's

looked at is what's called a motor threshold intensity, the motor threshold level is the minimum stimulator setting that induces an observable motor response by the patient at 50% of the applied pulses usually as as observed by movement of the thumb. So. You're obviously getting some kind of activation of neurons here and mostly, hopefully in sub seizure amounts. And so this is an important consideration in the FDA instructions that to to follow this stuff. The next slide As far as cost and cost effectiveness, there's hardly anything on this and I I think I believe there were just several studies and there was very limited data with uh most being done by uh industry The next slide. Other payer policies almost everybody covers a TMS for treatment resistant depression. OCD is a covered by Cigna and Premera. The next slide, but none of these other things are covered. And then there are numerous guidelines on the use of TMS, especially for treatment resistant depression or OCD. The National Institute of Clinical Excellence in the UK felt that the evidence on its efficacy was inadequate. And there's not a lot of guidelines on these other behavioral health conditions. The next slide. So our recommendations for your consideration are the TMS for the treatment of confirmed major depressive disorder in adult patients 18 or older is covered with conditions. Initial treatment and we kind of made this up, there's no evidence on this up to 30 treatment sessions is covered when all of the following criteria are met. Number one, failure of at least two different antidepressant medications from at least two separate classes at maximum tolerated doses for four to 12 weeks in separate trials and failure of an adequate trial of evidence based psychotherapy in the treatment of the depression and TMS is administered according to an FDA cleared protocol. Next slide. And then the other consideration is you know, what about repeat TMS treatment? And so the recommendation here is repeat TMS treatment for a recurrence or an acute relapse of major depressive disorder is covered when all of the following criteria are met. Number one, the patient had significant improvement in depressive symptoms after the initial course of TMS, a greater than 50% improvement substantiated with one or more standardized rating scales for depression and the improvement by the initial course has been maintained for at least three months. There's no evidence or precedent for the number of courses overall. The next slide. TMS is not covered for the treatment of these other behavioral health disorders. The next slide. I think that's it. So are there any questions right now and you'll you'll be getting into a lot of detail with this, but when the evidence vendor presents?

Sheila Rege Yeah. So committee members, let's uh address questions to uh, Doctor Franklin on any of his slides that we want him to go back on any of them. Uh. Kind of pretend like.

Josh Morse Sheila, are you able to see raised hands? Because we have a couple of committee members. OK, great.

Sheila Rege Yeah, I am. Janna has her hand raised and if if I can't, then feel free to put it in

the chat that you raised your hand. Go ahead, Janna.

Janna Friedly Uh. Gary, just a a quick question on the cost slides, is it it it, do we know if it is due to an increase in the incidence of of depression and mental health issues in the population? Or is it a combination of that, plus, this is a treatment that's being used more frequently for the treatment of depression. That is, that is contributing to the increasing cost.

Gary Franklin I I can't really answer the first question. I don't know the baseline change temporal change. I wouldn't be surprised if it was, I was definitely hasn't increased, you know, through the pandemic as there's, you know, stuff out there on that. But I I think it definitely has been increasing in terms of interest and use in psychiatrists offices we even had. One or two applicants to be on. Ohh, I'd psychiatrist with LNI, who only wanted to do TMS and know psychiatry. And we actually didn't allow that to happen. I feel like our doctors ought to be treating our patients. So I think there is a hugely increased interest that it it definitely among the psychiatry, psychiatric community and maybe again doctor Burns could speak to that.

Janna Friedly OK. Thank you.

Sheila Rege Yeah. Uh, sorry, doctor Burns, if you would, wouldn't mind Doctor Burns. I'm sorry if you wouldn't mind a pinning and helping us as a committee on that question. Thank you.

Tuesday Burns Sure. So specifically relating to the idea about increased interest, would that be kind of helpful place to start? Or.

Sheila Rege Ohh I I don't know Janna. We were looking at just Janne question in Janna, do you wanna ask Doctor Burns what you are looking for?

Janna Friedly Yeah. No, I was just curious if the if what we're seeing with this, you know, pretty significant increases in cost over time in the the state is is how much of that is just due to the increase in in incidents of treatment resistant depression and other conditions versus you know versus just using this more frequently for the for the population or a combination. Was wondering if we could tease that out.

Tuesday Burns Sure. Yeah. I would definitely say both. The simple answers both I to start with, I would say in terms of increase you know absolutely, doctor Franklin said absolutely the increase in not only recognition and diagnosis of treatment resistance and major depressive disorder has increased over the past several years. In the population in our state, and I would also say, you know, recognition, like I said, diagnosis of treatment resistance I think has also increased. I think for many, many years we really haven't, sort of encapsulated and recognized treatment resistance as quickly or as readily by definition, treatment resistant depression is really only a couple of failed medication trials and I would say in clinical practice we would see patients and being at UW

where I, you know I patients come to me through referral sources from the primary care doctors in the community at the UW clinics. And so a lot of folks I think are much more quickly triage to us and accurately defined as having treatment resistance. Whereas I would say several years ago a patient might have been on, you know 10 plus different psychotropic trials before they would arrive at us or even be considered to have treatment resistance, so I think we're better defining folks with treatment resistance now than we were several years ago. I think the in there is an increased number and incidence of major depression across the globe WHO and the CDC have numbers on that. But I think the other piece of it is and unfortunately this is my the cynic coming out of me is that with any technology that has been marketed to private clinics, umm, particularly the Neurostar device, and there was a lot of marketing done early on around with FDA labeling and a lot of outpatient clinics that were not affiliated with hospitals, they were just private practitioners, really it was kind of marketed at them. So I do think there was a bit of a delusional effect sort of in the past decade with smaller clinics becoming very interested in here's this new application that they could offer their patients where patients were not garnering when you see this it, you know, in half of all people with major depression, half of them are treatment resistant. So I think a lot of clinicians in the community were looking for an opportunity to give their patients relief were really eager to offer them something different. And I think that that was why folks were hoping and leaning toward buying these devices. So from an academic standpoint, there was a bit of a dilutional effect with folks in the community who weren't necessarily. And applying it as labeled or as accurately. So I do think that there was there was a bit of that there was an uptick for several years and folks buying these devices using them kind of ad nauseam. The example of the the the doc that wanted to only prescribe TMS mean that that doesn't make any sense. Why would you only do one application of anything as a you know as a clinician is trying to practice the gold standard and use evidence-based care that just doesn't make sense. But I do think there were some clinicians that were, whether it was because of marketing of the Neurostar device, accessibility of it, umm, some lack of guidance from the FDA and other regulatory agencies. I think they're that delusional effect did have an impact, unfortunately.

Janna Friedly

Yeah. And I I just sort of a corollary to this, I wonder, admit it, it isn't clear to me how how many of those paid when you say treatment resistant depression is 2 failed to medications, but how many are getting counseling therapy and appropriately and is that which does have good evidence for it and and if that's not available, it just it, it seems that perhaps that that treatment modality is not available to people or we're not using it appropriately.

Tuesday Burns

Absolutely, yeah, absolutely. I think that's a factor too. And we'd see now especially kind of Perry pandemic time where there's such a lack of resources, lack of access to to psychotherapy to basic counselling. So that's certainly there's a burden of that that's being applied as well. But I think it is, it is tough. I think if someone is given the option of taking a medication every day, showing up to an office five days a week or, you know, going to counseling weekly for 6

to 12 weeks, you know, I think some patients may not be as compelled to engage with, you know, evidence based, like with therapy or cognitive behavioral therapy. So there's there's certainly that in play. I agree.

Janna Friedly Thank you.

Gary Franklin Conor, did you have a question about the slide?

Sheila Rege Jonathan.

Conor Kleweno It was actually the the next slide, but I did have a question for Doctor Franklin on the I know you said the 30 treatments that actually that was the next that that slide I wanted to look at right there. But I know you said you there wasn't any evidence, but just wondering where the 30 kind of came from and is that something you thought was sort of an overshoot and undershoot or just want to get a sort of a quantitative sense from you on the on the 30 treatment doses and and you know obviously maybe Doctor Burns can and weigh in as well. But I just thought it was a interesting thing to to raise.

Gary Franklin Yeah, this is mostly what we see 20 to 30 treatments and I think a lot of the trials are in that range, but Doctor Burns what what is do you have any better evidence about how many treatments need to be done?

Tuesday Burns Yeah. So it it, 30 came from this idea of 5 treatments a week. So it would be Monday through Friday, you know, for four to six weeks within a tapering period. And that was what the initial studies that allowed for the FDA labeling and that was actually on the Neurostar device. Again, the cynic and be that was that was just looking at the necessity of that kind of continuum in terms of building a treatment response, maintaining it and then tapering off. So there there is logic to it in terms of how TMS works in terms of trying to sort of reset activity in certain circuits in the brain using, you know, ferromagnetic currents, changing electrical conductivity, neuronal activity. So there is there is a, there's a logic behind the repetition and how it sustained every device is a little different in that magic number I think is is airing on the side of kind of what the kind of what might be needed. And I would say clinically speaking there are protocol, there are evidence based and there's clinical practice and kind of or an argument for a lot of the times needing less. And I think nowadays with Theta burst and which you kind of you you alluded to Doctor Franklin. There are applications with the devices that we currently use in practice that allow us to actually treat patients much more quickly, and it is as little as you know, 5 to 10 sessions. So I think that 30 is on some of the older devices that were studied in the initial FDA labeling. But I would say it a lot of a lot of folks do do require less luckily, which is also it's good for cost factor and it's also good for patients willingness to actually commit to this duration of treatment some patients. Really, balk at the idea of committing to something for six weeks, it's almost every day. That's a big it's a big ask, especially for someone with severe,

debilitating depression. So the fact that we can actually accomplish some of this in a much smaller window time is great. And sometimes that 30 you know is needed depending on the situation and the device being use.

Sheila Rege John.

Gary Franklin So that I'm. I'm sorry. Can I just ask?

Sheila Rege Then I did that answer your question, Conor. OK, Jonathan.

Jonathan Sham Thanks just.

Gary Franklin I just talked to.

Sheila Rege I do want to make sure we open the lines at 9:00 o'clock for public. So we need to take a break at that point from questions.

Jonathan Sham It is a quick question for Doctor Franklin. I think on the next slide and that's the on the recommendation for treatment of. Yeah, this one, the recurrent disease. UM, so for the requirement of 50% improvement on the standardized rating scales, can you just talk about that? Is that a industry standard, standard in the field? Has that been validated? I guess in some fields you know 50% is quite a large response and can you just talk to talk a bit about where that number is from and whether that's something you see routinely?

Gary Franklin No, we we you know we I I think. I think a lot about to clinically meaningful outcomes and and how you define clinically meaningful outcomes. I'm not sure whether this should be 50% or 40% or 30%. This was mentioned in some studies, but I don't know if there's a magic number. Doctor Burns, what are you use?

Tuesday Burns So you know, I would say in clinical practice, you know, if someone has true treatment resistance, and I mean oftentimes patients where next step we're thinking about electric convulsive therapy if there is a 20 or 30% reduction in symptoms you know what a modulus or a handy to various objective rating scales there might be an impetus for saying this might be worth it if there is some hesitance about them saying do we need to hospitalize this person because of acute suicidality functional impairment are we considering electroconvulsive therapy. So in those kind of clinical scenarios, even less of a reduction in symptoms than 50 I might be very compelling, I would say I I do, I I do see that 50% and that that would be true in a lot of trials, whether we're talking about an intervention like TMS or a psychotropic trial, that is sort of a standard that we see. Um and so I, you know, I didn't. I didn't flinch at that. I would say that that's very common and I appreciate the fact that there's consideration of the need before treatment of recurrence because we know, especially with treatment resistant major depression, we know it's a recurrent condition. I wish very much that the durability of a treatment like TMS or any other treatment psychotherapy or medication would last indefinitely and remain durable. But we don't live in a vacuum and life tends to weigh on us, especially in these days. So folks do have

recurrence of illness, so the the promise of being able to have a repeat course of treatment I think is I, I appreciate that as a clinician for sure.

Sheila Rege — Any uh. Other I don't see any raised hands. We have a 3 minutes before we open the lines up for public comment. Who? Conor.

Conor Kleweno — Yeah, this is very quick question because since we have the 9:00 o'clock deadline, so for Doctor Burns, can you give us a sense about the sort of reimbursement facility fee versus provider fee? I don't know if you know the work RVU's associated with this procedure.

Tuesday E Burn — Sure. Let's see. I can't speak to I can't speak to RVU's. UM. But I can say that each pair has demonstrated sort of different willingness, and that has evolved. Premera has been sort of our our long standing pair regional payer that has been very supportive of reimbursement for TMS. I would say that depending on the device too, again, this goes back to different devices that you'll see in different practices and there's very broad variance there's a big variance and overhead costs. There are some devices that have a lot of overhead costs. There's some devices, the ones that we use in academic centers like Mag Venture or the Mag Pro devices that are used in a lot of these randomized trials and controlled studies that they have far less overhead costs. So I think we need to be sort of, you know, thoughtful about that. I think that what we don't want to see is, you know, there are, like I said, there are some products by some by some vendors that that probably have more overhead costs than is needed. I would say though that in terms of the amount of time, especially with newer evolutions of applications with the Theta burst, the amount of time that folks are actually spending in the office amount of time that's needed from the psychiatrist or from other clinical staff is far, far less than it used to be. The guidance that we're using with mapping. Of course, there's the, you know, the capital cost of buying a device and being able to get a functional connective MRI scan of someone which is amazing, so we can actually really deliver effective and precise treatment allows us to actually more accurately and much more quickly deliver treatment. So in terms of institutional clinical cost in that sense, I think that is going down significantly as our technology has improved. That wasn't as nitty gritty as I wish I could be, and part of that is just because I'm not currently at at UW delivering TMS, so I I don't wanna speak to anything outdated by giving you numbers that that are a few years old.

Conor Kleweno — That's OK. The the overhead obviously is a business decision. Do you know the CPT for that by chance? For provider please.

Tuesday Burns — I can. I can get them for you and I can have them for you and post them in the chat or pass them along. I don't have them at the top of my head right now, though.

Conor Kleweno — Thank you.

Tuesday Burns Yeah.

Sheila Rege Perfect timing. Uh. Doctor Burns, we are now at 9:00. O'clock and I will turn it over to Josh and Val.

Josh Morse Thank you, Sheila. UM, Val. Have you seen any? Has anybody requested to provide comment today in the chat?

Val Hamann I have not seen anything.

Josh Morse So I I have not. I haven't either and we, as we said at the beginning, we did not have anybody sign up in advance to provide public comments. So maybe now we can ask again, is there anybody in attending the meeting today who would like to provide public comment at this time? And you can acknowledge that in the chat, I think we have our attendees muted.

Sheila Rege Um Josh as a procedure, did we have that if people were having trouble with their electronics, that they could call a number saying they wanted to provide comments is that something we we have talked about? Or is that?

Josh Morse We do not have that out there, but certainly if you are attending the meeting, if you are hearing this, you can e-mail me directly. At josh.morse@hca.wa.gov. And I will monitor my e-mail. If for some reason you're not able to put in a chat or otherwise indicate that you wanna give comment.

Sheila Rege Great.

Josh Morse And Sheila we can circle back to comments. Perhaps after.

Sheila Rege Yeah, let's go on. Let's continue with questions and. Umm, if there's nobody else waiting, I would actually like a comment by Doctor Burns about, you know, kind of the number of times 10 versus 30, if any of the organizers, you know organizations of these algorithms or recommendations, best practices on that, I know the agency medical director set up to 30, but I'm just kind of curious what determines that? Thank you.

Tuesday Burns Sure, absolutely. It is dependent on the device you're using and it's dependent on the protocol and I know Doctor Franklin you mentioned, yes, there's a wide variance in protocol and there's still a lot of debate in kind of the in the, you know, the academic bastions and the folks doing the research about, you know, how many sessions are needed for a given indication based on severity based on location of stimulation based on you know, prior failed trials and psychotropics that sort of thing, so I would say, you know, the short answer is really that the the 30 treatments came from again the initial 2008, that those early days of the FDA labeling looking at treatment on the Neurostar device, the Neuronetics device. And as we have kind of refined protocol, there is more acquiescence, there's

more agreement on the fact that with the standard RTMS, repetitive transcranial magnetic stimulation treatments using a standard, you know oil device using standard 10 Hertz frequency treatment which would be 10 pulses per second, which is part of the application that we use as we're discussing for treatment resistant, major depressant, major depressive disorder. Umm, that looks at the number of trains, the number of pulses that are needed to be delivered and it was found to be initially 30000 pulses. So this idea, this idea of the number of pulses being delivered, being divided over a number of days and that's based on tolerability ,that's based on how long a session needs to be that sort of thing. The idea being that. We can't have someone, you know, sitting in a chair for five hours straight, and the idea of subsequent and repetitive treatment over a number of days being much more efficacious than one treatment in a week. So the duration of the actual treatment was part of that decision. How many treatments in a row and how closely linked they had to be kind of went into that. Umm, so some treatment durations might need to be six weeks long to treat major depressive disorder. The Protocol again, I know this is more speaking about today, but just as an example of protocols for OCD are considerably shorter. And so again it's based on this studies of how long it's taking, how many total pulses, how much total stimulation is needed for a given condition and that varies depending on what you're treating. But if we're just looking at depression, there's a total number of pulses that we need to deliver in a tolerable way over a short enough window of time that we're seeing a building sort of amplification of response rather than again, like if you took one dose of Prozac and waited a week to take another one, there wouldn't be kindling. There wouldn't be an a growth of response. They would be too disparate. I imagine the same is true for to what chemotherapy, dialysis. So many other medical applications of treatments. So this idea of this idea of 30 days came from that initial estimation of the amount of stimulation needed to be applied for major depressive disorder. But again, as their technology has improved and as we're delivering treatment in a much more targeted way, in a much more intensive but still tolerable way with Theta burst which is just a much more intense way of delivering stimulation and a much more targeted way using functional MRI and mapping, we're able to actually deliver far less stimulation and achieve the same response. So that then factors into again often time not only for the providers but also for patients themselves. So we're seeing that that the amount of treatment that's needed to deliver again it's the the same amount of stimulation where we're just able to achieve it in far less time. So I think it's our technology continues to improve this idea of 30 sessions that's going to be that will be kind of reserved for you know more outdated devices or outdated protocol. But as we keep marching forward, I think the trials that we'll be seeing for you know successfully treating an episode of major depression will be far less.

Sheila Rege Thank you. We just checking, circling back on public comments.

Josh Morse So we did receive an e-mail to the program inbox Val has put that in the chat. But

we don't.

Sheila Rege Shall we break for 10 minutes.

Josh Morse Yeah, go ahead.

Sheila Rege A while you figure out how to. Uh, have Doctor Sina Shah Hosseini. We can just take out break ahead of that. So you have time to figure that out. If they're not on and unable to log in, or how would you like to proceed, Josh?

Josh Morse Yeah, I don't know that they are in attendance at this time. So we may just want to circle back and check on that, but. Yeah, we we would be at a break time. And we can transition to the evidence report.

Sheila Rege Do you wanna go to the evidence or what? What is this committee one? Do we wanna go to keep going to the evidence report. Take a 10-minute break now. What? What would the committee prefer? Uh. Type in the chat break now. Or continue. Committee members. OK, 10 more seconds for committee members.

Josh Morse Think break is ahead by 1.

Sheila Rege Right, let's do a just a 10-minute break.

Josh Morse Ohh there's our commenter though, who has just joined. If we want to hear the comment and then take a break.

Sheila Rege Oh, there's a comment.

Laurie Mischley Yes.

Josh Morse I think the individual who indicated has has just joined the meeting.

Sheila Rege Oh, good. OK. Yes, let's do that and we'll take a break before the evidence report. Go ahead with a comment.

Josh Morse Doctor Shah, are you wishing to make a comment?

Sina Shah Hi, good morning. Yes, thanks for having me. Thanks for letting me join late and I I did have a comment, I didn't know where we were at in the agenda. My apologies, did you want to? Is that something I could do now?

Sheila Rege Yeah, doctors. But.

Josh Morse You can do that now. I've put up on the screen. Yeah, go ahead, Doctor Rege.

Sheila Rege Doctor Shah, if you would identify yourself. If you're providing public comment your name, conflicts of interest, and then just we would start a time when you'd limit your comments to 4 minutes.

Sina Shah Sure.

Sheila Rege Thank you for joining.

Sina Shah Thank you for having me. And you know the topics of of great interest to me. I'm happy to introduce myself. My name is Doctor Sina Shah. I am a child psychiatrist at Seattle Children's. I've been very up on and feel free to start the timer, I believe I can finish within 4 minutes. And you know, I've been very interested in TMS and, you know, working at Children's Hospital, you know, using TMS in the pediatric population, and that's kind of what I wanted to provide comment to today. I did just wanted to reference a little bit of background why I think this is such an important, you know a tool for children, you know that in large studies funded by NIH and from the treatment of for adolescent depression study, which was a very large study as well as the treatment of resistant depression and adolescence, known as Tortia, third of teens with depression, did not respond to treatment, traditional treatment, with therapy and or medications, and likely to of remission after two failed antidepressants was roughly about 10% per per medication they tried. So the financial cost of untreated depression is monumental. You know, being at children's, I'm sure many of you are aware about the mental health crisis in our state. In 2019, which is kind of a last kind of collated data, we have more than 40% of behavioral health related Ed visits to children's was really to suicidality and depression. TMS continues to be investigated and researched for various psychiatric disorders in kids, primarily major depression, uh, but also for OCD and autism, for example, treatment resistant depression is not uncommon and causes significant impact on individuals and their families. A lot of the literature right now, includes studies such as case series and open labeled studies with one also Sham controlled randomized control trial of RTMS where adolescent depression with generally positive results and large effect sizes in the open label and case series publications and in terms of safety, TMS has an excellent safety record in use similar to that in adults in 2017. In 2017 review in the journal Pediatric Neurology 42 studies involving 1200 and five children concluded the risk from TMS stimulation and children with similar to that in adults. And and and that safety in adults, uh, being, being deemed as excellent so compared to the direct and indirect costs from untreated depression in patients and families, the cost of TMS is relatively low considering the risk of suicide associated with treatment resistant depression, and in adolescence in general, it's high. It would be akin to using off label medication as we do already for some youth common practice when we refer to pharmaceuticals. Uh, from an equity perspective, TMS is available to children and adolescents who want to try it, but those that aren't fortunate position to pay out of pocket. This leaves, uh, you know, lower income families, disproportionately represented by BIPOC individuals without access to an important therapy tool our treatment tool. Umm. So coverage of TMS therapy is kind of what the bottom line of what I wanted to address today based.

Josh Morse Got about 30 seconds. Doctor Shah.

Sina Shah Yeah, sure. Based on the positive data from adults as well as positive reports from case series in children, we believe that TMS therapy should be considered as a beneficial nonpharmacological option when they're not too many of those exist for kids. It would also help address inequities and providing access to safe treatments. And alleviate the suffering to, you know, those children who are treatment resistant in that regard.

Josh Morse Thank you, Sir. That is, that is the time.

Sina Shah And you know that that's most of what I wanted to share. Thank you for letting me share my comments. Thank you.

Josh Morse Thank you very much.

Sheila Rege Thank you. After taking the time, any other comments? Requests. From the public. If not, we will then take a break. It is 915. Shall we just come back at 9:30? Let's do that. Give people enough time for a break and. Uh. And Josh, when we start, just remind me if there's any other public comment requests.

Josh Morse We will monitor for that. So we're going to take a 15 min break, back at 9:30, is that right?

Sheila Rege Correct.

Josh Morse Excellent. Thank you.

Sheila Rege Bye.

Josh Morse OK. It is 930. Sheila or Janna?

Janna Friedly I'm here.

Josh Morse And are you? Are we ready to go with the? Evidence report presentation.

Janna Friedly Yep, I think that sounds great. Looking forward to it.

Shivani Reddy Great.

Josh Morse Excellent.

Shivani Reddy So hello everyone. My name is Shivani Reddy and I am an investigator with the RTI, UNC evidence based Practice Center. I will be presenting the results of the health technology assessment on transcranial magnetic stimulation, or TMS, for selected behavioral health conditions. I would like to acknowledge the team that contributed to putting together this report and presentation .The goals of this presentation are to review some background on TMS, the policy context for this HTA summarize our methods and research results, and then present summary findings and conclusions, and we'll have some time for questions at the end. So TMS is a neuromodulation

therapy, which means it alters nerve activity in the targeted area of the nervous system. It is generally not a first line therapy for behavioral health disorders and as we will talk about later in the presentation, individual selected for studies have generally had prior trials of medications and or psychotherapy. TMS is an outpatient procedure and does not require sedation or post procedure observation like ECT. Sessions can last 20 to 40 minutes, and a typical course of treatment for depression may be about 5 sessions a week for four to six weeks. Those we'll talk about in a few slides, there isn't a standard protocol for TMS. Patients may experience tapping sensations or clicking sounds, and side effects can include headache, scalp discomfort, more seriously hearing loss or seizure, though these are generally uncommon. During a TMS session, a wand or coil is applied to the scalp. There's an electric current running through this coil that induces a focal magnetic field. That magnetic field penetrates the scalp and is delivered as pulses to the targeted brain area. When the magnetic field meets electrically active active material i.e. the cerebral cortex, it can induce electrical activity in that area of the brain. TMS is proposed to work by causing depolarization of the neurons, which can then activate neural networks that are implicated in behavioral health conditions. Treatment parameters include the wand or coil type. You can see some examples of different coils here which influences the shape of the magnetic field and the target brain area affected their traditional TMS coil is this figure of eight coil all the way on the right which penetrates about 2 to 3 centimeters into the scalp and these other coils create different shape magnetic fields that can target deeper and or bilateral areas of the brain. Other treatment parameters include frequency measured in Hertz. In general, high frequency protocols are 10 to 20 Hertz, which increase electrical activity and low frequency protocols less than one Hertz inhibit electrical activity. Intensity is measured as the percent of resting motor threshold, which is generally 100 to 120% and as Doctor Franklin mentioned, it's the intensity required to cause a twitch and a small hand muscle about 50% of the time. Other parameters include the number of pulses per session, the number of treatments per week and total duration for acute treatment. However, the Protocol for optimal efficacy is unknown and there isn't a standard TMS protocol, particularly for the non-depression conditions. There are three TMS protocols that were identified in this review and more commonly used in clinical practice. TMS is typically delivered as multiple pulses and referred to as repetitive TMS or RTMS. Generally, when we use the term RTMS, we're referring to the use of that traditional figure of eight coil, typically targeting the left or right dorsolateral prefrontal cortex. Deep TMS and Theta burst stimulation, or TBS, are specific types of repetitive TMS. Deep TMS uses specific coils to target deeper regions of the brain, like the dorsal medial prefrontal cortex and the anterior cingulate cortex. But cortices and TBS is a protocol that involves delivering higher frequency pulses and bursts, which mimic Theta brain waves. In general, treatments are shorter and use a lower intensity motor threshold. Continuous TBS tends to reduce cortical activity, while intermittent TBS tends to increase cortical activity. For regulatory approvals, TMS was first cleared by the FDA in 2008 for treatment resistant depression. There are currently 8 manufacturers with clearance for the conditions of depression, obsessive compulsive disorder, smoking cessation, and migraine with aura, which was not within the scope of this HTA. Indications include individuals who have failed at least one prior medication for depression. Require adjunctive treatment for obsessive compulsive disorder or a short-term aid for smoking cessation. Among the conditions considered

in this HTA, TMS is most often included in clinical practice guidelines for depression. It is generally recommended for patients who are treatment resistant, meaning they have failed at least one medication, if not more, and the NIHCE guidelines for depression highlight the lack of major safety concerns, but also the need to counsel patients on variable clinical response. Guidelines for OCD, generalized anxiety disorder and post-traumatic stress disorder make infrequent mention of TMS, including absence of major safety concerns, and that these may be helpful in some patients. For smoking cessation and substance use disorder, there was no mention of TMS among guidelines of specialty specific professional organizations. The state of Washington Health Care Authority chose TMS for selected behavioral health conditions for an HTA because of medium concerns of safety and high concerns for efficacy and cost. The selected behavioral health conditions include generalized anxiety disorder, or GAD, obsessive compulsive disorder (OCD) major depressive disorder (MDD), post-traumatic stress disorder (PTSD) smoking cessation and substance use disorder (SUD). Now I'll review our methods. Our key questions included questions of efficacy, harms, and cost and cost effectiveness of TMS for the treatment of selected behavioral health disorders. And our analytic framework is shown here. The next two slides include our inclusion and exclusion criteria using the PICOs framework. We included adults and children and the conditions and treatments discussed above. We only included studies with a mix of eligible and ineligible conditions, if the results were stratified by the population of interest. For both intervention and comparator, we would include TMS or sham TMS with or without concurrent medications and therapy and we excluded other neuromodulation therapies, like electroconvulsive therapy or deep brain stimulation. We excluded studies with no comparator, and I usually, no comparator, usual care or weightless control, as well as active comparators. For example, comparing teams to other treatments or comparing TMS protocols to each other. We focused on clinical outcomes that were based on clinical diagnosis or validated measures of clinical disease, such as the Hamilton Depression Scale or the Yale Brown Obsessive Compulsive Scale. We also limited our search to trials we did not include observational studies or single ARM studies. We only included studies conducted in countries that were very high on the UN Human Development Index, and we excluded studies that had less than 10 participants per study arm and were published in non-English languages. Here are some examples of the validated measures reported in this HTA. The most common depression rating is the Hamilton rating scale for depression, the 17-item version. Non depression conditions used measures like the clinician administered PTSD scale or CAP score or the Yale Brown Obsessive Compulsive scale, or Y-BOCS scale. Then there were some global measures that can be used across conditions. We conducted our search in PubMed, the Cochrane Library and Psych info. Clinicaltrials.gov was searched for ongoing studies. We perform performed dual risk of bias assessment for each study and conducted quantitative synthesis when appropriate. Finally, we graded the evidence using the arc EPC approach, which is based on the grade approach. In this slide, we describe the levels of strength of evidence from high, moderate, low, and insufficient. The strength of evidence is for a body of evidence for an intervention, a comparator, and an outcome. It includes the domains of consistency, precision, directness, and study limitations. Study limitations includes risk of bias or ROB, and is so ROB is 1 domain within the strength of evidence grade. The strength of evidence does not indicate magnitude or direction of effect.

And the SOE is based on the confidence that the observed effect lies close to the true effect, and whether future research would change that conclusion. For example, if a body of evidence for an outcome is rated as high strength of evidence, we are confident the effect estimate lies close to the true effect for that outcome, and that future research is unlikely to change that conclusion. In contrast, if we rate a body of evidence that's low strength of evidence, we have limited confidence in the effect estimate and believe additional evidence is needed before concluding that that effect is stable. We'll now move on to a summary of our findings. From our initial database search, we ultimately included 64 studies from 70 publications. We reviewed 61 RCTS for the efficacy question, 58 RCTs for the safety question and 3 studies for the cost question. In terms of a breakdown by condition, the vast majority of studies identified were for MDD followed by OCD and then substance abuse and smoking. We will go into detailed results by condition, but our top line summary is that TMS has moderate to high strength of evidence for benefit and major depressive disorder at post treatment. TMS has low strength of evidence for benefit at an OCD at post treatment. Evidence for the benefit for benefit and GAD, PTSD, smoking cessation, and SUD ranges from insufficient to low for benefit. For safety outcomes generally they were fewer adverse events for Sham TMS, few serious adverse events were reported for either active or Sham TMS, and evidence is lacking with respect to cost effectiveness outcomes and the efficacy of TMS at longer follow up assessment time points beyond post treatment. Some comments about the populations of identified studies. Disease severity is in column 2 here, umm, and ranged from moderate severe for GAD and PTSD. Umm to severe for MDD and very severe for OCD study populations, there was variable reporting for smoking and substance use disorder studies on disease severity. Treatment resistance is summarized in the last four columns. Treatment resistance was defined in different ways, though clearly MDD and OCD studies targeted treatment resistant populations for other conditions. Treatment resistance of the study population was commonly not specified. There was a broad range and the number of sessions administered for acute treatment in general. There was one session a day for the working week and four to six weeks of treatment was most common. 5 studies evaluated greater than one session a day for shorter courses of one to three weeks of treatment. And these are those five studies that evaluated multiple sessions per day. Some of the rationale for multiple treatments a day in accelerated protocols is that there may be a stronger impact on remission and response. They might have a faster effect and be more acceptable to more patients compared to five to six week treatment course, which would be more accessible to patients and maybe retain more of them in treatment. We will move on to presenting data by condition. The first is generalized anxiety disorder. You will see this slide for each condition, so I'm going to spend some time orienting you to the structure of the slide. On the top of the slide, we have the number of RCTs identified for the condition, the years the studies were conducted, the range in sample size, the treatment duration, and the follow up period. For this condition, there were two RCTs in both studies, umm, treated patients over six weeks and both studies followed them over 12 weeks. The set of five bars below show the distribution of studies across country in which the study was conducted, risk of bias of the studies included industry support, type of TMS and the use of concurrent therapies. For GAD, we identified only two studies and I want to highlight these were relatively small sample sizes ranging from 26 to 50. Both studies examined RTMS. On this slide is an evidence map, which

you will also see several times in this presentation. The Y axis lists the major categories of outcomes. And the X axis is the direction of effect favoring TMS. no difference favoring Sham or unable to determine. Umm. And this is for studies which had insufficient strength of evidence. So when we have insufficient strength of evidence, we can't make a determination of direction of a fact. On this map, inside the circle, we indicate the number of studies K and the total number of participants for that outcome. The color of the circle indicates the strength of evidence rating, so red is insufficient. Orange is low strength of evidence. Yellow is moderate strength of evidence, and green is high. So for generalized anxiety disorder, there was insufficient evidence for remission, response, and safety outcomes. Well, we judge the outcome of reduced symptoms severity to have low strength of evidence favoring TMS. The two studies favor TMS for remission and response for one of two time points, though not only statistically significant. Both studies favor TMS for reduction in symptoms of variety using the Hamilton Anxiety Rating scale at various time points. Which was statistically significant at these time points. Limited harms were reported across these two studies, including a single adverse event for each study, one of which was a seizure. The most common adverse event reported was facial twitching. And this is another look at the evidence map. Moving on to OCD, we identified 9 RCT's with sample sizes ranging from 21 to 100. Most of these studies were conducted outside of the US and had some risk of bias. Three studies were partially or fully funded by industry, and the majority evaluated RTMS. Across available efficacy and safety outcomes, we judge the evidence for TMS and OCD to be low strength of evidence. We identified one cost effectiveness study, which had insufficient strength of evidence. We did not identify any studies of remission. We were able to perform a meta-analysis for response defined as a reduction in YBOCS score of greater than or equal to 25%. Patients receiving TMS treatment were nearly twice as likely to have a response to TMS compared to Sham. In terms of symptom severity, five of nine studies reported symptom severity improvements in TMS compared to Sham, which was statistically significant, and for a five of the studies. This slide shows the forest plot where the response meta-analysis the columns from left to right indicate the author year of the included studies, the type of TMS treatment, the definition of response based on the percent reduction of YBOCS scores, the number of sessions the follow up time of the assessment, and then the number of intervention events, Sham events. The last two columns are the risk ratio and confidence interval in platform and in text. As you can see, most of the studies have risk ratio of greater than one favoring TMS, though many of them are not statistically significant. The pooled risk ratio was 1.96, though the confidence interval crosses 1, so we cannot exclude a null effect. We transform this relative risk into an absolute risk reduction, which was 151 more responses to active treatment compared to Sham per 1000 individuals treated with the confidence interval, including zero.

Tony Yen Pardon me.

Shivani Reddy In terms of harms, only two studies reported overall advert yes.

Tony Yen Is it OK if I ask a quick question about the prior slide?

Shivani Reddy Sure.

Tony Yen So on this forest plot over here.

Shivani Reddy Umm.

Tony Yen Umm, but I noted is is that I don't know if this is something that's significant from your analysis over here, but.

Shivani Reddy Umm.

Tony Yen And looking at the uh, what the Carmi 2019 study, that there seems to be, is there a discrepancy between the intervention events and the Sham events? I'm just trying to interpret that a little bit better.

Shivani Reddy So the 20, go ahead.

Tony Yen Yeah, like for example, what the intervention events. Does that mean that there were 16 intervention events?

Shivani Reddy There were sixteen individuals who met the definition of responding to treatment.

Tony Yen OK, 16 out of. Oh, OK.

Shivani Reddy And so out of 42. So 38.1% of them responded to treatment, whereas only 11.1% of them responded to treatment in the Sham group.

Tony Yen OK, I apologize. I was I was trying to understand how the yeah, sorry, I misinterpreted of that. Thank you.

Shivani Reddy No problem. Umm So in terms of harms, uh, we only do, we identified 2 studies which reported overall adverse events, which were generally not different between active and Sham. There were nearly no serious adverse events reported and the most common specific harm included headache and localized scalp discomfort. We identified 2 studies with subgroup analysis for OCD and one study there was no difference in treatment effect by age and in the other males were more likely to respond to treatment than females. We also identified one cost effectiveness study for TMS and OCD. Compared to monotherapy with antidepressant medications. Deep TMS had an incremental cost of $6,425.00 but was more effective for an incremental cost effectiveness ratio of $1,647 per unit reduction in YBOCS score. A similar ratio was observed when compared to a treatment with a combination of an antidepressant and an antipsychotic medication, which is another regimen for treatment resistant OCD. And this is a second look at the evidence map but I think I might have, I think I might have missed the first one, so I'll just go over this one quickly. We found low strength of evidence for response and symptoms severity as well as low strength of evidence for safety and unable insufficient and unable to determine direction for cost effectiveness. Moving on to major depressive disorder. We found the largest body of evidence for this condition with 36 RC UH-36 RCT's and sample sizes ranging from 25 to 325. The majority of studies were some or low risk of bias, and there were studies of three types of TMS protocols, RTMS, DTMS and TBS or Theta burst stimulation. Overall, we found high strength of evidence for the benefits of RTMS. Moderate strength of

evidence for Theta burst stimulation for remission and response outcomes, and low strength of evidence for deep TMS. A reduction of symptoms severity across all types of TMS was moderate strength of evidence. Harms and cost effectiveness were low strength of evidence. For response and remission, we calculated old relative risks of close to two for RTMS and around 4 for Theta burst stimulation, though with wider confidence intervals. We did not have enough studies to pull deep TMS studies, though we did observe improve remission and response across those two studies. The next few slides show the forest plots. This is the meta-analysis for remission. The columns are set up in a similar way to the previous forest plot and in this plot we have 3 strata. For one, for each type of treatment, RTMS, TBS, and DTMS. The diamond at the bottom of the list of study outcomes indicates the pooled effect estimate and confidence interval. This is the meta-analysis for response and similar to remission, the risk ratio for RTMS was close to two with a narrow confidence interval. The risk ratio for TBS was close to four, with a wider confidence interval. And the 2 DTMS studies favored TMS, though the confidence interval crossed one for both, so we cannot exclude a null effect, and this is why deep TMS is rated as low strength of evidence for remission and response. This slide shows the meta-analysis for change in symptoms severity, where we calculated a standard mean difference of -.65. This is roughly equivalent to a HAMD difference or reduction in a HAMD score of 3.8 points, and it is equal to the minimum clinically important change established for this measure. 8 studies reported on any adverse events. One study reported a greater number of adverse events in the active TMS group compared to Sham, and the remaining studies reported no difference between groups. Two studies reported, umm, two studies reported serious adverse events, with none in the Sham group and the remaining studies reported no differences. There was one seizure in the TMS group and no difference in suicide ideation between groups. There were no deaths, including no suicides across groups. The most frequent, specific harms for headache and application site discomfort, which occurred at higher or similar frequency in the active TMS group compared to Sham. In terms of subgroups, there was no difference in clinical response by age or sex among the two studies reporting these analysis. One study of veterans observed higher rates of remission and individuals with MDD alone for active group compared to Sham where there was little difference for active versus Sham and individuals with MDD and comorbid PTSD. We identified one study each for adolescence, pregnant patients, and older adults. There was no difference between TMS and Sham for these three studies. The protocols for these populations were fairly similar to other studies, so the duration of acute treatment was a bit shorter. For accelerated protocols, we report that some outcomes showed a greater risk ratio than the pooled estimate, such as the Saint Protocol, which delivers 10 sessions per day, and another study by to Duprat et al, which administers 10 sessions a day. Uh, which administers 5 sessions a day over one week. However, the confidence intervals were wide and approached or crossed one for these studies. One study with two sessions a day showed the greatest standardized mean difference among all studies in the symptom reduction meta-analysis. We identified 2 studies on the cost effectiveness of TMS for treatment of depression compared to pharmacotherapy. In the base case for both studies, TMS cost less and was more effective. In the study, using a one year time horizon, the cost savings per quality ranged from $746 to $7,023 dollars, depending on if productivity costs were considered in the study using the lifetime horizon cost savings per quality ranged from $9,000 to $25,907.00 depending on the age of

diagnosis, with younger ages accumulating more savings. And this is another look at the evidence map. For PTSD, we evaluated 4 studies with sample studies ranging from 20 to 134 and protocols for RTMS, DTMS and Theta burst stimulation. Overall, we judge there was insufficient evidence for remission response and severe adverse event outcomes and low strength of evidence for symptom severity and adverse events. There was only one study, each for remission and response outcomes, and the rates were very low or not statistically significant. For change in symptoms severity 2 studies used low frequency RTMS showed improvement in CAP scores for RTMS versus Sham, statistically significant in the larger study. In that smaller study had confidence interval, confidence intervals that included the null effect. One study of Theta burst stimulation showed no difference from Sham, and one study favored Sham over deep TMS, so the results were not significantly, statistically significant. Of the four studies, one study reported on any adverse events, which was relatively high but similar across groups. There were mixed findings about severe adverse events, which include suicide ideation and severe anxiety with severe adverse events reported in the Sham group only, the TMS group only or similar numbers across both. Once again, the most common specific harms were headache and treatment site discomfort. And this is a second look of the evidence map for PTSD. Smoking cessation. We identified 5 RCT's with sample sizes ranging from 29 to 262. Three of these studies had high risk of bias and all examined RTMS. The strength of evidence ranged from low for remission and symptom severity, as well as adverse events, to insufficient for response and safety and severe adverse events. Studies defined abstinence in different ways and generally favor TMS over Sham, though the findings were not always statistically significant. Similarly, there were various measures of nicotine use, including biomarkers of carbon monoxide levels and cotinine levels, which were lower in the TMS group. And one of two studies showed statistically significant decrease in nicotine dependence. Like other conditions, information on harms was limited, and the most frequently reported specific harms were headache and application site discomfort. And this is the evidence map again for a smoking cessation. And finally, our last condition is substance use disorder. We picked up a total of 6 studies, four studies of alcohol use disorder and two of cocaine use disorder. None of these studies received industry support, and two were high risk of bias. We did not find data for all the outcomes. And with the exception of symptom severity, the strength of the strength of evidence was insufficient. Like smoking, there were different definitions for abstinence and use, and there were mixed results whether TMS was favored or statistically significant. There is limited information on adverse events and serious adverse events and specific arms, harms were similar to the other conditions, headache, discomfort at the stimulation site where present in both groups. There was one study looking at subgroups of individuals with the comorbidity of depression, in which there were fewer days of cocaine use in patients with higher depression scores. And here's the evidence map again. This slide shows a summary of the strength of evidence, the Y axis includes the conditions in this HTA and the X axis includes the outcomes. The colors once again indicate the strength of evidence. Gray boxes indicate there was no evidence available for that combination of condition and outcome. The text inside the box indicates the direction of effect and as a reminder, red indicates insufficient evidence, so we cannot determine the direction of a fact. And we can see that there was the highest strength of evidence for MDD efficacy outcomes favoring TMS and low strength of evidence for no difference between, no difference between groups or favoring Sham for harms. And on to our

discussion. Some limitations of this evidence base is that there were many studies with high risk of bias and small sample sizes resulting in imprecise effect estimates. Studies rarely reported race and ethnicity characteristics of their study populations, so we really can't say much about how this technology performs in different racial or ethnic subgroups. One of the biggest limitations in terms of clinical application of this treatment, there were a limited number of studies that reported outcomes at follow up times past the end of treatment within the randomized control design, randomized control trial design. So we're limited in speaking to the durability of treatment effects. For each outcome, only one to two studies had follow up of three months or longer. In general, results will we're durable at three months with respect to remission response or reduction in symptom severity for GAD, OCD, MDD, and SUD. Only two studies evaluated outcomes at 20 weeks and 24 weeks, and these were both MDD studies. Both studies reported on changes in symptoms severity, which was durable at the later follow up time for one study, umm and statistical testing was not reported for the other. In terms of the limitations of this HTA, we did not perform a comparative effectiveness review, so we did not compare type, types of TMS to each other, or TMS to other treatment options. For practical reasons, we abstracted symptoms severity scores for the primary indication for TMS. So we collected data on Hamilton depression scores for major depressive disorder, but we did not abstract other outcomes that the study may have reported related to other conditions, such as the Hamilton anxiety score. We did review harms by condition, however, we have no biological reason to believe that harms from TMS would be conditioned specific. So we interpret the evidence is suggesting a low risk of adverse events or severe adverse events for TMS as a procedure. We ultimately included only trial study designs, which generally have a short follow up and cannot offer evidence concerning longer term outcomes, including adverse events. A more comprehensive assessment of longer term benefits and harms may require a broader evidence base that includes observational studies. We did not use data from the MOD database given concerns about validity of the data and we did not include non-English studies or studies included in countries that were not very high on the UN Human Development Index. For context, we would like to present information on other payer policies. TMS is covered for the indication of depression by several payers. 2 payers cover TMS for OCD, and there is no Medicare NCD for TMS or any for, for TMS, for depression or any other condition. Would you wanna highlight that when TMS is covered, there was a range of criteria for the approval of TMS. The type of TMS was not always specified, and in general up to 36 sessions were approved. For treatment resistance criteria, this ranged from failing at least one medication matching the FDA indication to failing up to four medications from at least two classes and failing a medication was defined as having an adequate trial of a medication, usually up to 8 weeks, intolerance to medication or contraindication to a medication, and some insurers also required a trial of psychotherapy. There's a lot of ongoing research interest in TMS, particularly for substance abuse, so we anticipate this evidence base will grow. In summary, TMS has moderate to high strength of evidence for benefit in MDD at post treatment. TMS has low strength of evidence for benefit in OCD at post treatment. Evidence for benefit for GAD, PTSD, smoking cessation, and SUD ranges from insufficient to low for benefit. For safety outcomes, they're generally reported fewer AEs for Sham TMS and few SAEs were reported for either active or Sham TMS. Evidence is lacking with respect to cost and cost effectiveness, outcomes and. Efficacy of TMS at longer follow up assessment

time points is also lacking. For future research considerations. For non-depression conditions, they're likely needs to be more work on determining the optimal treatment parameters, ideally evaluated in larger Sham control trials. Future trials should include measures of disease severity and treatment resistance to support clinical decision making on which patients and when it's most appropriate to use TMS compared to another treatment. And longer term outcomes to evaluate the durability of treatment effect and to identify harms that may only emerge later would also be helpful. That is the end of the presentation and I'm happy to take questions.

Sheila Rege Anybody who has questions, please feel free to raise your hand or put something in the chat. I see someone from Conor.

Conor Kleweno Uh, yeah, thanks so much for that presentation. I was wondering if you could sort of critique at least one study. I'm gonna mispronounce it. It's a van Eaton Hoven. But you know, when I kind of look through a meta-analysis, I I tend to try to look closely at the most recent studies, particularly when the clinical intervention is somewhat technology related, because the assumption is whether the technology is improved, the techniques have improved selection for patients who will respond as improved, that particular study showed no difference. Umm and I just didn't know. I I didn't pull the study yet, but I just if you had any information on on that because it it would seem you know you would want to look at that and bias some more heavily and let's unless there's something much different about this study design than something from 2001. For a technology such as this, where it seems like there is a lot of, you know, inherent improvement over over time that what I would assume.

Shivani Reddy So I will say that I I don't have this one at the top of my head, I think the one thing I'm noticing is the small sample size, but this is something that I can take a look at. I don't remember this one having a particularly different protocol then the other ones, umm, and it had about 20 sessions here, so I, uh, that's something that I I can take a look at and bring back after a break if that's if there's anything that's pertinent that would make that study appear any different. Umm.

Sheila Rege Yeah, that that actually may be helpful. And also I wanted to say thank you for putting in you know where what page number it is in the report. That really helped me follow through.

Shivani Reddy You're welcome.

Sheila Rege Any other questions?

Conor Kleweno Think on 47. It had it to there doctor, Reddy.

Shivani Reddy Sorry I'm I'm I'm trying to make all of you appear so I can see your faces. So yeah.

Sheila Rege Yeah, let's all turn our cameras on as committee members, please.

Shivani Reddy Is it OK if I stop sharing the slides?

Sheila Rege Oh, I I think so. It does anybody need any other slide looked at? Or questions.

Conor Kleweno I was just gonna say that data is also on 47 which you know same study with. The the.

Sheila Rege Oh, can we go to that page 47? Scroll back on the slides.

Shivani Reddy Yeah, sorry. Slide 47? And I will remove myself here.

Conor Kleweno Yeah. Thank you. Just zero responses. So that may be small. Simple. Thank you.

Shivani Reddy Yeah, yeah. And A and a very wide confidence interval.

Conor Kleweno Things I was, I was, I was pointing out. So I'll. Let other committee members talk as well

Sheila Rege And now we have Jana. I think was next.

Janna Friedly Thanks. I I guess I have similar to to Conor. You know, there are a couple of studies that jumped out at me that I I would would love to to discuss in a little bit more detail for OCD when I again looking at your your forest plot there were two, two studies that. Had significant findings and then the others that that did not and you know I struggled a little bit in the report understanding sort of the risk of bias for those for those two and you know and again we can come back to this but like Hawkin and in particular when I read through the paper and the clinical trials entry. There was no there were no methods presented in the paper. It skipped from the the the introduction to the results, and so it was.

Shivani Reddy Oh.

Janna Friedly It was almost impossible to get any information on.

Shivani Reddy So that paper, I believe actually the methods are at the end. Some journals do that where they put them at the end because because I'm remembering, there was one paper like that too. And I I believe it was that one. But I can definitely take a look. Umm. Umm.

Janna Friedly Yeah, I I didn't see it at really at the at the end either.

Shivani Reddy OK.

Janna Friedly I mean, there were some. Ohh you. You're right they are. Yeah. No, you're right. OK, thank you. I'll. I'll go back and and look at that and and and there was in the the Carmi study that one is 1 as well that. And. Uh had a pretty significant difference in attrition from in the in the treatment arm versus the the the Sham arm. So and there were some discrepancies in their descriptions of the number of patients that were invited and and I didn't see any discussion of that. So I I just you know there were there were.

Shivani Reddy Mm-hmm. Umm.

Janna Friedly I think 6 patients that they excluded, one because they became suicidal, so they didn't include that data as a, you know sort of a non-responder, they just excluded that data and too because of adverse effects. And so it just raised a little bit of concern to me that they were that they were not including those in the analysis which makes it look more favorable. So I I just wanted to.

Shivani Reddy Yep.

Janna Friedly Comment on that or if you had any comment.

Shivani Reddy And that's those were rated as, umm, was rated as high risk of bias for those reasons that you mentioned.

Sheila Rege We're, We're gonna have Conor go again.

Conor Kleweno Yeah, just the same on this slide. So the Carmi which we've at least been notified that had some high risk of bias, it seems like did a study showed no difference. So then the next year did another study. And so I just didn't know how that figured in your metric, when you have sort of a repeat author with a potential conflict. Do you know what I mean?

Shivani Reddy Umm. Mm-hmm.

Conor Kleweno Like you have independent authors doing different things with their inherent biases, but you have somebody with what we've been kind of told has a high risk of bias then repeating a similar study after, you know, having a confidence interval cross zero, then repeating again and finding sort of a marginal crossover 0 and again low number so.

Shivani Reddy So I think that the 2018 study was a pilot and the 2019 study was a larger study. And there are the 2019 study was rated as. Some risk of bias. Uh, I can't tell you off the top of my head the the exact reasons that we we downgraded it. Umm to some risk of bias and it did not have the, umm, as many of the as, as many reasons for bias as the 2018 study, UM, but I our interpretation was that the 2018 study was a pilot and then they were doing a larger trial based off that pilot for the next year study.

Conor Kleweno So that it wasn't that the authors bias changed it was that the study design changed your bias evaluation.

Shivani Reddy I think that the, I mean I have to go back and look at the 2019 study, but I'm assuming that there was something that had improved between the two studies, such as maybe the attrition wasn't as. Wasn't as concerning. I don't know if that's something you'd be able to look up Leila quickly.

Leila Kahwati Yeah, I I'm looking at their our tables right now it looks like the 2019 study mitigated some of the issues that the 2018 study had in the deviations from intended interventions domain, that's the domain that's around blinding, masking, umm, deviations that are sort of outside of the randomized context. The other domains looks similar and then the missing outcome domain also was only was low for the 2019, so the attrition problems were not as serious compared to the 2018 study. And as Shivanni said it's not uncommon

for authors to do a proof of concept or a pilot study. That's how they sort of are able to estimate the potential effect size, is that then they they power their next study on. So that's a fairly common thing that we see in not just this literature, but across trial trials of new sort of interventions. There's a pilot proof of concept and then that's data they use to figure out how hard recruitment is gonna be, how large they should power their study, what kind of attrition they can expect.

Conor Kleweno At at definitely get that. Thank you.

Sheila Rege Clinton, thank you for waiting.

Shivani Reddy Hmm.

Clinton Daniels Hi, thank you. During the the public comment, we had a a clinician speak about using TMS in pediatrics and adolescents and I was curious if you could comment on the studies that looked at the effect in age differences. I think you said there were three of them, particularly as related to MDD, Depression.

Shivani Reddy So that there was actually a public comment when we posted the draft key questions and that's when we expanded our picots to include children. UM. We really didn't find, we only found that one study that was specifically done in adolescence that was a randomized control trial and I think that that public commenter mentioned some other studies that were not randomized control trials. And then in terms of subgroup analysis, I believe there were only two studies, umm, that looked at age and we didn't see a difference by age. So the interaction term was not significant for these studies.

Sheila Rege I I'd be interested in our clinical expert, Doctor Burns, would you care to comment on real life practice? In that court for age.

Tuesday Burns For age? Yeah, absolutely. So I think one of the biggest factors that we see in terms of predicting clinical outcome that relates to age is atrophy is cerebral atrophy. So obviously, as we age, there is atrophy of grey matter. So that increases the distance between the skull, the scalp and wear a TMS coil would be placed and the conducting sort of you know the conducting matter that we're trying to engage with ferromagnetic currents and induce an electrical current i.e. the brain so that is the one kind of factor that we see. This is something that can also be extrapolated to anyone that's had regardless of age, stroke, any kind of sort of injury which causes you know cerebral atrophy. So I would say that would be one factor is worth thinking clinically about how to apply this. A lot of folks who are, you know about 65 or are at an age limit, or have medical complexities or concerns, you know, we would be getting a brain CT, we would be getting possibly if possible an MRI to kind of rule out the possibility that the atrophy is such that we couldn't anticipate the strength of our coil penetrating enough or adequately to get that desired treatment effect. So I think that's really clinically speaking, the one factor that we consider with regard to age.

Clinton Daniels So does that does that mean in theory this the brain would respond better in a younger population where there's a a higher brain volume, I guess?

Tuesday Burns In a lot of ways, yes. In a lot of ways, yes. So you know, clinically speaking, I I can just say that you know the youngest folks that I've treated have been in the adolescent sort of 16 year old age group. And I would say that typically what we see is a lot quicker, umm, achievement of sort of, you know when we're mapping someones motor cortex we see a much more robust response in terms of calibrating being able to achieve the desired stimulation at a lower level of intensity. So we do see that and I think it can be again we can correlate that with kind of brain volume for sure.

Sheila Rege Is there more of a risk of seizures in the younger population or not so much?

Tuesday Burns No, not at all. Not that I'm aware of.

Clinton Daniels Then one last follow up with the studies that did look at age that are reported here. Do we know if those ages included people under 18?

Shivani Reddy That's something we'd also have to look up, but I actually don't think so. I think most of I, I actually think the majority of these were all in adults with the exception of that adolescent population, but we can take a quick look at those two studies as well.

Clinton Daniels Thank you.

Sheila Rege That would be helpful. And then who had the question that's being answered by Lila? Would you like have to care to ask again? I'm sorry, Clinton are you done? And we'll come back to that.

Clinton Daniels Yes, yes, thank you.

Sheila Rege Sorry I who had the question that's being that, u was going to be looked at and is now being answered and I'll have Shivani this.

Shivani Reddy Sure. So I think the question was what you know, is there a reason that there was null effect for that study, was there anything particularly different about the study population or protocol? And it doesn't appear that there was. However, there was a stricter definition of remission, so it might have been harder for participants to reach achieve remission based on the definition of the study. Compared to some of the other studies.

Sheila Rege OK. Jonathan. Ohh who, who asked that question? Do you have any follow up on that question on that before we go to Jonathan. I think we're gonna.

Conor Kleweno That that was me, I guess. And so my conclusion would be we have an equivalent study in terms of quality showing no difference, you know maybe 1 nuance of remission that wasn't wasn't met is that, is that a fair conclusion for me to take home?

Leila Kahwati Well, this is Leila. So quality is not the result whether it's positive or negative doesn't impact the quality so you can have a perfectly high quality study that has a null effect, so. Yeah.

Conor Kleweno No, I'm not. I'm not saying that I'm saying a quality in term, maybe I'm not using the right word, but in terms of the other studies on that diagram, right, so there's nothing about this study that would make me wanna throw it out. It has the integrity, the research design that is of reasonable equivalence to the other studies on that list so that I can interpret that fairly as a null result.

Leila Kahwati Yeah, I'm just looking to remind myself what the risk of bias rating was on that one. Let's see. So that's a high risk of bias study. But as are other some of the other ones on the the plot, so it's not the only high risk of bias study on the plot if that if that makes sense.

Sheila Rege I think Jonathan had a question.

John Bramhall But what I did is sorry it's a it's a. It's almost a casual question. It's not directly related to our conversation. That's the problem. What I want you to know. Shivani, did you come across studies that looked at the this intervention effectiveness on pain? And I'm sorry, it's not a systematic question. It's it's just a general question because I'm intrigued. Other people who have chronic pain, have they been put through TMS and did it have any effects? Sorry, it's a bit of an unfair question, I know.

Shivani Reddy So what I can tell you is that, uh, when we were initially scoping this review, uh, we were what we took a look initial look at the literature and clinicaltrials.gov there are many conditions that is that this technology is being used for beyond behavioral health disorders and I can say that chronic pain did come up fairly frequently. I can tell you that I excluded a lot of chronic pain studies because it was with not within the scope of ours with of this review of behavioral health, selected behavioral health conditions, so I can't really speak to the efficacy of TMS on chronic pain. But there are definitely people who are studying it.

Sheila Rege I think, Jonathan had a question I hope I'm catching this right.

Jonathan Sham Yeah. Thanks, Shivani, for the the thorough presentation. Just a background question, umm, could you just review the outcome definitions for response versus symptom severity for MDD and how may differ for the other conditions?

Shivani Reddy Uh-huh. Sure. So for, see if I can pull this back up here. So for a response definition was a 50% reduction in one of the standardized the validated scores used here. There were a few studies that made some modifications to make that response to definition, but we're really looking at it's a dichotomous outcome, so patients either met, they had a reduction in their HAMD-17 score that was 50%, 60%, 70% of whatever and they went in the yes category. The symptoms severity score was a continuous measure, so. It's looking at changes over changes over the course of assessment. So this is we're looking at the percent looking at the number of points reduction that was done. So it's really a dichotomous versus continuous outcome and I think that is, you know, we talked about some of the other payers will look for, you know a 50% response and I'm I actually doctor Burns might know this, but I thought that might be tied to this idea of like the definition of a response 50% reduction in symptoms severity and that's a clear clinical response to the treatment. While as for symptom severity reduction, you don't have to be tied to a specific threshold to be included in the analysis. Did that answer your

question?

Jonathan Sham Absolutely. Thank you.

Sheila Rege Laurie, I haven't heard from you. Do you have any questions or I think, Tony, I haven't heard from you either.

Laurie Mischley I I am struck by the lack of protocols. I just find a little unsettling. I I'm not, I mean, where you direct that and how and which frequency. I mean in my understanding of how one manipulates the brain and the consequences of that, I'm I am, I find it unsettling, how far along we are in the conversation for how little we know about what we're actually doing and what people are doing and what we're studying. So that's probably where I'm getting the most hung up. I am inclined to favor if we're going to do it for anybody, we should also include younger, like I don't find myself committed to that 18-age limit. I was struck by some of what has been said about the pediatric population. And in the wide confidence intervals of so many of the studies, I find little disconcerting.

Sheila Rege No, good point. Tony says no questions. How about Chris, Chris Hearne, any any questions? Any other questions, Shivani, excellent summary and report. Really appreciate it any. Any other questions at this time?

Jonathan Sham Yeah, maybe we can ask and I'm not sure if now is the right time or or or later there's a spot for this, but for Doctor Burns. Can you just come down the the training involved in this? You know this is a a technical procedure, you know, I'm not a neurosurgeon, but I would imagine that small changes in directionality and you know, the the protocol was just referenced. But I'm just you know where you place it, how you place it. Again it seems like something positive is happening at least MDD, but it just seems like there might be high variability based on, uh, different technical applications of this technology, and I just maybe you can comment on training as it pertains to that.

Tuesday Burns Absolutely. I'd love to speak to training. I would love to speak to comments about protocol and how that's universalized as well. So you know, first off with regard to training, I think many of us undergo training at facilities, bigger facilities. I trained and learned to do TMS with Holly Listin B and Anthony Montoni and Tony Montoni at Columbia Presbyterian. A lot of providers do go to these sort of expedited kind of fellowship programs when they're already in practice, when folks are early in training, a lot of this is something that's provided at training sites during psychiatric residencies. Some folks after their initial four year psychiatric residency, then go on to do a neuromodulation or a neuropsychiatric fellowship and training is included in that as well. So I would say for folks in clinical practice, it would then be, you know, later in life going back to do training at an institution such as Colombia or Hopkins or Mayo, or one of the bigger kind of one of the bigger groups that offers this. And it's a combination of didactic learning as well as clinical hands on learning and workshops. So there's that. There's that piece of it. There's also when you are a, you know, someone in clinical practice and you're interested in purchasing a device, there is a subsequent training and certification that providers need to go through with the device manufacturer themselves and that has to be demonstrated in order to, you know, obviously be able to for the device manufacturer to feel confident about letting use their device, but also within the WAC, I

believe in state regulations needing to demonstrate safety and safe practice in your clinical setting and using the device with written that speaks to the idea of you know having folks on site who can manage someone if there is an adverse outcome such as a seizure that sort of thing, making sure that there is access to, you know, a protocol for getting something to someone to an ER, calling 911, those sorts of things. If an adverse outcome did happen. So there's sort of the academic training, there's the clinical training that happens and then there's obviously the device, the very device specific training that's going to go on and as we mentioned, you know, there's several several different devices and several different manufacturers. So it would be different for each device. Umm, I do think that, you know, it is tricky when looking at the research to kind of discern really well what is the clinical protocol, what are the the actual clinical application look like when the rubber meets the road. So I'd love to clarify that because I think we'd look at the research, it does look like a disparate array of many different approaches and many different sort of protocol and I think you know there there is, I'm, I'm sure that feels unnerving, but I can say in clinical practice it does look very different. So I would say in clinical practice what we're doing and we're when we're speaking about major depressive disorder at the overwhelming amount of evidence which it may be, it doesn't it doesn't cut come to the top right now in terms of when we're looking at the research in in broad strokes is that there is evidence for a certain application of high frequency treatment to the left dorsolateral prefrontal cortex. Now we have studied for years, TMS aside, we have looked for years at trying to understand really, functionally what we're aiming to target when we're treating major depressive disorder and you know, we have come very far from just the very basic serotonin hypothesis, this idea that there's a deficit in neurotransmitters inclusive of serotonin, like we've really evolved beyond that and psychiatry, and it's necessary now that our interventions continue to evolve beyond that. So research has shown us that the deficits which underlie major depressive disorder, which manifests as anergia, amotivation, dysphoria, severe functional impairment, suicidal ideation, those when we look at functional imaging of folks with major depression in a major depressive episode, if we look at a pet scan of someone's brain in the midst of a major depressive episode, what we'll see is decreased glucose metabolism. We'll see Hypo functionality most prominently in that left dorsolateral prefrontal cortex. So with regard to TMS, that has been the target of treatment and so in large part in clinical practice, when we're treating major depressive disorder, we are aiming our coil at that left dorsolateral prefrontal cortex, because what we're trying to do with the understanding again independent of research done looking at teams, we understand that this is the part of the brain, this particular network and our frontal lobes is what is in such activities and such deficit and what we see is that when you look at folks again, regardless of intervention, when you look at folks in remission from a major depressive episode, you see that that activity and that dorsolateral prefrontal cortex has rebounded and you can see a normalization, especially in contrast to the rest of the circuitry of the frontal lobes. So we know that that is we can extrapolate that that is a that is a response that that is remission, or at least response from that depressive episode. So what we're trying to do with TMS is target that particular area of the cortex. And we've learned with, you know, different devices, different, different coils what we're trying to do is penetrate deep enough and we're trying to do it at such an intensity, at such a frequency, with such a duration of treatment to not only turn those circuits back on, not only to reset and increase activity in that circuit in the frontal lobe but to maintain it to keep it on, so to speak. So really

most clinicians that's their target and that protocol involves at 10 Hertz treatment. So it's 10 pulses per second and that's with rapid the repetitive TMS. When we do Theta burst which is the more intensive, much shorter bursts of treatment again it's kind of it's it's higher frequency, it's more intense, but we're still targeting that one part of the dorsolateral prefrontal cortex. So you know, when we go to things like looking at OCD, post-traumatic stress disorder, pain, they're absolutely different positions that we're going to place our coil there are different locations, different targets of treatment, but for the most part, what we're seeing and what this group is really looking at is a protocol that's looking at high frequency treatment applied to the left dorsolateral prefrontal cortex. So for the most part, really that's what we be looking at and there, so there is a streamlining of the protocol that we would be using. So that's kind of and I'm happy to keep talking on that, I can talk till blue in the face about the different positionings of the coil, the different applications of treatment and again it all goes back to functional imaging studies that we've looked at to understand really what's going on in the brain during an episode of either severe OCD or severe major depressive disorder, or Q trauma response to PTSD. I don't know if that starts to answer your question or just makes the water more muddy.

Sheila Rege Conor, are you good with that?

Conor Kleweno I think that was Jonathan's question, so I wanna make sure he's OK with that.

Sheila Rege Oh, sorry.

Jonathan Sham Now that's helpful.

John Bramhall Yeah, sure. Absolutely, doctor Burns. Thank you. I. So I I was. My question was sort of picking up a little bit on Laurie's issue with the protocol. And I I just, yeah, I wondered and you sort of answered that the functional imaging studies. Sort of objectify if that's the right word the disease state and then of course the logical sort of question to ask is well A the does the does the TMS have, you know, an effect on a similar region? And you, you answer that for me. Thank you. But I also wondered whether imaging was used to again, this word, objectify the positioning of the coils and the design of the coils. Do you have information that shows that well, if we refine the position of our coil to give this functional imaging result, then we see a better intervention clinically that's this sort of question, and obviously you have.

Tuesday Burns Yeah. Absolutely. And the more recent work that's been done at Stanford, so in Stanford, they're the Saint trials and that we're done at Stanford in 2020-2021. And so Stanford is now adapted the Stanford neuromodulation therapy technique. And the idea is using not only functional mapping, so functional connectivity mapping. So live time, real time functional MRI of the brain while the coil is being positioned to understand in advance right what area we're targeting, where that is in this particular individual who's sitting in the chair at that time. And then in real time actually being able to apply and position the coil as precisely as possible, that's also paired with in the Saint studies, which I would encourage everyone who's curious to look at because they're really just just beautiful. And for a clinician, bring me so much hope. But they're looking at not only the use of really functional imaging and connectivity mapping

alongside data, alongside Theta burst stimulation, so alongside the idea of using this very intense, very quick, high intensity, high frequency stimulation that again mimics that Theta bursts, that Theta wave brain activity and what they seen is much better response rates, which makes sense, right when we're better positioning, we're actually targeting because the area of the cortex were targeting, we just only a couple centimeters down, but it's a pretty small area. And when you think of all the clinicians out there in the world that the vast variability that you might see in clinical practice, you sneeze, right? You have an off day and it's repositioned, so there's a lot of variability, so as we better been able to understand the importance of being precise and targeting that location that in conjunction with really effectively stimulating that location has led to a significant response. And again I'm just quoting because this is just such a beautiful study that I love. But I mean they were seeing 90% of folks entering what would be categorized as remission and that for a psychiatrist is really I had to say because I work with treatment resistance 2/3 of my patients do not respond to 2, 3, 5, 10 medication trials to see to see response rates in remission rates that they're that high is pretty magical, but I I I think you're right that it has a need to continue to evolve. It has evolved where we're doing much more precise and targeted work. Psychiatry in general for those of you you know who aren't in my field, we haven't always been very precise, right? We're getting to the point now with understanding you know the impact of epigenetics and really trying to in a very targeted way, treat folks who for years we were giving SSRIs to and saying only maybe a third of them respond. So to get into this realm of precision, targeted therapy is really, really something special. And you're right, we need to keep pursuing it and we need to keep kind of fine tuning it because we owe it to our patients. That, you know, this is the number one disabling to major depressive disorders. And number one, I think The Who still says and number one source of disability in the world, the amount of functional impairment cost burden is significant. So it's it's overdue for sure.

Sheila Rege Thank you. That question I actually my mistake was Jonathan S. I'm gonna start if you could opine on whether that answer was what you were looking for or is that sufficient? The original question.

Jonathan Sham Yeah. Thanks. Thanks for telling him that information. I left a little message in the chat, but it seems like kind of the technical training is, well, quite frankly, similar to other procedural or interventional techniques in medicine where it's you learn from a mentor. Uh, I think it's interesting that industry is kind of filling in some of those gaps later on. And I just, you know, I think you mentioned this, but there seems like they're not a ton of regulations about, you know post hoc training post Residency fellowship training. That's just kind of interested to see that and how that evolves over time.

Sheila Rege Than Conor has had his hand up. Thank you, Conor.

Conor Kleweno Yeah, thanks. And let me know if you if this is the time to ask this. I was wondering if Doctor Burns could feel the question about the research, you know, Doctor Reddy did a great presentation. But as we know our our content experts are also often really situated to comment because I mean they even know the authors personally sometimes. So I was wondering if you know Doctor Burns again getting back to these slides, we have a a grouping of studies for as far back as you know 2001 or two or

whatever. And yet we have ones that are more recent and you were citing I think a. Sage and a St. or whatever like that. So you know from your kind of content expert position like you would say hey, you should really look at the whatever study that's where it really got specific some of those things we were talking about. Authors that had a protocol, you know, identifying the left dorsolateral prefrontal cortex in their protocol and really did it, you know, something that you think represents what you described as contemporary clinical utilization. So you know what, what should we as a committee members really look at in terms of some of these studies or or vice versa. Hey, that study really didn't do a good job.

Tuesday Burns Right. That's a good question. And you know I've appreciated kind of looking through the list of the RCT's that were studied for this group and prepared for this group. And I think a lot of my, you know, my personal kind of clinical experience and need to kind of stay kind of at the at the cusp of sort of what we're learning. You know, I rely on, umm, I've relied on a few different papers that have recently kind of come out looking at and reviewing sort of everything from the past five to 10 years to kind of really understand what people are doing, what we're doing well, what we're not doing so well, I would say, you know, in particular Fitzgerald, Paul Fitzgerald and Mark George are two folks it have done, you know, just a broad and brought about of work with various applications for TMS, and I think the most recent paper that they did was I think a couple of years ago and it was looking at essentially all of the data pulled from 2014 to 2018 and looking at all the different applications, umm, protocol for major depressive disorder. And so it's a clinician. I look to something like that to really garner a sense of where things are going clinically, what is worked, what has not worked to really. Guide my protocol to guide my what I believe to be the standard of care from the evidence base. I would say that, you know, I think they're going to be they're always going to be small studies here and there. There always going to be sample size of 10, 5,6, there's going to be a case series of folks that are trying to apply this to a novel or novel application or they've noticed something with a patient that you know, they're applying TMS for a major depressive disorder. And they're noticing that, hey, they're tentatives improved, right, which actually tentatives is an application for a TMS treatment. And so there's always going to be these smaller pockets. And I think because we are so junior in terms of the life span of TMS, you know, really it's just been the past 10 to 15 years that these studies have been kind of generating info and data for us that I think there's a lot more to come. There's a lot more streamlined and more heady data to come. But I think the hard thing, and I see it with all of you and I feel it myself, is looking at some of these studies that are so small that it's such a small sample size and such a low effect size it is. It's hard and it doesn't feel as compelling, which is again, why I often look at these bigger reviews to be able to really get a sense from a clinical standpoint of like, where are things going and what are people trying. Umm, so I'm happy to site and offer up some of those I can put in a chat. Some of the ones that I reach for that I find to be really helpful in giving me a sense of clinically what my colleagues are doing out there across the country and across Europe. Umm I I I I don't know that I entirely answered your question now so. Yeah.

Conor Kleweno Well, I I think sort of I guess you know if you look at the list we have and if you can editorialize, hey, you know again you don't have to do it now, but maybe in the chat for me, you should really look at the Cole 2022 but not the Chew 2020 or so you know for

you had been so like I could do the same for orthopedic surgery studies, right, you you collect a bunch over 20 years, it's it's a mess of showing nothing in everything all at once, right or whatever that is so.

Tuesday Burns Yeah. And so the the Cole papers are perfect, that those are the Saint studies. So the coal work is the stuff that's out of Stanford. So I would definitely say that would be something close to my heart that our recommend looking at what I will do is I will just open up another window and look through and I'm happy to kind of highlight from like top to bottom kind of what I would say clinically would be most relevant if that's helpful.

Sheila Rege I I think that that maybe have Conor you're you're getting the feeling that may be helpful and Josh, help me out here because we, we have to look at the evidence report that Shivani is presented. Is that OK for us to ask our clinical expert to put that into chat from a protocol standpoint?

Josh Morse I think so.

Sheila Rege OK.

Josh Morse Yeah, I mean I I yeah, I I think this is a great discussion, great insight into evidence in the practice so.

Sheila Rege Then yeah, let's do that, and we're gonna. We're gonna have a break right after this. Doctor Barr. So you you can take your time and do that because they may be some more questions before the break is supposed to be in 6 minutes. But who, who's question was that on the subgroup analysis and the age?

Josh Morse And I just enter. I'm sorry. I'm I'd like to also maybe ask Doctor Reddy her thoughts on that?

Sheila Rege Oh, OK. Doctor Reddy, sorry.

Shivani Reddy Umm. Specifically on which study? So I I think the doctor Burns is gonna, you know, in terms of what impacted the field in a clinical way, she'll probably have more to say about that. I mean I think the one comment I just wanna make is that yes, there were a lot of small studies with confidence intervals that you know might cross one. But I mean part of the power of meta-analysis is that it allows us to combine these studies that don't have sufficient power on their own. And we can definitely see for the MDD studies that we have more precise effect estimates with tighter confidence intervals around them. And so I think that that's something that even though there are a lot of smaller studies here that we were able to combine them to have a more to have a pooled effect that tells us more of a story.

Sheila Rege Stop.

Shivani Reddy At least for MDD.

Sheila Rege Josh, what was that your question for Doctor Reddy?

Josh Morse Yeah, yeah.

Sheila Rege OK. Whose question was the subgroup analysis? But Doctor Reddy has kindly answered, and I'm sorry I switched between first and last names. I apologize.

Clinton Daniels That this is Clint, it was it was my question.

Sheila Rege OK. Are you satisfied with the and and doctor Reddy If you want to elaborate on what you posted in the chat.

Shivani Reddy Yeah. What I what I did was went to our evidence tables to look at inclusion criteria and only Stern reported there an age inclusion criteria of 18 to 50. The shoulder study did not report an age inclusion criteria, but the mean age was 53. So I think it was unlikely that we had a significant number of adolescents in that study.

Clinton Daniels Got you. So it it sounds like very few kids if any. However, from Doctor Burns, it sounds like there's not elevated risk or and it's you know considered standard practice still to treat adolescence. Thank you.

Sheila Rege I I had a question just following up on the training. So it seems like the harms the safety concerns are low, but when this happens just to the, you know, getting into a psychiatrist for me is difficult for patients, and I suspect for everybody else. Is there a protocol aware when when a patient undergoes this, especially if it's 30 treatments, that there's an expectation that the primary care team is is notified is there and and and and is it only psychiatry that's doing this? The other specialties that do this with a weekend training, kind of if you give me some color on, on kind of what happens in real life for the committee or for me personally, that would be very helpful. Thank you.

Tuesday Burns Yeah, absolutely. So I can't speak to, you know, if you were in an academic center, there would probably in an academic center, you know that Columbia press you might have. You might have pain docs, you might have anesthesiologist working alongside psychiatrist or working alongside neurologist to treat complex conditions. Someone with really horrible neuropathic pain due to Ms. right? So you might have that constellation of a treatment team approaching a patient, which is great. And I love that. I think we all love that idea of us all approaching a patient who really, comprehensively and from a multidisciplinary sense. I would say in clinical practice isn't something you're not going to go into a primary care doctor's office and see a teams device sitting there? So in terms of who can actually purchase teams devices there is there are restrictions around that, so you wouldn't be a, you know, a family medicine doc out in West Seattle and be able to purchase a TMS device. They would need to be evidence of board certification in psychiatry neurology in order to do that. Umm. And they would also need to be, you know, a sense of, especially if we're talking about if you're talking about building insurance, insurance will also payers, especially commercial payers are going to have requisites. The CPT codes need to be billed by a psychiatrist by a psychiatric practice. So there's some regulatory sort of influence there. I would say just generally speaking, I've not known of a practice that's not included, a psychiatrist that delivers TMS in an outpatient setting. However, when we are treating patients, you know in our

clinical settings there is, you know hope to really be collaborative, especially patients that have seen other disciplines that may have other medical conditions. I always aspire to collaborate and staying close contact with all of those docs, especially if it's someone that is regularly seeing a primary care doctor or neurologist or a pain specialist or you know their orthopedist for any, any ideology of concern. So that everyone is aware, right and it's not necessarily just because of risk. I mean, I have treated patients who are very complex, who have had a history of retinal detachment, right? Who have you know, ferromagnetic implants in their head and I have to be mindful of those things. Cochlear implants, I've treated patients cochlear implants. So there are all manner of reasons why I'm going to be very, very mindful about how I collaborate and making sure that I'm collaborating with all the other providers for caring for a given patient. And I think, you know, there's, there's also just the the beauty of being able to understand holistically just for the sake of really, really, truly understanding the effect of treatment, what else might be getting better? What else might be improving, or if there is any risk of something, another medical symptom or condition being impacted by it?

Sheila Rege Thank you, Doctor Reddy. Any comments from? The review of the literature and what you you saw.

Shivani Reddy Trouble unmuting? No, I think. Uh, I'm happy to take any other questions, but um.

Sheila Rege OK, we have Clinton. I'm sorry, we we do have one last hand.

Clinton Daniels I I have a question for Doctor Burns, but I think Gary Franklin had something maybe more relevant to what was just discussed than my question. In the chat.

Sheila Rege Yeah. Gary, would you like to go first? I saw your hand raised briefly, so would you mind? You have to unmute, Gary. Doctor Franklin.

Gary Franklin Sorry, Doctor Burns, you mentioned that you thought only certain types of specialties could purchase this or apply it. Who regulates that?

Tuesday Burns Yeah, that's a really good question. And at present, as far as I know, it would be the manufacturers of the devices.

Gary Franklin OK, so it's not really regulated.

Tuesday Burns Not as yet. Not that I know of.

Gary Franklin That means no, there's nothing to stop of a primary care doctor from purchasing this thing, right?

Tuesday Burns That's a good question. I would say though, for this standpoint of someone who wants to, whether it's Neuronetics or Mag Venture or Brainsway, if they are hoping that their product is going to demonstrate efficacy enough so that a next the next clinician down is going to buy the Brainsway instead of X, Y, or Z device you're going to want to make sure that that device is distributed. It's going to behoove them to make sure that device is

distributed to people who are going to know how to use it and use it in an effective way. So I think on some level they are going to be motivated to make sure that the device is, you know, purchased by people who are actually going to be able to effectively use it because there is the risk and I think that's been seen over the past decade. It's getting better now with recognition of stuff like this that without proper training, without kind of the right protocol, there's going to be a delusional effect. And that's something that you see, it may not be something that was rising to the point of when we're looking at randomized clinical trials, but in clinical practice, if there's a dilutional effect of, you know, dozens of people in the community buying these devices, not using them effectively and not seeing response, then people are going to stop by the devices. Patients are going to have less faith in the devices ability to actually offer a treatment that's effective and give hope. So I think there's motivation there, but I think you're absolutely right that it, it speaks to all of this that there needs to be a regulatory sort of leveling here for sure.

Gary Franklin — But there's no post marketing data that the companies themselves make public as to who's buying these things or who's applying them, we don't really know that, right?

Tuesday Burns — Correct. Yeah. Not if the public, I would say as a purchaser of a device, that is data that you are that you can be privy to simply by the fact that they encourage networking with other folks and sharing of information and clinical sort of data. But no, there's not there's nothing that the public is a is aware of, these are privatized companies in large part some publicly traded. But I think for the most part they're private.

Sheila Rege — Conor, you had a comment on that?

Conor Kleweno — I was just gonna say uh, efficacy doesn't necessarily drive business decision models here. So if that were true, like the nutrition industry would be nonexistent, right? So so some business models are drive utilization and tell it's no longer utilized and then then you've made your margin and you move on, right? So that I understand your point that necessarily like you know quality will will rise to the top, but that's not necessarily what certain business models are in the market, whether it's this, nutritional supplements or any other aspects of what healthcare system of the fact that I hear Neurostar TMS every morning on on my morning radio show, you know, sort of big puts that into question as well so.

Tuesday Burns — Ohh absolutely and I and you know I can't agree with you more. I keep unfortunately dropping and the switching, you know Neurostar or Neuronetics because that was the case where they, you know they were heavily marketed to any old mom and pop outpatient psychiatry clinic for many years. But if you were to go to any academic center who's really really concerned about quality of data you wouldn't see a Neurostar device in that that facility so. That that is an issue for sure.

Sheila Rege — Doctor Franklin, does that change anything in in your way you recommend this or that be hard to do, I think. Uh, you're muted.

Gary Franklin — That that would be hard, hard to do. I mean, I mean, you know, you could do that, you could say in your coverage with conditions that it should be only applied by trained

people and they should be specialists in the area. But we've never done that before, I don't think.

Sheila Rege No. Umm. If there's no other comments on that aspect, Clinton.

Clinton Daniels Yes. Thank you for Shivani. I was curious if you could comment just a little bit on if any of the studies included recurrent users of TMS and then for Doctor Burns. I was curious when someone's identified as a responder, what's the expectation along term or they do they need 30 treatments every year or you know how does that vary?

Shivani Reddy So that's a good question. Thinking about our inclusion exclusion criteria, I don't think we specifically excluded recurrent TMS. Recurrent uses of TMS, but I would say that I I'd have to go back to the the tables, but I'm pretty sure that most of these were people who are having it for the first time. A lot of the exclusion criteria were like they could not have had prior ECT or I think that some of them might have actually excluded some people who have had prior TMS, but I think that for the most part that you're not, we can't really use the studies we have to tease out the difference between primary treatment and recurrent treatment.

Tuesday Burns And I can speak to just one, we're thinking about this, this population of folks with treatment resistance. So these are folks that have had multiple episodes of major depression already, which of course puts him at higher risk for recurrence of major depression. With regard to TMS, what we see in comparison to typical psychotropic trials, pharmacologic interventions, we do see a a lengthier durability what and you know, I would have to find citation for this, but the the clinical sort of, you know, approach to it is looking at sort of a range of 6 to 12 months with the idea that nothing you entered remission got a good response or remission and did nothing after that stopped treatment and they did nothing. Went back to old patterns of behavior, old patterns of sleeping, didn't take any medications, didn't do any lifestyle changes. There would be an idea that treatment effects would begin to decay in that kind of 6 to 12 month window. Luckily, you know, you know, we we really discourage folks from going back to, you know, behavior as usual and life as usual after a treatment like this, particularly given the investment of time and money. So the idea is you see the treatment effects can be sustained with ongoing cognitive behavioral therapy, with maintenance TMS. And I can speak to that a little bit more or even with medication trials. What we do know is that folks respond differently to medications. And therapy, following course of brain stimulation and that scene across the board, whether we're talking about TMS or ECT, the idea is that the the new set point, the new baseline is different. So if you brought those circuits back online, if that dorsolateral prefrontal cortex is now being perfused, it's now active again. The likelihood of folks being able to respond to and respond to a much lower dose of medication or being able to respond to an engage in therapy is much higher. So the hope is that. After of course, of treatment, people will begin to do the things they'll have the energy, they'll be more resilient to be able to engage in therapy, to be able to get back to work, to get back to life, to stop drinking, to stop using maladaptive coping skills, which is going to extend the the the period of remission. I would say that with regard to, umm, with regard to your question about sort of meeting TMS again there is data and there are several papers that have looked at the need to do booster sessions. There need to do maintenance TMS and

that's still there isn't there isn't really a sort of a final say on what that looks like because each also each person is unique. Each episode of depression is unique. I've had patients personally for whom, you know, I haven't seen them for years after course of TMS and then they come back. With the depressive relapse and that one is different, it's harder to treat or it's easier to treat, it's just different and that's the flavor of major depression. Unfortunately, that each episode can be a little bit different, but I would say that in general, what we notice is that when we have scheduled check-ins with people, let's say three months after your last TMS treatment, we have an office visit to just talk about how you're doing. If we're eight and this is true of medications as well, we're able to catch symptoms sooner when they're more in a mild range or even hardly detectable versus in a severe range, the time to treat the the resources needed to treat are going to be far less so. Instituting a really proactive approach to it rather than saying, hey, come back when you're depressed again, tends to be much more efficacious and lower cost, lower burden on the patient and on the system. So we really try to strive for that proactive model of preventative care and when doing so fine that we're actually doing and using a lot fewer treatment sessions thereafter when we take that stance. Is that tend to speak to what you were wondering about?

Clinton Daniels Yes, it did. Thank you very much.

Sheila Rege Great. If there are no more questions, uh, we are due for a break. And looking at time, it would be coming back at 11:20 is that's still good or do people think they need longer stay on time? 11:20 is good. Alright, we'll be back at 11:20. Bye.

Sheila Rege Hi there. I think we have a quorum. I'll have staff verify. OK. I see a lot of people, so I think we're back. Umm. So we're on to our discussion, if we want, we can have Josh. Put up our decision aid to help facilitate. Ah, how would people like to start? I'm open to suggestions. We're at kind of in the discussion phase among committee members. I'm going to make sure nobody has any questions, or, uh, our experts anymore. And Doctor Burns, thank you for all the citations. I would, if uh, nobody is going to volunteer on a strategy, I would propose we use our clinical aid and, uh, kind of take a depression, and OCD as separate topics and depending on how that goes. Uh, we could then look at the others anxiety, post-traumatic stress, tobacco, substance abuse. Is is that OK with the committee? Any anybody? Separate.

Conor Kleweno Are you saying depression and OCD combined or keep them? Yes, I agree, agree.

Sheila Rege So. We actually have. Josh, if you would pull that up and I I'm working with only one computer, so I if I pull it up, you may I may disappear on everybody. But let's see if I can the, umm, part where we're looking at harm, you know, kind of the principle one determinations are evidence based, health benefit and using evidence, I might just start at kind of the confident, non-confident. You know, we looking at safe, effective providing value, uh, just on safety, how comfortable about we that the evidence has shown us that it's relatively safe and we could go around the table or or if you wanted, just open it up for anybody to comment. And explain.

Josh Morse I could suggest could I?

Sheila Rege Yeah, go ahead.

Josh Morse Jump in so. Well, staff prefilled this part around outcomes and and this what we do is we go from the report from the slides on the the outcomes that have been reported. And.

Sheila Rege Good, that's how.

Josh Morse We have reported in here in the prefilled draft just there, but if you'd like, we can go through this, and if you have any outcomes you think are important that we haven't included, we can add them or we can jump down as you if you want to, down to the, the, to this part where the the informal voting on the sufficiency of the evidence with comparators and Val and I failed to say this the beginning, this is Val's first meeting today, so steep learning curve and Melanie is away. So we're doing this together while Melanie is away, so we do have a spreadsheet prepared to accommodate this part and we can adjust it based on your decisions around how you're going to either group or take on the specific conditions for treatment so.

Sheila Rege Why don't we see what the staff has prefilled and see if we can add anything? I'm not seeing prefilled, are you?

Josh Morse Oh, sorry. Uh, so we added here under safety outcomes. Yeah, there's nothing specific, for example, so if you if you felt that, for example, seizures was a specific safety outcome you wanted was relevant, you know that could be typed in here if there's something that was that we missed.

Sheila Rege I would, I would like seizures at it on so because we have that discussed in some of the studies and even though it's it was a low likelihood. Was anything else that any of the committee members felt, including Doctor Burns, you that we should consider in terms of safety? Training was another one because I got the feeling and had to be very specific on where it went for each disorder. I don't know how we would put that there.

Josh Morse Yeah. Thank you.

Janna Friedly Can I, can I ask where, so where would significantly worsening of symptoms or suicidal ideation would that? Would that be incorporated in the serious adverse events and adverse events?

Sheila Rege I would think so, but.

Janna Friedly I.

Sheila Rege You don't know if that would have been. Uh, there, it's it's not a side effect since side is not a side effect of the treatment.

Janna Friedly No.

Sheila Rege It's a the disease side effect though I I I'm a little worried about including it as a side

effect of the. Uh,

Janna Friedly Well, I yeah. And that's where I was struggling. I I I I struggled with some of with with this in in particular. I I I don't know that it's reported well enough to really understand understand it, but there were some reports of, you know, suicidal ideations and and there you could theorized that a treatment like this could potentially worsen symptoms in some people, and they it's frequently not really reported. It, outcomes are not necessarily reported in a in an easy way to tease out if there are subgroups of patients that actually get worse on the treatment compared to a Sham. You know, most often it's reported as sort of mean improvements. So I I don't it's, yeah, that's something that I have been trying to tease out. I don't know that we can actually tease that out and maybe that maybe that's not not reported in this population and it's hard to it clearly hard to, hard to tease out, you know, the just the natural progression of a disease like this. But if it's compared to a Sham treatment you you would be able to try to attribute that to the to the treatment potentially?

Tuesday Burns And I can say, and I'm not sure if it's referenced in the literature that's available to this group right now, but that has been looked at and comparing rates of suicidal ideation. I mean that is tracked with each treatment session as part of either PHQ 9 or the HAMD or the modulus, but that is something that's tracked each time. And I would say the studies that I'm aware of, have compared and seen no difference in terms of worsening and suicidal ideation between Sham and active treatment, and there have been very explicit studies that have actually looked at the impact of decreasing suicidal ideation with improving mood across treatment with TMS. I think for a lot of these studies, as is true with any kind of psychiatric study, whether it's medication or an intervention, you know the disease progression is often going to be fraught with suicidal ideation. As you said, it's a symptom of the disease itself on I think there are some people that do need to be excluded because they have to be hospitalized or because staying in treatment and not knowing if they're getting Sham or active treatment isn't, you know, it's it's, it's not ethical if there are worsening in terms of their depression worsening as would be the case over the course of a depressive episode.

Janna Friedly Yeah. And then.

Tuesday Burns So while I I don't.

Janna Friedly I was gonna say that and that that makes sense to me, I struggle with how do you how do you report and analyze those? Because I I see some will just they will just drop out of the study when and not not be analyzed and sort of true intention to treat analysis and that that makes me a little bit uneasy.

Tuesday Burns Right, absolutely. I would just say I would just reference back to the studies that have been done comparing impact on suicidal ideation, between Sham and active. And again, it's again, I can't quote the body and the end or the effect size, but there has been demonstrated safety in terms of not worsening suicidal ideation and effect treating suicidal ideation. And that is something especially with the newer evolutions with data birth treatment, significantly improved suicide ideation.

Janna Friedly OK, so it it may be a, a a moot point.

Sheila Rege Doctor Reddy?

Shivani Reddy This is Shivani. Ohh yeah, I just wanted to say that there were some studies that looked at some suicide scale. So I think the Columbia suicide risk scale and the back suicide ideation scale and there weren't any differences between active and Sham groups in the studies that we captured.

Sheila Rege So then, Shivani, you're saying that is not a potential side effect identified by the evidence?

Shivani Reddy Well, I think it's to Doctor Burns point it's it's really hard, and as we're talking about it's it's confounding by indication it's a little bit hard to tell whether, natural progression of disease versus the side effect of the treatment. But when you compare the two groups that didn't seem to be a difference between the two groups that were being rated on these validated suicidality scores.

Sheila Rege OK. Conor.

Conor Kleweno Uh, yeah. Not to perseverate on this. I guess I just really agree with Doctor Friedly here. You know, if this were a new SSRI, it would absolutely be listed as potential, umm and you know, teasing out whether it's progression of disease or side effect is clearly difficult. And if you have a low number study showing no difference is not compelling to me because it's gonna be a low incidence anyway and so you you'd have to have huge numbers to show to prove no dis, no difference, I would say and so given that it's a an event that's really high risk that you know, I do think it's a relevant conversation that that Janna brought up, I guess so I'm happy to have our clinical experts sort of put us at ease, but I just, I just thought it was a very concerning thing that we should at least have on our rubric when you know, discussing these.

Tuesday Burns I mean, I I suppose the reassurance I can give is that, you know, as suicidal ideation is often a symptom of severe treatment resistant depression, it is something that's monitored and tracked across the course of political treatment with any medication or with TMS or ECT. So these are active conversations that are had between provider and patient on a regular basis each day of treatment, particularly the beauty of TMS being season five days a week, often you get to it that's that in a more close way than you would with a medication intervention where you might not get to see them quite as often. So I would say it is something that's that's discussed as part of the informed consent process and any, like any psychiatric intervention that's always going to be discussed in the context of worsening symptoms in the context of the risk of it not improving symptoms quickly enough and in that in and of itself causing the psychological despair of not improving and the disappointment causes. But I would say that that is definitely a conversation that's had with patients, with their families, just to ensure that folks are aware and monitoring and it ties into the collaborative piece, whether if they're seeing a therapist on a regular basis once or twice a week, their families are seeing them every day, so it is something that does require, you know, a different level of monitoring than if I were instituting a a new medication for lipid

management or hypertension, I am going to be talking to this patient on a much more kind of, kind of intensive on a much more intensive level and monitoring those symptoms much more closely for sure. Because you're right, it is scary and it's an outcome that we never want to see and you know, I think having just really transparent informed consent at the beginning is a huge part of of that.

Sheila Rege I uh, I think the voting members are inclined to keep it in there is is, would anybody who thinks it should be removed talk about why they feel strongly should be removed. This is just I'm just trying to get a straw poll kind of discussion going so everybody's heard. Not just the yeses.

John Bramhall I don't feel strongly, Sheila and I put a comment in the chat. It's just, you know, the the the test that would have to be conducted would be TMS on on me and then the question, does it cause damage to me? In other words, a control subject. And and I I don't know that we have that from the data. I mean maybe it can be teased out. You know, if we say something that's dangerous then it it we sort of implied that it's dangerous to an a normal person is is that, is that a reasonable sort of position to take?

Jonathan Sham I don't, I don't think so. I guess I would maybe disagree with that assertion. I mean, if you have an at-risk population that you're exposing intervention to you really care about the detriment of the at-risk population, you know, maybe they're more susceptible to the adverse outcome. So I don't think it has to harm a control group. Now I agree with you 100% that we probably don't have the the data available to answer the question, so they're they may just be us remarking that there's insufficient evidence, but I would state that it you don't have to have a control group harm to to demonstrate adverse effect.

Sheila Rege Anybody else who feels strongly that we should not put that there? Remove it that it would actually cause more harm than good to have that? Oh oh. Or encourage tracking of that as a potential harm for this technology? I don't think it's that we're saying it. It causes it, it's just keep an eye out, it's kind of hard monitoring.

Josh Morse Yeah. And if I could say, is Sheila just about this again, about this part of the the decision aid and its utility, I think it really is just for, for conversation purposes. You know, to have the conversation like you just had a, you know, around outcomes that people have observed and that they think were important to them, whether or not they're supported by the evidence or not. I mean, I hear you, but I'll saying that seizures and suicidal ideation probably are both really important outcomes and then you've talked about the fact that the evidence may not say that there there's a high frequency of them or what the issues are with the evidence so.

Sheila Rege Right.

Josh Morse I really appreciate the conversation and, but this isn't holding you to anything. This is just for conversation.

Sheila Rege Moving on now to. Any other harms or we're gonna move on to effectiveness efficacy? And that was considered kind of a medium risk. Do we have anything prefilled out?

Josh Morse — We have remission, response, and symptoms severity on there. I don't know why we have this listed twice, but should only, we have two boxes, so there is, there's room for this to continue. That's what this is, is an extension. If you came up with more than three other outcomes.

Sheila Rege — So so, remission, response. Ohh so we'll be we'll be looking at that as criteria remission, response. Or severity of symptoms as the evaluate efficacy.

Tony Yen — Sheila, what do you think about adding durability?

Sheila Rege — I like that, Tony. Unless and and again, we don't have to vote on that. If if anybody feels strongly, just put something in the chat saying I totally disagree and you can chat or you can speak right away. Any, anything else that we should look at? Umm. On efficacy, might my thought is and being a radiation oncologist, maybe you know the first time we tried treatment it it works the second time we try and treatment the same treatment, it doesn't work as well and the side effects go up and I don't know if with this technology the same is true. So like retreatment, increases harms and radiation and decreases efficacy is that and I'd be interested if any of the studies looked at that, Shivani or Tuesday, if you have any, any comments on that?

Shivani Reddy — So we didn't specifically look at retreatment studies, so we can't speak to that from the evidence base.

Sheila Rege — Tuesday. Have you seen that, that? Retreatment increases seizures or anything like that, or there, there aren't any, there don't many people.

Tuesday Burns — Umm, no. Definitely not. And the the idea is, you know with with retreatment, typically there will be, there will be a lag between the course of treatment, right, and when retreatment is initiated. So at that point, what we know objectively is actually someone's motor threshold. So the threshold not only to initiate treatment to, to activate the necessary cortical circuits and also the, the the sort of the ability to activate if it were to happen seizure activity. So synchronous kindling seizure activity that you know that is going to go back down after a lapse in treatment because by definition side effects, risk is actually gonna drop off, the further you get from treatment. And then you're restarting again as you begin to stimulate again. And that's just what we know about the brain. We know about the brain that it's going to motor threshold is going to drop that down. The further away you get from treatment.

Sheila Rege — So that's that's a non-issue. Anything else in when we're looking at efficacy?

Laurie Mischley — Can can I just ask you real quick on that last the point about retreatment can I assume, given the burden of on the patient, to go in as frequently if they have to as they have to go in? Is it safe to assume they had an impressive response the first time? Is that your experience given how burdensome it is on the family and the patient?

Tuesday Burns — Yeah. So the idea would be again, it's always going to be cost benefit and if someone did have a robust response to it and then experienced a depressive relapse, I typically found that folks would be very willing because I think something that's really not been emphasized and I'd like to emphasize it from a clinical standpoint is at the tolerability,

even if you're going in five days a week, you're there for half an hour at most. And the tolerability of a TMS treatment versus a medication trial, there are no systemic side effects with TMS. I know we worry about the risk of seizure, but in terms of GI dysfunction, sexual dysfunction, migraine impact on hepatorenal systems, all the things that can happen with the psychotropic trial, that has to go through second pass metabolism, right that goes from here all the way to finally get to the end target organ, that's bypass with TMS. So the tolerability of TMS for many of these people is so much preferable, so much more preferable. So I would say that's that's never been a hesitation that I've had with folks in terms of representing for treatment. And I think again it goes back to that preventative stance and being very proactive in making sure folks are staying in treatment with other providers are just checking in so that you can catch things for really into relapse before severity increases too much.

Sheila Rege If we have nothing else here and I don't see any other hands raised, we can move down to the next, cost. Oh yeah, cost and cost effectiveness. We need some help in filling out, uh, and I know Conor, you had questions on CPT and you got some answers. Umm.

Tuesday Burns Can I just highlight Shivani, you had a slide actually that looked at cost of when comparing, I think medication trials, one of your slides talked about that and you actually had you had dollar amounts.

Shivani Reddy Yes, we had incremental cost effectiveness ratios. I was actually just quickly looking for the OCD versus the MDD one. So compared for the MDD studies. TMS was cost effective compared to, uh, I think actually compared to medications. Umm, we don't have it, we didn't find any studies comparing it to ECT. Umm. Sorry, I'm just pulling that up right now.

Sheila Rege And while she's pulling that up, Laurie, did you you have your hand raised?

Laurie Mischley I said it. I'll I'll put it down.

Sheila Rege Okay.

Shivani Reddy UM. Yep, so. There were. So you know, there was very little evidence on cost effectiveness that we found and in, in both cases, they were compared to medications. And so one of them was, so for OCD, they were comparing to a monotherapy with an antidepressant like an SSRI or an SNRI and then also similar results compared to a combination treatment of an SNRI or SSRI with an anti-psychotic and that had an incremental cost of about $6,000. But it was more effective for an informal incremental cost effectiveness ratio of $1,647 per unit reduction in YBOC score, which you would, you're looking at about Doctor Burns might know this a little bit better, but it probably like go four or five point reduction in YBOC score to be considered clinically significant, and then, similarly, there was cost effectiveness for MDD comparing to pharmacotherapy and the two studies had a different time horizon, so one just looked at one year and another one looked over the course of age 20 to age 50 and with a longer time horizon and the starting TMS and younger age, it would be more cost effective.

Sheila Rege Umm.

Tuesday Burns And I'm happy to. Oh, sorry, go ahead.

Sheila Rege I'm just kind of for the voting committee members. I'm kind of interested in a, maybe a straw poll of whether committee members are concerned about cost or cost effectiveness just or we feel that we have enough data on this that we can move on. So if you say yes we, that means we're comfortable that we reviewed the data and whatever little or there isn't that and we're OK with an understanding of that to to kind of make recommendations. So yes, means we're good with the current the, discussions as of now, no means we'd like to spend more time here talking about cost to cost effectiveness. Just put it in chat. Think I'm hearing it that there was very limited data but, but people feel that, you know, kind of we have access to whatever there was as much as we could tease it out, uh, and now what I'd like to do is kind of go through, uh, uh, he straw poll of just, you know, kind of and and even I think for safety in the straw poll, we can just take the technology as all the technology you know for all conditions. Umm. I am going to go to special populations eventually, but then we'll, uh for effectiveness uh, we'll, we'll do it by each category. Is that OK? So. So we we did talk with special considerations. We've talked about age in in our study parameters, we'd asked about sex, comorbidity, adolescence, pregnant women, and older adults. Doctor Reddy, I I don't think there was any data on any difference, for those subgroups would you like to call attention to anything that we may have missed on those?

Shivani Reddy So there were very few studies with subgroups or special populations, really one or two here or there, and there were no differences with small exceptions. So I believe for OCD, there seemed to be greater effectiveness in men compared to women in one study and then for, S, SUD there was a study looking with comorbid depression and so patients who had comorbid depression with SUD tended to have a stronger response to TMS treatment for their substance abuse as well, but those are two small examples among a, a very small handful of studies we found. Otherwise there was really no difference for these subgroups.

Sheila Rege Anybody else wanna opine or ask about the special subgroups. Before we go to safety, straw pole. Umm. Let's talk about definitions on safety. If we say unproven, it's unproven compared to a Sham safety profile. Uh, less, it's less safe than the Sham. Equivalent, equivalent safety than a Sham. More in some, more safe compared to a Sham. Uh, more and all does that, is that good? So would you like us to? We can raise our hands or type it in. What would you like? How how would you like to do that?

Josh Morse So yeah. So for safety, we're going to do all conditions together, is that correct?

Sheila Rege Correct.

Josh Morse OK. And so Val, can you share your screen?

Val Hamann Yes.

Josh Morse So we have this document ready for, now we have safety broken out by condition. But

	what? Why don't we do safety? Ohh no you have it. Super.
Val Hamann	Yeah, I already copied it over, so this also includes others which we obviously don't have to add any information to those so.
Josh Morse	Great. So I think we're ready for your vote and we'll get it down on this document.
Sheila Rege	Do you want to, uh, go by roll call? We can start.
Val Hamann	Umm, I can definitely.
Sheila Rege	Go ahead.
Val Hamann	I can definitely do that. I'm not able to see well for hand raised, so someone would have to tell me that if you went that route, so whatever.
Josh Morse	Yeah, roll call might be. Might be more efficient doing it this way.
Val Hamann	OK. So John Bramhall.
John Bramhall	I say equivalent for safety.
Val Hamann	Clinton Daniels.
Clinton Daniels	Equivalent as well.
Val Hamann	Janna Friedly.
Janna Friedly	Equivalent.
Val Hamann	Chris Hearne.
Chris Hearne	I would say equivalent.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven.
Val Hamann	Laurie Mischley.
Laurie Mischley	Unproven.
Val Hamann	Sheila Rege.
Sheila Rege	Unproven.
Val Hamann	Jonathan Sham.

Jonathan Sham	Unproven.
Val Hamann	Tony Yen.
Tony Yen	Unproven.
Val Hamann	OK. Did you want to do efficacy for the, all conditions or move on?
Sheila Rege	No, let's do efficacy. We'd have to break that out. Let's do efficacy for depression.
Val Hamann	OK. OK, John Bramhall. Ohh sorry. Sure.
Sheila Rege	This time we cannot go from the bottom, so we don't put John on the spot right away unless OK with it.
Val Hamann	Sure. Oh, and we're in efficacy, so or you didn't wanna breakdown safety for this?
Sheila Rege	Ohh, that's right Tony. Tony would go first. For.
Val Hamann	Yeah. And you didn't wanna do safety for. Depression, correct?
Sheila Rege	The safety was for everything.
Val Hamann	Yes, OK. Just wanted to double check. OK, so Tony Yen?
Sheila Rege	So this is just depression.
Tony Yen	So we're talking about efficacy and major.
Sheila Rege	Just depression. I'm kidding.
Tony Yen	And MDD. OK, so more in some.
Val Hamann	Jonathan Sham.
Jonathan Sham	More in some.
Val Hamann	Sheila Rege.
Sheila Rege	More in some.
Val Hamann	Laurie Mischley.
Laurie Mischley	More in some.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven.

Val Hamann	Chris Hearne.
Chris Hearne	More in some.
Val Hamann	Janna Friedly.
Janna Friedly	More in some.
Val Hamann	Clinton Daniels.
Clinton Daniels	More in some.
Val Hamann	John Bramhall.
John Bramhall	More in some.
Val Hamann	OK. Would you like to do cost for MDD?
Sheila Rege	I know I'd like to stay on efficacy and let's do OCD.
Josh Morse	We start in the middle, make it challenging.
Sheila Rege	Yeah.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven.
Val Hamann	Laurie Mischley.
Laurie Mischley	Unproven.
Val Hamann	Sheila Rege.
Sheila Rege	Unproven.
Val Hamann	Jonathan Sham.
Jonathan Sham	Unproven.
Val Hamann	Tony Yen.
Tony Yen	Unproven.
Val Hamann	Chris Hearne.
Chris Hearne	Unproven.

Val Hamann Janna Friedly.

Janna Friedly Unproven.

Val Hamann Clinton Daniels.

Clinton Daniels Unproven.

Val Hamann And John Bramhall.

John Bramhall Yeah, unproven.

Val Hamann OK. And move on to other conditions.

Sheila Rege Yeah. So does anybody want to take all other conditions as one or would you like to do this for each condition separately? Let's type in all in, you know all meaning the the other four, all in one or separate. Does anybody have a strong desire to have it separate? Hearing none, let's take the rest of the condition.

Gary Franklin Sorry, Sheila. If we happen to if a lot of stuff appears for OCD in the next few years and we review that and you don't do it separately here. It might be harder to relook at that so that

Sheila Rege You know, we've done OCD's gonna be done separately as is MDD, so. OCD. OK.

Gary Franklin Uh, OK, yeah. But even, but even among these other ones, if a lot of new data comes along, say, for substance use disorder and we rereview that, but you don't have it sorted out as to it's an individual decision here, I just would recommend doing them separately.

Sheila Rege Good point. Let's do it separately. Go ahead.

Val Hamann So sorry I was.
Sheila Rege Separately, so we can go to generalized anxiety.

Val Hamann OK, give me one second to just copy this over.

Sheila Rege Sorry about that.

Val Hamann No, no, no problem.

Sheila Rege Uh, Gary while she's doing that. Was it a problem on safety? Do have done.

Josh Morse If I could, maybe I could just ask. What I hear, Doctor Franklin maybe leading towards is that your decision at the end when you vote on a on an outcome you may want to break that out. It sounds like by condition it sounds like that's what Garry's suggesting. Is that where you're going with that, Gary, about having this?

Gary Franklin No, I was just saying that instead of doing them all together for efficacy effectiveness, I would break them out because something might occur in the future where we have to review it. But if you don't have an individual decision now on effectiveness that it might be hard to look at.

Sheila Rege We we can do it for the straw poll too. That's fine, so, what we could do to help expedite it if you're typing is fast enough. Uh. Yeah, it's fine. Let's let's do it separately.

Val Hamann OK.

Sheila Rege I was going to say let we can just say out I'm this, this, this and this for blah blah blah blah. You can take me first I if I had to start, if it started with me, I would say unproven for general anxiety disorder, unproven was posttraumatic stress disorder, unproven for tobacco abuse and unproven for substance abuse disorder. Is that OK? Is that too fast?

Val Hamann And that should be fine. I can go in and yeah, make, do the edits in a little bit too. So like you told me, all for all of them, so I can go in and easily put that in for each of the sheets and then if someone say had an equivalent for, say, PTSD, I could put in next to that X PTSD or something like that. So. If that sounds OK?

Sheila Rege OK, you can make that work then. That'll kind of save going back.

Val Hamann Sure.

Sheila Rege You know, through foot drop off.

Val Hamann Sure. Uh, Jonathan Sham, if you wanna tell me your feelings for. Yeah.

Jonathan Sham Agree on unproven for the remaining conditions.

Val Hamann OK, Tony Yen.

Tony Yen Unproven for remaining conditions.

Val Hamann John Bramhall.

John Bramhall Yes, uh, more in some for MDD as we said and then unproven for OCD and the other conditions.

Val Hamann OK. Clinton Daniels.

Clinton Daniels Unproven for the remaining.

Val Hamann OK, Janna Friedly.

Janna Friedly Unproven for the remaining.

Val Hamann Chris Hearne.

Chris Hearne	Unproven.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven for the remaining.
Val Hamann	Laurie Mischley.
Laurie Mischley	Unproven for all of them.
Val Hamann	OK. Are you wanting to transition to cost now?
Josh Morse	There's a note. I wonder if we could go back to the safety vote and just make a quick change as Doctor Fridley is indicated.
Val Hamann	Yes.
Josh Morse	She wants to change her.
Val Hamann	Yes, I changed that.
Josh Morse	Oh, you did? Thank you.
Val Hamann	Yep.
Sheila Rege	OK, we'll let uh, yeah. Let's go to now we're going to go to cost and cost effectiveness. Again, this is a straw poll, so. Ah, it's not the final decision. So. I'm open to somebody asking about whether we should separate it do the MDD and OCD as separate and then kind of, do the rest, or do you want to just take all of it at once? Open to Conor.
Conor Kleweno	Uh, yeah, just a clarification. So this is again cost versus Sham and we're assuming the Sham is it, I guess I didn't specify the Sham procedures, the same machine just not turned on the right way. So the cost of like theoretically buying that machine and the tech and all that kind of stuff would be the same or. Is that, does that make sense?
Sheila Rege	Yeah, I'd ask. Uh, uh, Doctor Reddy, do you have an opinion on that looking at the studies?
Shivani Reddy	So they looked, uh, compared to, uh to medications, so cost effectiveness of active TMS compared to medications.
Conor Kleweno	But for our vote, Sheila, are we doing again versus the Sham procedure? Is that our?
Sheila Rege	That was.
Conor Kleweno	Are we are we doing cost versus standard of care with this one? I'm just I don't wanna clarify, sorry.

Sheila Rege	And and that is that is up to us as a committee in the original documents we we circulated, we kind of had asked that it we think about it as Sham but they were no studies. So you know we're looking at. I'm open to guidance from anybody. Janna.
Tony Yen	Sheila, when we're looking at cost effectiveness, I think we just, you know use the data that we have, which is the literature and Shivani was very kind enough to point out that there was really the cost effectiveness was not versus Sham was versus medications.
Sheila Rege	So we we use it worse as medications then.
Tony Yen	Yeah, that's what the data, that's the literature that we have right to make decisions.
Sheila Rege	Right.
Conor Kleweno	Thanks, Tony. That was, that was my assumption. I just wanted to make sure we're on the same page. Thank you.
Tony Yen	Yeah. Welcome.
Sheila Rege	So then I think given that I think the cost effectiveness we would have to do it. Let's do depression kind of on its own and OCD on its own, because that's where I saw more data, uh, or more studies, not more data and and then depending on how that works out, we can decide what to do with general anxiety and the rest. So.
Tony Yen	I agree Sheila. Thank you.
Sheila Rege	Is everybody ready for MDD and you can choose how you wanna start. I've gotta think about this now.
Val Hamann	OK, Chris Hearne.
Chris Hearne	Unproven.
Val Hamann	Janna Friedly.
Janna Friedly	Unproven.
Val Hamann	Clinton Daniels.
Clinton Daniels	Unproven.
Val Hamann	John Bramhall.
John Bramhall	Unproven.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven.

Val Hamann	Laurie Mischley.
Laurie Mischley	Unproven.
Val Hamann	Sheila Rege.
Sheila Rege	Unproven.
Val Hamann	Jonathan Sham.
Jonathan Sham	Unproven.
Val Hamann	Tony Yen.
Tony Yen	More in some.
Val Hamann	OK. So for OCD. Yeah.
Sheila Rege	And that was depression less to OCD now.
Val Hamann	OK, Clinton Daniels.
Clinton Daniels	Unproven.
Val Hamann	John Bramhall.
John Bramhall	Unproven.
Val Hamann	Janna Friedly.
Janna Friedly	Unproven.
Val Hamann	Chris Hearne.
Chris Hearne	Unproven.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven.
Val Hamann	Laurie Mischely.
Laurie Mischley	Unproven.
Val Hamann	Sheila Rege.
Sheila Rege	Unproven.

Val Hamann	Jonathan Sham.
Jonathan Sham	Unproven.
Val Hamann	Tony Yen.
Tony Yen	Unproven.
Val Hamann	OK. So would you do you want to break it up then for GAD, PTSD. What? What are you thinking for that?
Sheila Rege	I'm OK with us doing what we did before, just just with Doctor Frank precaution, to, to just us say, you know, there was the remaining 4 unproven for all four or four and some for all four or whatever we want.
Val Hamann	OK. Janna Friedly.
Janna Friedly	Unproven for all others.
Val Hamann	Chris Hearne.
Chris Hearne	Unproven.
Val Hamann	Conor Kleweno.
Conor Kleweno	Unproven.
Val Hamann	Laurie Mischley.
Laurie Mischley	Unproven for all.
Val Hamann	Uh, Sheila Rege.
Sheila Rege	Unproven for the four remaining.
Val Hamann	Jonathan Sham.
Jonathan Sham	Unproven.
Val Hamann	Tony Yen.
Tony Yen	Unproven for the remaining.
Val Hamann	John Bramhall.
John Bramhall	Unproven.

Val Hamann Clinton Daniels.

Clinton Daniels Unproven.

Val Hamann OK.

Sheila Rege So you'll work through that. Does anybody wanna discussion before we kind of take a a straw poll on, uh, whether we're ready to talk about cover and I think again with this, we should take depression on its own, OCD on its own, and then decide depending on, the discussion. Any more discussion at this point? Or questions? Again, this is kind of a straw poll, um, going around the room. It would be like we used to have those cards remember in the old days.

Josh Morse Right. And thank you for that reminder. So for those who haven't been here in a non-virtual environment, the committee used to vote using holding up different colored cards that have the these it said you would choose a card that said on proven or a card that said equivalent you had quite a thick stack of cards. And we would record this. You didn't have a visual or a summary of how the vote was, so you may have been keeping score on your own, but we weren't really showing that. But if we go back to the MDD tab. You know the past few meetings we have been, if you if if this is the if you can scroll up to the top. This, you know, provides you with a essentially a record or a you know, of, of how you as a group feel about the evidence for this condition and and what it supports or might not support, but again, this is not binding, this is has always been the non-binding vote portion to begin to, I guess funnel your thoughts as you start thinking about coverage.

Sheila Rege We fill this out so it should start showing. I don't know why it's not. It.

Josh Morse Yeah, you know, well, that's no cause you this, this is just a blank because you did the safety. Val recorded that somewhere else. But yeah, the efficacy part here is the part I was thinking of.

Sheila Rege OK.

Josh Morse You can see the difference in the way. People. Yeah, there's the safety summary. So.

Sheila Rege OK. So moving on now, to, uh, well, we used to do is kind of a. Uh. Let's do a kind of a straw poll at this point point on depression. How many of us are leaning towards, uh, and this is this is not our final vote, but no coverage, cover with conditions, I can't see that, yeah, uh, and we can actually does, does anybody want a discussion on that or can we start putting out thoughts on paper here for MDD depression. John, I'll put you on the spot. Where would you go on this MDD?

John Bramhall For MDD's umm, I would support coverage with conditions. I have to think about my conditions, but that's why I would go ahead, go to to line D for me.

Sheila Rege OK, let's have you. Let's have that recorded and we'll we'll we'll figure out conditions later. Go ahead. Next.

Val Hamann	Clinton Daniels.
Clinton Daniels	I'm the same uh covered with conditions.
Val Hamann	OK.
Clinton Daniels	And I would do, I would do all ages as well.
Val Hamann	Janna Friedly.
Janna Friedly	I'm leaning towards covered with conditions, but really struggling with the conditions.
Val Hamann	Chris Hearne.
Chris Hearne	I would cover, cover with conditions.
Val Hamann	Conor Kleweno.
Conor Kleweno	I would say given there's an established coverage with conditions policy that I would lean that way, agree with my colleagues with probably a little bit more teasing out of the conditions.
Val Hamann	Laurie Mischley.
Laurie Mischley	Cover with conditions.
Val Hamann	Sheila Rege.
Sheila Rege	Same cover with conditions.
Val Hamann	Jonathan Sham.
Jonathan Sham	Covered with conditions.
Val Hamann	Tony Yen.
Tony Yen	Cover with conditions. I just need to confess this is one of the topics that we've covered so far that I don't fully understand and that I really had to look at the, you know, just using the literature as a guide to make this decision because despite their explanations put forth, I just, I still don't understand how this works. But you know, the evidence at least shows that it does work in some way or the other, despite my lack of understanding. Sorry about that.
Sheila Rege	Well put.
Tony Yen	Yeah, that's my ignorance over here.

Sheila Rege	Umm. Let's do the same, we'll figure out the conditions later. But let's do the same on OCD and see where each of us fall and you can pick how you do this, where you go, who you pick first.
Val Hamann	OK, Tony Yen.
Tony Yen	Not covered.
Val Hamann	Jonathan Sham.
Jonathan Sham	Not covered.
Val Hamann	Sheila Rege.
Sheila Rege	Not covered.
Val Hamann	Laurie Mischley.
Laurie Mischley	Not covered.
Val Hamann	Conor Kleweno.
Conor Kleweno	Not covered.
Val Hamann	Chris Hearne.
Chris Hearne	Leaning towards not covered.
Val Hamann	Janna Friedly.
Janna Friedly	Not covered.
Val Hamann	Clinton Daniels.
Clinton Daniels	Not covered.
Val Hamann	John Bramhall.
John Bramhall	Not covered.
Val Hamann	OK.
Sheila Rege	And then, uh, based on uh, uh, we we probably at this point, we can you can do, let's do it, let's just this is kind of gonna lead to, you know, this is being recorded and it's gonna lead to kind of a decision. Let's do anxiety and PTSD, separately and tobacco and substance of, you know, kind of do that separately. Just.
Val Hamann	OK. Yep, no problem.

Sheila Rege	Just to make sure. Everybody's clear. And we don't have somebody say not covered to all or something.
Val Hamann	Mm-hmm.
Sheila Rege	Thank you for doing all this on the fly. That takes a lot.
Val Hamann	No problem. OK, so I'm starting with GAD, Chris Hearne.
Chris Hearne	I'm leaning towards not covered.
Val Hamann	OK. Janna Friedly.
Janna Friedly	Not covered.
Val Hamann	Clinton Daniels.
Clinton Daniels	Not covered.
Val Hamann	John Bramhall.
John Bramhall	Not covered.
Val Hamann	Conor Kleweno.
Conor Kleweno	Not covered.
Val Hamann	Laurie Mischley.
Laurie Mischley	Not covered.
Val Hamann	Sheila Rege.
Sheila Rege	Not covered.
Val Hamann	Jonathan Sham.
Jonathan Sham	Not covered.
Val Hamann	Tony Yen.
Tony Yen	Not covered.
Val Hamann	OK. Do you want to jump over to PTSD next?
Sheila Rege	Yes, please.

Val Hamann	OK. Uh, Laurie Mischley.
Laurie Mischley	Not covered.
Val Hamann	Sheila Rege.
Sheila Rege	Not covered.
Val Hamann	Jonathan Sham.
Jonathan Sham	Not covered.
Val Hamann	Tony Yen.
Tony Yen	Not covered.
Val Hamann	Conor Kleweno.
Conor Kleweno	Not covered.
Val Hamann	Chris Hearne.
Chris Hearne	Not covered.
Val Hamann	Janna Friedly.
Janna Friedly	Not covered.
Val Hamann	Clinton Daniels.
Clinton Daniels	Not covered.
Val Hamann	John Bramhall.
John Bramhall	Not covered.
Val Hamann	OK. And down to smoking? Jonathan Sham.
Jonathan Sham	Not covered.
Val Hamann	Tony Yen.
Tony Yen	Not covered.
Val Hamann	Sheila Rege.
Sheila Rege	Not covered.

Val Hamann	Laurie Mischley.
Laurie Mischley	Not covered.
Val Hamann	Conor Kleweno.
Conor Kleweno	Not covered.
Val Hamann	Chris Hearne.
Chris Hearne	Not covered.
Val Hamann	Janna Friedly.
Janna Friedly	Not covered.
Val Hamann	Clinton Daniels.
Clinton Daniels	Not covered.
Val Hamann	John Bramhall.
John Bramhall	Not covered.
Val Hamann	OK.
Val Hamann	And then we'll jump over to SUD. Clinton Daniels.
Clinton Daniels	Not covered.
Val Hamann	Janna Friedly.
Janna Friedly	Not covered.
Val Hamann	Chris Hearne.
Chris Hearne	Not covered.
Val Hamann	Conor Kleweno.
Conor Kleweno	Not covered.
Val Hamann	Laurie Mischley.
Laurie Mischley	Not covered.
Val Hamann	Sheila Rege.

Sheila Rege	Not covered.
Val Hamann	Jonathan Sham.
Jonathan Sham	Not covered.
Val Hamann	Tony Yen.
Tony Yen	Not covered.
Val Hamann	And John Bramhall.
John Bramhall	Not covered.
Val Hamann	OK.
Sheila Rege	Can you summarize like we, like what we've gone through condition by condition for us?
Val Hamann	Umm so. It looks like.
Sheila Rege	You know, we have to say 7, 7 covered with conditions, 2 on you know two not covered. Can you summarize just for depression? Or.
Val Hamann	Yeah, 9 covered with conditions and then the rest. So OCD, GAD, PTSD, smoking and SUD, were all nine or non-covered.
Sheila Rege	OK. Can we start talking about conditions on the uh, MDD and as a starting point, can we look at what we currently have as covered.
Josh Morse	We can do that. So we have prepared a document.
Sheila Rege	We also have a better idea, so let's start with a the template of that.
Josh Morse	So the the existing condition, the existing decision is from, this decision for nonpharmacologic treatments for treatment resistant depression and the, these, there is no specific criteria, the limitations of coverage just say that ECT is covered and TMS, repetitive TMS is also covered. That's the existing TMS decision.
Sheila Rege	OK. And can we pull the agency medical directors recommendations that was in this slide?
Josh Morse	So we have those here as well on this document and we can delete or I can pull up the slide if you wanna see the slide version.
Sheila Rege	No, no, this is this is good. Any discussion? Anybody want to change their votes or? Uh is what your vote was kind of on the straw poll still stand? And Conor, I see your hand raised.

Conor Kleweno Just a question whether that's for the expert of the committee is should we do anything different for, you know, under 18 versus over 18? Seemed like there was a couple of comments about it and a compelling public statement as well. And I don't, I don't have the expertise to know what similarities or differences there are for some of these conditions for, you know, treatment like would you necessarily have two trials for medications for a 10-year-old prior to this versus an adult? So I just don't have that knowledge.

Josh Morse Eh, is doctor Burns. I think doctor Burns. OK, she is here. Thank you.

Tuesday Burns Yeah, absolutely. So I would say, yeah, I would say. It's tough because treatment resistance, treatment resistant depression isn't defined in the same way for kids and adolescents as it is for adults over age 18. So I think if we are looking at this as treatment for treatment resistant depression, it's hard to just do a blank at all ages. application and I would also say that there are the studies vary drastically in terms of the number that have been done in folks under 18. And then even still less under 13. So I think just broadly all ages is very, that's a little tricky. Umm, I would say most so I know we had someone from Children's Hospital, umm, and I would just I I I would issue a worry about offering an all-ages sort of invitation to all providers. There's a huge difference in a child psychiatrist at Seattle Children's providing treatment of academic center to a patient who's clearly been seen determined to have true treatment resistance and in need of a lifesaving intervention like TMS versus a 13-year-old that's being seen in a private practice somewhere with a provider that maybe has an unregulated Neuronetics, Neurostar chair and decides they want to give them TMS. So that's a little bit of a concern that I have about the all ages piece.

Sheila Rege Just, Judy actually raised her hand. Let's, let's make sure as the agency medical director, she has anything on process before we continue this discussion, Judy.

Judy Zerzan Yes, I don't, uh, on processed, but I wanted to say with apologies to Gary that we had a side chat and we might wanna consider a modification of the failure of a trial of psychotherapy, given that, particularly for our Medicaid population, it is really hard to find a therapist and I suspect that's also true for the commercially insured population. And so we think it's best practice to do psychotherapy and I really like some of the things that Tuesday said about how this works best when it's in conjunction with some of those other supports or changes. And I I wouldn't want to completely exclude people that have treatment resistant depression and haven't been able to get into a therapist from, from trying this therapy. So I think I think you have a couple of things to discuss about what that might look like and also what the ages might look like. Although I will say tha, umm, if it's silent on the pediatric population then I think ERB and Medicaid can make their own policy about it that this policy is just for 18 and over. Josh, you can correct me if I'm wrong, but also if you wanna say something about the evidence or wanna make sure as Tuesday said that you don't want it to be sort of willy-nilly and do you wanna have some conditions then you can do that too.

Sheila Rege Conor.

Josh Morse I don't have anything to add on that. Judy, thank you.

Sheila Rege Conor, let's just to make it easy. Let's first, as a committee, talk about what conditions we want for a 18 and over and then we can go and deal with the bugaboo of the, the less than 18 is that OK, we can do for a discussion of that till we get this part ironed out.

Conor Kleweno That's that sounds great.

Sheila Rege Umm. Jonathan.

Jonathan Sham You know, just a question of background, probably for Doctor Burns. It has to do with this first tab of failure of at least two different antidepressant medications. Can you give us a sense of what the failure rate of first line therapy is and what the subsequent failure rate of second line therapy is to give us a sense of what kind of population we're kind of selecting for here?

Tuesday Burns Right. We're definitely selecting for a more the the higher severity because with each subsequent trial failure, the likelihood of response continues to precipitously drop. And I don't have at the top of my head like this starting trials that we're looking at SSRI's and antidepressant interventions. But you know those were from couple of decades ago and they essentially found that each subsequent trial, so they believe that the first SSRI trial in the average kind of all come from a population of major depression and major depressive episode, I think the response rate was I believe it was, 40 something percent with subsequent response likelihood decreasing with the second and third trial. Umm, so you know the the take away is that by the time we're getting to that, OK, they failed, a person has failed to trials, the likelihood of them responding to 1/3 antidepressant trial is very low at that point. So it does kind of offer the impetus for considering that next kind of branch on the decision tree treatment resistance, which is, you know, the TMS, ECT, that sort of thing.

Jonathan Sham I know there was kind of a heterogeneous study populations across all the trials, but on the whole, did you get a sense that, uh, inclusion criteria was after failure of one versus failure of two. I just wanna make sure we're not under treating by limiting it to failing two.

Tuesday Burns I'm sorry. You know, you go. Sorry.

Shivani Reddy Ohh I can speak a little bit for well for OCD, GAD, and PTSD. It was most often one to two medications failed and then for MDD, UM, let's take a look here, it was most usually 2 medications failed, umm, a couple studies require them to patients to fail, three to four drugs and six studies only required them to feel uh one medication. So for the most part, it was two medications.

Tuesday Burns And we've seen clinical practice. It is very, very uncommon for folks to come for a TMS evaluation after only failing two trials. One because their provider PCP wouldn't have be considering this algorithm of two or two or three trials. But the other piece is that, you know, most of the payers have actually required trials of three or more medications, and some payers delineate that one of those trials needs to be have an augmentation

strategy which would be in addition to a basic antidepressant, adding any typical antipsychotic or adding lithium. So a lot of the patients that we would be seeing would have already, it would be rare to really see that patient that's only failed two medication.

Sheila Rege Going on to question, I think Tony, you were next unless and Janna, I know you're next to, but Tony was first unless we want, is that OK, uh, to go on?

Tony Yen Uh, no question. I was gonna comment on the conditions. Is that OK or I thought?

Sheila Rege Yeah.

Tony Yen I was thinking about actually just starting the starting point would be good for what the medical director was recommended. Would maybe the modification of excluding the part about psychotherapy because of Judy's comment about the inaccessibility of psychotherapy, probably within this entire region, if not the country. But perhaps that's a good starting point, and the reason you know the the medical directors recommendation will be here is pretty consistent with what we're seeing within the available literature. Really appreciate Tuesdays comments about what's being done clinically, probably within the community about failing 3 drugs. But again, I have to stick with the literature over here as much as I can because I don't know any better.

Sheila Rege What would it be helpful to, and I'm speaking out of turn. Tony, why do we say that failure of we just say recommend concurrent psychotherapy not make it a requirement, but acknowledge the fact that even the literature said most of those in in a perfect setting had psychotherapy.

Tony Yen Yeah.

Sheila Rege Is that true, doctor Reddy? Am I, I am misspeaking? Is that what most of the literature had?

Shivani Reddy So I would say that many of the studies the patients were on medications and they were in terms of psychotherapy, there were only two studies that, you know prescribed psychotherapy as part as a cotreatment and otherwise it was, umm, psychotherapy as usual. So it really can't quantify how many of the patients were concurrently receiving, umm, psychotherapy, umm, were a lot of those studies, uh, so I would I I don't think that we can speak to how ubiquitous cotreatment with psychotherapy was and these trials versus with medications. Umm.

Sheila Rege So then then I stand corrected. And then the only thing I'd asked this committee to consider is because of Tuesdays recommendation that it shouldn't just be a standalone that and and I don't know if we need to put it in there, that recommend that medications continue. You know, it's not that if we if we approve this or that they can't continue on medications. Just to make that clear, but I don't know if that needs to be done from an agency standpoint or not, or if that's assumed.

Tony Yen I think that may be able to prescriptive, I don't know, like uh, I'd leave it up to you, the

individual. Perhaps I'm trusting uh, the the individual psychiatrist who's administering this type of treatment, or the provider who's administering this type of treatment to make that judgment with that patient.

Sheila Rege It wasn't. It wasn't a judgment, it was more I don't want, uh, somebody in an agency miss thinking that if this was approved, then medications would not be approved since it says failure of medications. That that's because what I was hearing from the studies was that they did continue with some medications. Is that correct, Doctor Reddy or Doctor Burns?

Shivani Reddy For for many of the studies, they patients were continued on medications. There were a handful of MDD studies where they specifically stopped the drugs beforehand. And then I think there's also the caveat around removing drugs that could increase seizure risk.

Sheila Rege Right. And and an agency medical director, you would tell us, I just, you know, I don't wanna be prescriptive on it, but if if a treating physician felt that there was a New York medication coming on that they could give at the same time as this, that it it would not be denied. That's where I was looking. Tony, if that makes sense to you?

Janna Friedly And Sheila, I'll, I'll, I'll add, I I think that also to me is important for psychotherapy as as well. You know that that those can be concomitant treatments with and may may actually be more beneficial, but but they're not, they're not mutually exclusive. I don't know if that needs to be written in the recommendation or not, but.

Sheila Rege We haven't in the past. I think I just wanted opinion from the agency medical directors that they understand what I thoughts were. Can somebody, Gary, Gary? I'm gonna jump you up to the top.

Gary Franklin Yeah. Yeah. So, yeah, thank you. I I think I agree with whoever said I think it's a little prescriptive that you know you're already dealing with a tough patient who has failed a number of treatments. We could say something like, you know, we encourage concomitant therapy, psychotherapy, and or ongoing pharmacotherapy, but not mandated to be done. And also if we say that it kind of helps us with those applications of psychiatrists that only wanna use TMS.

Janna Friedly mmhmm.

Sheila Rege I like that it is, uh. Tony, are you good with that?

Tony Yen Yes.

Sheila Rege Ah, no, not recommend we could say recommended or encouraged.

Tony Yen Yeah.

Sheila Rege I like Garry's Word of encouraged.

Janna Friedly As appropriate.

Sheila Rege As a.

Gary Franklin Great. Concomitant psychotherapy and or pharmacotherapy is encouraged as appropriate.

Tony Yen You know, I I think that's fine. It's just that it's it's. Yeah.

Sheila Rege So we and or and hide or.

Tony Yen Yeah.

Clinton Daniels Is it encouraged or not precluded like like we're not limiting whether they wanna do that as opposed to we're recommending it. I feel like those are slightly different.

Janna Friedly I would agree. I I think we we mean it's not prohibited or it's not. Umm.

Conor Kleweno Is allowable.

Janna Friedly Is allowable. Yeah, that's good.

Tony Yen Yeah, Sheila, from my perspective is that the the less that we say sometimes the the more clear it becomes is in terms of like hey, we encourage this, we would prescribe that. Umm, you know when we set kind of like very clear criteria like you gotta do this? And then up the other stuff is. Up to your judgment, right?

Sheila Rege But I like the allowable because that means they don't get a denial, and it lets that that's what that was.

Tony Yen Oh, OK, alright.

Sheila Rege I I just don't want them to get a denial if. If they're trying to also do psychotherapy. Is that, tt does anybody have heartache with the room, uh, the motion on the table to remove what Tony said? Remove that and then the additional adding note, concurrent psychotherapy and or medication treatment is allowed as appropriate. Uh, we should probably say and or antidepressant medication treatment, we don't mean heart and stuff like that.

Gary Franklin Yeah. Could I just ask Judy Zerzan, are you OK with that language for Medicaid?

Judy Zerzan Yeah, I think so. The part about encouraged is that I think it's a little more effective potentially with it. But yeah, they're not precluding, I agree. But yeah, I think that that sounds fine and actually more of the chit chatting, it can be harder, I think to get a therapist on commercial insurance, you might have to private pay since so many folks do that. So yeah, I think I think this is good.

Sheila Rege Janna would I, I know I brought you in. Anything else that you wanted? Any other

point?

Janna Friedly Yeah. Well, I I I think what I am, I'm still really struggling with is, uh, uh, that I appreciate, you know that Doctor Burns is incredibly thoughtful in the way that she applies this and and I think has raised the point that, um, in children in particular that you know the the psychiatrist at Children's Hospital may be very different than out in the in in practice and that there's a wide variability in how this is this is applied and and that is particularly concerning and children. But I also have the concern in, in adults. And so I I just I I worry that that being administered, according to an FDA cleared protocol, doesn't, umm, it doesn't mean that people aren't going to be out there in their private practices without proper training and and using this you know these these reco, these conditions are fairly broad, or the or they, the the hurdles are fairly low and we're we're lowering them, which which may be appropriate. But I just I I worry that this is going to be something that is widely, more widely used than maybe indicated and and that there's no good regulation of that, so that that's what I'm struggling with and I'm I'm not sure how to reconcile them.

Tuesday Burns I mean I would get.

Sheila Rege And to help with the what Janna I mean is is bringing up.

Tuesday Burns I mean, I would say that the one the one sort of right kind of noting this is the fact that you've already clarified the the necessity to demonstrate treatment resistance. And this is a treatment for patients in a treatment resistant depressive episode. So by default, whomever is going to be providing this treatment should be following them and managing their treatment resistant depression and demonstrate evidence of that treatment resistance. So you've outlined that you've narrowed it down to narrowed it down to people who are, you know, psychiatric providers. So at least that the worry isn't going to be about someone who isn't managing or appropriately treating their depression, it will be someone, as such, I think the trick is just also acknowledging that there might, within each practice between each practice be differences in the device that's used and how it's monitored in the training that provider has in order for it to be rendered effective. Provider X in the community versus provider A in the community can both give someone a prescription for Prozac and it's gonna be up to the Pharmaceutical industry in the pharmacy to kind of dispense that Prozac. But there can be some, you know, there can be some subjectivity between how TMS is applied between two practices. So I kind of hear what you're saying and I'm less worried about the who than the how, so to speak, and I'm not sure if that's something that can be flushed out the condition in terms of requiring certain certification or training with each provider.

Sheila Rege Yeah.

Gary Franklin Sheila, could I say one thing, Gary here, we had a situation in Olympia where I know for a fact that one of the psychiatrists doing this stuff on marketed pretty heavily to MSWs. And of course, the MSW's are not using medication, umm so I'm I'm not actually sure that everything you just said is completely true, at least in this community, as as to who is checking who's screening, who's making sure this was done, or this other thing was

not done. So I think the more guidance we put in here, like about the definition of treatment resistant depression. Uh, the better for for the, for us, for the payers.

Sheila Rege We're going to try, Gary. We're gonna keep at it. John's gonna solve all the problems. John B.

John Bramhall Well, I think about all the problems and I know about solve. Yeah. I mean, so I think so originally I'm thinking about the, so we're at the stage now of putting constraints on the availability of this therapy, UM effectively. Uh, and I'm surprised, actually, I didn't realize that ECT was just a covered benefit period. If if I'm if I'm correct and so my experience with ECT and I assist with them quite often is that it's treatment resistant in some ways an intractable depression that's treated with ECT. So so the existing policy for the agencies seem to be understanding or expecting this a clinical decision and I I so far as I know that works out in practice so the same could be said for for TMS. You could leave it unconstrained and say it's a clinical decision by the by the the clinician who's working with the patient to decide on optimal therapy. But that's very open-ended. On the one hand, I want to see, I would like to be convinced that we had constraints about who can do it and I don't just mean license provider, I mean this whole, this whole issue of training. I mean, I think we sort of ran up against this with acupuncture in the past like, well, you know, who can do it and and who's good at doing it and who can demonstrate that they know where to put the needle and who can demonstrate where they know how to put the probe that that probably should be something that is a little bit more explicit than just missing. And, and the observation doctor Burns you, I mean you commented on the downsides to pharmacotherapy right the the the side effects, if you want to call them that, it seems like if we have if we agree that this TMS is an effective intervention for major depression and we've looked at studies, thank you, Shivani, that some of them explicitly eliminate from their study protocols treatment resistant people in in a variety of ways. Some of them do so the the sort of, uh, existential question is, well, if this is an effective intervention for depression, can it not be a primary intervention? Yeah. Why would we need the agency to say you've gotta go through two cycles of pharmacotherapy before moving on to there? So that these are just sort of internal questions that, yes, I have the opportunity to vocalize, thank you, and so the three things are ETC seems to work pretty well with no constraints at the moment, could we do the same thing for for TMS? The second thing is that if it's an effective therapy for people who have not gone through any other intervention for their depression, then why would we put a constraint about pharmacotherapy? What have you? And the third thing is, you know who can do it and do they know what they're doing? And is that, is it fair to release untrained people using unclear protocols simply because they have a machine on an unsuspecting population of people with a, you know, a pretty lethal disease.

Sheila Rege I agree.

John Bramhall Thank you.

Sheila Rege No, that's. That's well said on so I think we've we've kind of brushed on training and stuff. But Gary, you had your hand up, it was that, was that just? Uh, you hadn't taken it down?

Gary Franklin Yeah, that was that. Yeah, that was that was perseverating. Thank you.

Sheila Rege Uh. Conor.

Conor Kleweno Yeah, I think this is what's been said. You know that nothing in this coverage makes anything guaranteed that the treating physician is the one following them and then doing the TMS and and to John's point, the reason you don't have sort of corner ECT places because of risk, right? You need somebody there to manage the airway cetera. Well with TMS, you don't need any of that, you can just plug one in, put it on their head and go and so I think there is more of a risk that it will not be controlled with compared to ECT. The other two questions you brought up were were excellent, John, I I think those are part of the crux of what we did often we'll deal with with these discretion, discussions.

Sheila Rege I like Gary to go ahead of me.

Gary Franklin So my understanding is that somebody walks in the psych office and they get this thing put on the psychiatrist might start it, but then they don't spend the rest of the time with them, it's I think it's monitored by other people in the office, it could be a an MA or who, who knows who? There's, there's no guidance around that at all, umm, so that makes me a little bit, as a neurologist with the slight risk of seizures that no mandate to have anti-seizure stuff in the office, that all makes me kind of nervous.

Tuesday Burns And I and I have to say that's another place where there is great variance in the community. So you will have some clinics where the psychiatrist will sit with the patient the whole time for that entire 30 some odd minute session and you will have other clinics where in fact it is aomeone with a BA, someone with a bachelors degree, a medical assistant, someone that's sitting with a patient after the psychiatrist has already, you know, determined the motor threshold, determine the location of stimulation, completed determination at the level and intensity of stimulation in the protocol. So it varies drastically. And I think that is the thing to, to kind of I would love for this, you know, committee to really to consider less about the, the treatment itself and more about like who is, who is applying it? Who is prescribing it? How it's being administered, I think that's more the worry for sure.

Clinton Daniels Does it matter who hangs out and administers it? Like what if the psychiatrist sets them up? It just, are they making any changes during the treatment, or are they just literally sitting there till it's over?

Tuesday Burns So some of the time, you know, there has to be an adjustment, let's say a patient moves, so the coil is usually kind of placed depending on the device. Some devices it's a helmet, literally the Brainsway device is a helmet and you really don't have a lot of wiggle room there. But sometimes there is movement of patient sneezes, a patient moves and things have to be adjusted. And then there are other times where discomfort might arise, eyebrow twitching, eye twitching, facial twitching or pain can come up again, sometimes because of movement and adjustments have to be made. So it's important to have the the psychiatrist nearby. But I think there there is a good span

of time, whereas psychiatrist might, as with you know, any other kind of procedural type intervention there might be a nurse or an MA in the room. And the psychiatrist maybe might go next door to talk with another patient for a few minutes. So that's definitely not within the realm of, you know, that's certainly in the realm of possibility and safety, but I think it's a matter of proximity, too, right? If someone has a seizure, someone with, you know, a ACLS certification needs to be nearby. That's sort of thing.

Jonathan Sham And I just I guess add you know when you're talking about how much to regulate this specific technique or protocol you're using, I mean just look at the data of or the effective size, the studies that showed an effect, it's pretty heterogeneous the protocols and multicenter, single center again, I realize it's done under the context of a clinical trial, but when you look at the protocols, specifically in the studies, they're not all the same and so I guess I would really. Uh. Be hesitant to overregulate, you know, switch specific protocols are being used. Because all of these showed in effect in the end.

Sheila Rege I agree. My turn. I I I would like us to, in some way and and we we could just make it very open-ended that, uh, and we could even put it on the bottom where we said allowable that the physician or or by a trained physician or something we don't have to define training. It's it's up to whoever. Uh. I talked to one of my psychiatrists who does not take Medicaid or anything, and the comment was for repeat the and in their mind they thought about, umm that somebody would have to have an improvement and I'd like Doctor Burns's comment on this, uh and improvement for at least two months and at least 50% with TMS and so I wonder if we should, I I can't see anybody when it doesn't work, any patient going through another 30 or 10. But I wonder if we if we should take a separate category, category of repeat and have something sensible in there, or just leave it up to the physician. So in my mind, I'd love to say for repeat TMS the individual should have shown at least 50% improvement, or you pick a number, I don't know what psychiatry does on on some scale for at least X number of months, 1-2 months or something you know not having somebody ohh didn't work three times, let's put you back in. Uh, because these are mentally not as stable patients and and I'm thinking of, you know, maybe more may work, maybe the mindset. So that's that's one on repeat that I would like us to consider. And I can I can type in wording in the chat. And I just, I'm trying to make this bigger here, Is a covered benefit with conditions, I'd love to say, by adequately trained so I TMS is administered according to an FDA cleared protocol by an adequately trained physician, I mean can we just say that?

Laurie Mischley I don't know what that really says. I think everybody considers themselves an adequately trained physician.

Sheila Rege Oh, just I'm thinking. Sorry. I'm thinking of adding it after protocol, not as a.

Josh Morse In the notes.

Sheila Rege No, no, I after protocol. So TMS is administered according to an FDA cleared protocol by an by a trained physician, let's just say by a trained I don't know, how do you, how do you say that? But.

Janna Friedly That's probably not going to eliminate anybody really.

Conor Kleweno Yeah. I mean, unless you have some adjudicating body that's gonna certify, I don't know how that's gonna work.

Sheila Rege So then we should just leave it out. OK? I'm OK with that. But I and we do say initial, but and we'll come come to the repeat, I'll, I'll add something. The other thing, and I'd be interested in the experts opinion, I know there was something recently is what I got heard some new technology recently developed when neuroimaging like an MRI is now being recommended. I don't think that's recommended for all and, um, we didn't have any data on that, but you know, so I don't think we can say anything about imaging. In this, because I don't think we, I I mean, I haven't even discussed that. So forget what I said. So forget training, forget neuroimaging. We'll just try and figure something out for repeat. Laurie is laughing at me. Laurie, what would you like to say?

Laurie Mischley No, I I I find myself also going around in a couple circles here.

John Bramhall Well, Doctor Burns is, is there any regulation in this that we could pick on, I mean so so it credentialing in bigger systems credentialing serve this function right? And so if someone wants to do, I don't know plasmapheresis they they have a they show a credential that they've gone to a course or something. And and bigger institutions have more constraints, as you know, there's always the chance that in this kind of therapy can be a one off if someone who's not in a big institution. Is there anything objective that we could use as a qualification for someone to be doing this therapy?

Tuesday Burns That that's a really good question. Yeah, because there's so many folks that are going to be in a private practice that are not affiliated right with the hospital and I would say a couple of things, umm one option could be tying something to medical society for TMS. There could be an option to more accurately use wording to specify that it is a psychiatrist with training in neuromodulation. Umm. And to demonstrate that you know, someone might have to demonstrate that they did either a visiting fellowship or took a CME course. There are many of those out there. I mean, I think you might get into the weeds about determining which ones going to be in an acceptable one, but there are many ways in which people in the community can get appropriate training that's not from the device manufacturer itself. I mean, I think deciding where to put people, where to kind of direct peoples that's harder because there are many to choose from, some better than others, but we could certainly specify that they undergo a continuing medical education training for brain stimulation. Some of these folks have not, as I said at the beginning, some of these folks have or at the younger generation and this is part of their resident psychiatry residency training. You know, I received ECT training and psychiatrists and see if it's teams came after my training so then I went separately after the fact. Umm, we don't want to be that limiting, but I I certainly think it's really appropriate to ask that folks do some kind of CME training and that it be prescribed by a psychiatrist that is one of the requirements that most of the commercial payers have that it's prescribed by a psychiatrist, not just a general physician.

Janna Friedly Is there any precedent in in prior decisions to specify that that any kind of training requirements for for treatments or specialty?

Josh Morse The one that jumps to mind is whole exome sequencing. Where I believe, you said there had to be a referral from I I can look it up. That's the one that jumps to mind where it wasn't a, a referral from anybody it had there were some a specialty I think referenced in there.

Janna Friedly But no, no, no other one where we've specified any kind of training requirements to use a technology?

Josh Morse Training requirements? Not not that's jumping to mind.

Jonathan Sham Me, in general, I mean that would be under credentialing under whatever institution, no matter how big or small you fall under. I mean that that is typically the governing body for your ability to do a procedure at that and then institution. Might be out of scope for this?

Sheila Rege I think it's I agree with John that it's out of scope. I understand they may be once you know some small shops somewhere that that do it. But I I can't see, I I can't see a way of putting that in is. So let's go back to our language. OK, let's let's take a straw poll. Janna, based on does anybody wanna say anything about training? If you do want us to spend more time on training, yes, spend more time and no means we're good with it. Can you type in yes or no on whether you want to spend more time talking about adding some training requirement. I don't see anybody with a yes, so I think, think we're going to leave that. Umm. Does anybody want to do, what would I get any support in trying to say retreatment to be a separate category or you're OK just with this? Leave this generic and leave it up to the treating doctor? I would like I typed it in kind of to, say, repeat TMS for MDD, major depression disorder in adult patients is a covered benefit with conditions and then add that there's been some improvement.

Conor Kleweno I think that's reasonable, Sheila.

Sheila Rege So Josh, if you could type a whole different? Yeah, what I just said there on that chat, can you see it?

Josh Morse Yes, I'm.

Sheila Rege And when I say the above criteria met for initial treatment.

Josh Morse OK. I will go back and correct this. I'm just going to get the words out here.

Sheila Rege No, that's good. Josh, would it bother you if Chris speaks while you're typing?

Josh Morse No. Uh.

Sheila Rege Chris, go ahead.

Chris Hearne I think uh, adding specific criteria for improvement for retreatment in theory makes a lot of sense, but I do worry that defining what the appropriate amount of of improvement we should look for or ask for is a little bit tricky. 50% sounds like a good

round number, but you know, I can imagine individuals who have treatment resistant depression and maybe they got a course of this treatment and they had a 30% improvement and that could be a big difference in their quality of life and that that this wording excludes that sort of patient. So I'm just a little bit unclear how to, how to, where to put that line I suppose?

Sheila Rege Could we just say some improvement or significant improvement or something like that and leave it subjective?

Chris Hearne Yeah, I think I think that actually sounds pretty good. Just leave it it they, they can't have gotten worse and they can't have stayed the same.

Sheila Rege So say so it would be under #2. What would, what would we like significant improvement or some improvement?

Laurie Mischley Some evidence of improvement.

Sheila Rege Some of it I like that some evidence of improvement.

Janna Friedly I.

Josh Morse Replacing the 50%.

Janna Friedly I.

Sheila Rege Correct, 50% or more by some evidence of.

Janna Friedly I would have take out the word some, I don't think you need some, ust has shown evidence of improvement. I do.

Sheila Rege OK, evidence improvement. And the improvement in symptoms are maintained. Is that reasonable? And I'm just going by what it was a curbside just talking to somebody.

Janna Friedly I.

Gary Franklin It's it's. This is Gary. It it seems like we ought to really be putting the pressure on the this is not a cheap therapy to use validated instruments to demonstrate this improvement, not just somebody sticking their finger in the air and say ohh they're they're better. I mean it seems like we want to start collecting some information on these patients at baseline and follow up. Whether or not they it request additional treatment.

Sheila Rege What?

Gary Franklin So if you said say sum and don't you don't leave in the part about using validated instruments. I'm not sure we're gonna have left.

Sheila Rege I'm open to suggestions Gary of how to put that. I mean I I was thinking of how, you

know, putting in some using some rating criteria, but I went away from that.

Janna Friedly Well, the way you had it before was greater than 50% improvement substantiated with one or more standardized rating scales for depression. If there's concern about 50% improvement as the as the, the, the, the cutoff, then you, you you could say 30% improvement. I I'm not sure what what we're basing that on, but that's where it's hard to come up with a specific cutoff I think for this. But I I suppose that's what we we look at in the in the studies.

Conor Kleweno I mean, if we wanted to be formal, each of these instruments should have an MCID, right, that's associated with them? So if we if somebody wants to pick one or two or whatever, this should be something.

Gary Franklin Right.

Janna Friedly And MCID's are a little bit problematic because they're based off of populations, not individual patients.

Conor Kleweno Well, it's all problematic, right? But but I think the instruments to if an instruments developed, it should have by definition and MCID inherent to it.

Janna Friedly Yeah.

Conor Kleweno Right. They have if they develop one, there should be something ascribed. It's a 30 point scale and MCID for this is too. I I I agree with you, it's population based, but theoretically that if it's a an appropriately designed instrument, it should have a, an increment with it.

Gary Franklin That there had been instruments used in psychiatry.

Sheila Rege I like Laurie's. I like Laurie's, or we could say will you type this in clinically significant improvement.

Janna Friedly I.

Sheila Rege Do you wanna just say using a validated instrument or there's some standard rating scale?

Janna Friedly Well, I I think Sheila the problem, I think it is that when you get into this then it becomes really who, who defines this so I could see a payer saying Well, I don't think this is clinically significant, but then the provider saying yes, it is clinically significant and if it's not defined by a specific number and with there's been other treatments where we have specified you know in order for injection procedures, for example thinking about lumbar radiofrequency ablation that you have to get 50 or 80% improvement in the diagnostic blocks in order to qualify for an injection. So there are there are examples where we've used a specific cutoff it's it's usually based off of, umm, you know, evidence, I think where we're struggling here is we don't clearly have evidence that will help guide us on when somebody should have a repeat, umm, a repeat course

and and at what that wasn't really fleshed out in this in this report, with the evidence that there is.

Sheila Rege Let's ask Doctor Reddy doctor Reddy in in the evidence, when they when you were looking at the studies, was there any study that had a definition for retreatment was was 50% ever used?

Shivani Reddy We did not look at uh, we did not look at population specifically for retreatment. UM, I I do wanna point to table 4 where we have the MCIDs of for various validated scores, including the three major depression scores that are used, but we didn't specifically look at a population that had failed TMS and then was being retreated, so unfortunately that that evidence isn't available.

Sheila Rege Well. Can we, I mean clinic, I I like Laurie's clinically significant improvement. Uh, and leave it up to whether, I'm hearing Janna says she would prefer 50 or some number in there. OK, let's type in OK, as is or user number. Let's see what that straw poll is. Ohh, I'd number John has John B. Tony, you're on. What do you mean by you prefer using MCD?

Tony Yen Alright, so so the. I think you know each of the validated scores actually have, uh, and probably saying this incorrectly to me, uh minimally, clinically, can't even see this stuff, anyway, the minimal clinically important difference, umm I think that's a quantity that I think we're seeking that is is, is is making a difference or not. So just using some sort of validated score is this clinically meaningful like we can sometimes change the score by one point and that's not gonna be any it's it's not meaningful, we're changing numbers, but we're not changing perhaps was considered clinically validated to be a difference whether that be on the Hamilton Depression score or whatever their score that we might want to use. I think people do use different stores scoring systems over here and so I just think that there there should be some sort of and I do I I do take Janna's comments very seriously that that makes sense on a population level, but that's really what we have, I think to really kind of ring to bearer, just in some sort of objective sort of way this actually has to make a meaningful difference but what does that meaningful difference is that? I'd like it to be something rather than your, is that clinically meaningful difference is at one point is that two points. I just want to make sure it's it's it's it's achieving some sort of threshold.

Jonathan Sham But as Doctor Reddy said, we didn't this data that we reviewed didn't evaluate this population for this indication, right? I mean we don't know whether patients who maybe just for one point shy of the MCID, uh wouldn't benefit from subsequent treatment. It's just that's a that's a whole in in the data we reviewed. So I I guess, I think that pushes me more towards not including a number because it's not validated for this particular indication.

Tony Yen Yeah.

Sheila Rege Laurie put her hand up.

Laurie Mischley Yeah, I don't manage depression in the office and I know that in, in a lot of conditions

what we do for research studies like these outcome measures, we there are a lot of outcome measures we use in research that we don't use in clinic. My question is how routine is it when you're treating a patient with depression to be administering these skills before and after any treatment. I mean are we asking providers to change how they manage the disease and start to incorporate these scales, because of this.

Tuesday Burns I can say that everywhere I practiced TMS, we have used validated scales. It varies whether it's a MADRS, HAMD, a PHQ 9. But I would say every, every evidence driven clinical setting is going to be using an objective rating scale, and those who maybe wouldn't typically do that because of lack of academic interest or research data collection, that sort of thing are going to actually are currently being required at that by payers by commercial payers. Commercial payers, will require that as well as an outcome measure. It's usually the PHQ 9 that they're requiring, which is typically every two weeks but it's often done once a week because TMS is happening five days a week. So it's not far from practice and it should be the standard for sure. I think the idea is clinically I would say that you would not typically rechallenge with TMS if someone did not have a response with their first series of TMS. So I think clinically speaking, providers won't do that. The idea is what is a response? Again that can that can be subjective for sure.

Sheila Rege I think I like the just validated instrument that leaves it open to, you know, somebody likes something, some new new great thing comes up and DSM is not changed in time. So personal personal level like that, I think the big issue we're all struggling with is, uh, whether to define a number or not, correct me if I'm wrong or just a clinically significant. Umm. So let's do a type in if you want Include number, avoid number. We get one or the other as a choice and see where everybody is. How many of us want to include a number? Can you do a hand raise?

Conor Kleweno Or can we from Tuesdays is the is the number easily attained that we can? Is that a reasonable thing from a practicing clinician that we can get?

Tuesday Burns I I I think it varies. I don't think there's a standard. I think it could range between 30 and 50% improvement. I'll say that much.

Sheila Rege And we had no evidence that we're we're we're kind of making this up so.

Tuesday Burns Right. It's exactly it's. It's a little arbitrary without that.

Conor Kleweno How about relative to the instruments that you mentioned?

Tuesday Burns So I would say relative to that, typically speaking, when you're talking about a validated scale like a HAMD, MADRS, or PHQ 9, I would say in terms of demonstrating clinically significant improvement it I think the HAMD is 30% improvement, I think others are 50, so I think that's where I get those numbers, but I think that the bottom number would probably be 30 and that would probably be the lowest number that would be needed.

Conor Kleweno It looks like Doctor Friedly may have solved our problem so that we can move along. I liked her comment.

Sheila Rege Doctor Reddy, was there something in, in literature, or you're just saying that's a informational point?

Shivani Reddy That that was the MCID for the HAMD was 30%, so that was where I think Doctor Burns was getting her was pulling that number from.

Sheila Rege OK. So Janna, will you guide us on how you would like to change that? Or Josh is already taking care of it? I think we all agree.

Janna Friedly Yeah. Or a 30% or more, I guess I did not guess it's 30, 30% or more improvement. Or minimally or minimally clinically important difference on a validated scale. I think that.

Sheila Rege Like.

Janna Friedly Puts a number, but also provide some flexibility for if the clinically important difference is different than that. Yeah, and you know, and in most studies, you know, thinking about pain studies, you know, 30% is a reasonable, you know, sort of score for for improvement in pain anyway, which I know is different but but I think that's reasonable based on what what we're seeing, I don't know, you know, PHQ 9, I think is probably more widely used clinically, maybe not in these these studies, but I don't know what the MCID is for the PHQ9.

Sheila Rege Yep. Janet is this? Is this what you had in mind?

Janna Friedly Yeah.

Sheila Rege And it's assumed it's a validated scale for depression.

Janna Friedly I would clarify that validated scale for depression.

Sheila Rege I think there should be a comma after difference. I know we were supposed to take an hour lunch break. How does everybody feel about that versus eating lunch while we're doing this.

Josh Morse I think we had 15 minutes for lunch.

Sheila Rege Yeah. OK.

Josh Morse Yeah.

Sheila Rege Let's go back to our our wording, because we usually take a break anyway, but I wanna make sure. Yeah, I would, I agree with Conor. I'd love to finish. But. So we have we have that we have the repeat, we have the bugaboo about children where the medical directors have said we could be silent.

Josh Morse So we can delete this part, is that right?

Sheila Rege Right can how many would prefer to be silent on children? Please type in silent or say no, for silent or silent means, yes.

Judy Zerzan And one other piece for Medicaid that Josh reminded me of is that there's EPSDT, which means that any service a kid needs, we have to evaluate and so it would absolutely fall under that and so if we got a request, yeah, we would evaluate for medical necessity and cover. Yeah.

Sheila Rege OK. So the first one should say Ohh initial treatment is is, that's good. Just to it almost seems like to be grammatically correct. Oh, I'm fine with that. You the agency medical director saying help us clean it up. Would you like to say initial TMS for treatment or confirm in adult patients? And then up to 30. That's fine.

Josh Morse I see where you're going. I can clean this up so.

Sheila Rege We could take a break while that's been cleaned up and I I would like a a shorter break as possible at or we can take the 15 minute.

Janna Friedly I think given how far behind we are, we should take a very short break if we take one.

Sheila Rege Yeah, just go run and grab a bar or something. So are we OK? It is 20 minutes past. Are we OK? Coming back at 30 minutes past or even 5 minutes. I like John John B5 minutes. John Brown. Thank you. 5 minutes.

Judy Zerzan Hey, Josh, are you on?

Sheila Rege I hope everybody agrees that was a break to review the, the language. If you could look at what's projected on the screen. Thank you everybody. I'm really sorry we're going later. I will take a hand raised for any proposed changes. Josh, could you screen down? Keep going down. OK. And now we have. I will take the agency medical director first, Judy, in case there's something we're missing.

Judy Zerzan I just wanted to make sure and I'm not sure if it was at the top, but to make sure that it's for treatment resistant depression. I think this just says major depression disorder.

Sheila Rege What? Would failure of at least two different anti medications you would like to say treatment resistant and that. That was what we was correct.

Judy Zerzan I don't know. We. Yeah, it. I mean, it's sort of the failure of two different medications gets there. But. Yeah, I don't know. I don't feel super strongly about it.

Clinton Daniels That was my question as well, so I'll I'll over my hand. I was curious if it was redundant to say treatment resistant or if that would maybe also help guide clinicians for what we're looking for for people that should meet this.

Conor Kleweno I think the redundancy is helpful.

Sheila Rege Where would you put it?

Jonathan Sham It.

Clinton Daniels Right in front of the bold language, maybe treatment resistant, major depressive disorder or depression disorder.

Conor Kleweno Agree.

Jonathan Sham Is treatment resistant MDD an independent ICD 10 code?

Tuesday Burns No. It is not.

Sheila Rege Tuesday, shaking her head.

Tuesday Burns It is not a different code no.

Jonathan Sham I guess that's the only reason I might keep it the same, because it's not, you know you're naming entity that is doesn't like I guess exists on its own, and you're defining it later in the the the policy here. And we shouldn't make up a new a new medical entity here.

Sheila Rege Yes.

Josh Morse And you put this right after it and say major depressive disorder that is resistant to treatment, just say it a different way. And that's not redundant, I guess that's a question for me.

Laurie Mischley Pharmacological treatment to be. Technically correct.

Tuesday Burns So it will say like.

Laurie Mischley I mean, this is another.

Tuesday Burns Well, treatment resistant depression is like if you were getting treatment from a psychiatric treatment resistant depression is it's a well-known term. It's just the definition can vary. So it just depends on how precise or how flexible you're trying to be with your language.

Sheila Rege I in that case we can say uh we can, we can just say, confirm treatment resistant. I I I don't think that we're creating a new term. Jonathan, I see where you're going with this, but I think it's common language, if it's common language among psychiatrists and it's not pulling.

Jonathan Sham Yeah, yeah, I guess I I think the the common language is fine. It's just I guess I wouldn't be worried about misidentifying what we're trying to treat if it's very clear subsequently, you know the, the protocol and and what's necessary to have treatment covered.

Sheila Rege I had one other question for Tuesday. Does the it doesn't matter if depression is, uh, accompanied by psychosis? Or does it? Is that a? Exclusion criteria.

Tuesday Burns It's not an exclusionary criteria per se. It depends on the severity, I will say that much, but that's something that's a that's a clinical kind of decision making process. You know we the ICD10 codes would be like the difference between F 33.1 F 33.2 or three, but that would be a clinical decision to make.

Sheila Rege Yeah, let's not confuse it, Janna. Sorry.

Janna Friedly Um I have two comments. One does the word confirmed need to be there? Is there any reason for that it seems like an unnecessary word, but to me that's minor. But and and and then just from a grammar standpoint, TMS for the treatment of treatment resistant sounds funny. So I I was wondering if maybe we even needed for the treatment of um in and and just say TMS for treatment for treatment resistant and major depressive disorder, if you want to simplify. But the main question I had was, do we need to specify for the repeat TMS they number of treatments as we did for initial treatment? Is it the same protocol? Is there a need to specify that? Maybe that's a question for the agency and Gary.

Gary Franklin Well, this the 30 treatments was kind of a guess, so I don't know what the heck to say about this one. I guess I would leave it up to the clinician since we don't have any guidance on that or we could say the same thing, you know, putting the same number.

Janna Friedly Or we can leave it the way it is, I just, I wanted to clarify if that was something that was important for us to specify.

Laurie Mischley I'd be inclined to.

Sheila Rege We could specify up to 30. Up to 30 treatments.

Laurie Mischley I was going to say I'd be inclined to keep it consistent. It doesn't make sense to have a boundary for one and not for the other.

Sheila Rege Yeah. So repeat the same thing. Any other discussion on this?

Gary Franklin Just for completeness, there is a lot of talk in the literature about, you know, should you avoid the treatment in any particular kind of in patient, say people that have preceded preexisting epilepsy or anything like that and there's no clear cut guidance on that, so I wouldn't say anything about it.

Sheila Rege I would agree, Gary. I I did see some when I was just doing my own kind of research, something about psychosis, severe psychosis, but I think leaving it up to the treating physician. Is, uh, if everybody is OK with this, we're going to be, uh, as a process coming up with a final vote and remember, we will get time to look at it again, uh, it won't be finalize till the next meeting, when we look at it and the public will be able to comment also in case you missed something. Josh, would you like to put that in better language for me?

Josh Morse I'm sorry Sheila, put in better language, the two-minute break. Or.

Sheila Rege Should we do another two-minute break? I, we've always said we would do another two-minute break and we could, but this is not the final final. We then.

Josh Morse Yeah, I have a quick question, I guess for Doctor Z, maybe for Andrea, about the age 18 or older or and for you, Sheila, I guess so is the implication that you're not making a decision for people under 18 and how will that affect our UMP population? Because for Medicaid, I think we know that for people under 21, umm, with EPSDT, Medicaid can make decisions about that, but for the UMP population, I don't think you're saying it's not going to be covered for people under 18, it would be kind of the discretion of the. Is that right?

Judy Zerzan Yeah, that's what I that's how I would interpret this is that it's just silent on before age 18 and so yeah, UMP can make its own decision or we can make criteria if we want to for kids.

Josh Morse Great then maybe we need to make a note of that in the notes here. That'll make it much easier to interpret going forward.

Judy Zerzan That is a good idea.

Sheila Rege So let's keep this projected. I am going to give everybody now, protocol says 2 minute break Umm, so we should probably, even though I would like to rush it up, we should take a 2 minute break with everybody sitting here with the cameras on and looking at this. Now we could ask Josh to go up and down.

Josh Morse Yeah, I mean. I believe that's that's the whole thing right there right now.

Sheila Rege My timer says it has been 2 minutes. I think uh, since the agency has decided, when we say determination does not apply to age 17 or, or younger and younger, and nobody's gonna assume that it's a covered benefit for OCD, GAD, we don't have to say for any age group TMS is not covered for any age group for the treatment of other behavioral we don't need to say that.

Josh Morse No, I think that's a good call out. You want to put this note above that.

Sheila Rege Umm. You could just say TMS is not covered at any age group for the treatment. Because I think that was the intent. I know Clinton, you have your hand up you may have a better suggestion.

Clinton Daniels No, my thought was on a different item where it says tobacco use disorder, I wonder if that should instead say smoking cessation. So I haven't, I haven't seen the phrase tobacco use disorder in in the report.

Sheila Rege Yeah. What did the report say?

Clinton Daniels I think it was smoking cessation.

Shivani Reddy Smoking.

Sheila Rege So the report said, smoking.

Shivani Reddy Smoking cessation.

Sheila Rege Smoking cessation. OK, then let's be consistent, good point. Are you good Clinton with that?

Clinton Daniels Yes, thank you.

Sheila Rege And Jonathan, you are next.

Jonathan Sham Just a question for Tuesday. Umm in clinical practice after the kind of second round of TMS, how common is it to have subsequent rounds after that?

Tuesday Burns I think it really depends on sort of the the clinical situation. I would say folks who had a history of recurrent major depressive disorder, the thing to prepare for is the fact that they may have recurrence in the future, whether they've been treated adequately with the medication or with TMS or with ECT. Those treatments, none of them are going to reduce the risk of subsequent major depressive episodes. So there are patients, especially now that we're 10 plus years into very clinically common use of teams where they might have a relapse every few years, so the likelihood of the lifetime only needing one or two courses of TMS in someone with recurrent treatment resistant major depression is pretty low.

Jonathan Sham That.

Tuesday Burns So personally, I've seen patients that then come back, you know, a couple of years later they're depressive relapse and then we have to manage that with the new course. So I guess it depends on like when you're thinking about lifetime kind of prevalence or you're thinking about our particular window of time.

Jonathan Sham The reason I ask is I guess I I just want to be careful we don't get boxed in by the language of um, 30% improvement, uh, the most recent TMS course I can imagine someone getting a second TMS course not having as much improvement, but they still really benefited from the first time and then years later trying to come back and because on the second round they didn't have a 30% increase, there's the limited in coverage, so I wonder if that can be softened and we're trying to select, you know, we're trying to prevent overuse, but select for people who can benefit, perhaps identifying for people who had that initial benefit would make sense, understanding that you may not get as big of a difference on subsequent treatment episodes.

Sheila Rege Jonathan, what would you suggest? Or I mean does is the minimally clinically important difference cover it?

Jonathan Sham So I I'm perhaps there's eliminating the most recent team scores or at any point in TMS

treatment or something like that. If we're gonna keep the 30% by just with any TMS treatment, perhaps something like. Yeah, with any prior or prior.

Janna Friedly Yeah, with prior TMS treatment individual 30% or more improvement.

Jonathan Sham And that way we kind of strike a balance between, you know, limiting and and keeping it open for folks.

Sheila Rege So you don't want most recent, you want, prior.

Jonathan Sham Correct. Yeah. At any point, they just have to, it has to have worked at some point in their treatment course.

Laurie Mischley Just. On the same topic, a point of clarification for 3. Is it sufficient to have in the chart notes? Yeah, it helped for more than a couple months last time. Or do we, are we asking for documentation of this validated measure at the six-to-eight-week mark as a prerequisite to moving forward? If someone doesn't have something, some proof of 30% benefit that, I mean, what are we asking for here exactly?

Tuesday Burns I would say, clinically speaking, it might be difficult to kind of track that number if someone does well at the end of their treatment, maybe they've had 50% improvement in symptoms, but they go off to Hawaii because they're feeling great they don't have depression for the first time, you might not get that number at a 6 or an 8 week interval and that would be a shame to then lose out on the fact that you responded so beautifully. So that is tricky and a really good thing to think about.

Sheila Rege I would like some, I I hear what Tuesday saying, but you know you you can't just keep going through this treatment, if if your duration is not, uh, you know, I mean, it's just, seems like, maybe at that point something else should be tried but. That's just me as a radiation oncologist.

Gary Franklin Yeah, let's say.

Tuesday Burns And I think he's moving.

Sheila Rege Umm. But anyway I'm I'm going by order and I I spoke out of order. I should not have. I should put my hand up Laurie. Yeah, yeah, I can't hear you. I'm sorry.

Laurie Mischley I said my question.

Sheila Rege Should anybody have any, we should actually talk about that does just on this point is anybody raising their hand on this point, the improvement in symptoms #3.

Gary Franklin Yeah.

Sheila Rege Who? Who was that speaker?

Gary Franklin Gary.

Sheila Rege Gary.

Gary Franklin So so if somebody does 30% well on the first treatment and 5% are not much on the second treatment, you you don't want to keep doing it if it doesn't keep working, so I don't know why you wouldn't refer to the most recent treatment.

Sheila Rege Gary, I actually, I I know what Jonathan was trying to do. I would prefer the most recent treatment, that was my original language. Because at some point I would think you'd get refractory.

Jonathan Sham But I guess that's what I was asking about the the timeline, you know, if you if you follow immediately with the second course but then wait three years, would you expect that refractory period to be over if for them to get the benefit again? Again this is apparently not you know a hole in the data that we have but.

Sheila Rege But three years they become a new patient. It becomes an initial treatment again. No, but.

Jonathan Sham What two year? Two years, whatever it may be, I assume some period of time. That's why I was kind of getting a sense from Tuesday of what the standard course is for repeat treatments. Umm, because you just you can't, you can't, uh, consistently get 30% over and over and just statistically speaking that's gonna be impossible. So we wanna just open it up to folks who it worked on.

Sheila Rege And I I think minimally clinically important difference gets you out of the 30%. No?

Jonathan Sham But I that's from baseline though, you know, I guess it's the idea of main maintenance therapy versus initial therapy. You know if if you know from from very bad to OK and then if you're maintaining OK, you're not seeing an improvement, it's just you're still maintaining an OK risk score, so again, this something Tuesday can remark on but but again, it's just not getting caught up in mandating and improvement in the numbers each time if you're at an acceptable level of acceptable score.

Tuesday Burns So I think a good way to think about this is if you if you really categorize it based on current episode or not. Because I think what what I'm hearing is a worry about, OK, they showed some improvement but then within a few weeks they relapsed. So that's not really really remission and that's really still probably the same depressive episode. That's not remission and then all of a sudden in new depressive episode has started that would really be considered and for anyone clinically you think about like this three to six month window of time where you know you would really lump it all into that one depressive episode. So perhaps it's about thinking how you categorize or distinguish different depressive episodes because there isn't necessarily a a refractory nature meaning response to the in the first episode, then a year later they had a relapse and the response wasn't as great because there's so many confounding variables. But then, you know, three years later, they have a depressive relapse and they, you know, want to try TMS again, I wouldn't want them to not have access, I wouldn't want them to not have access to that. So I think it's distinguishing, you know, the idea of keep trying. You know it's, I keep trying in a one episode because no, of course you wouldn't do that. But

	is it, they did well in responded in an episode, but not every episode has responded to it. It's still fair game. It's the same thing with medications, we'll go back to old medications at someone may have not responded to in the past, and each episode is so different. So to eliminate it tool from a very distinct episode doesn't isn't really clinically what we would do. What we wouldn't keep going with TMS in one episode if someone wasn't responding.
Sheila Rege	I'll, I'll have Gary come in and this is just to the point of kind of the response being just any prior treatment or the most recent.
Gary Franklin	Yeah, I I think I would go with most recent just because I don't wanna keep doing this for $5 to $15,000 if it's not doing anything.
Sheila Rege	So you're also OK. Thank you. Conor, will you speaking on this?
Conor Kleweno	Yeah. I would just say I'm fine with either, really. I'm probably more.
Sheila Rege	You're tired.
Conor Kleweno	More, more in line with Gary. I would also just say so from grammar, if you at least means not arrange right. So it's gonna be at least six weeks or at least eight weeks.
Sheila Rege	Umm.
Conor Kleweno	So just.
Sheila Rege	Yeah, that makes sense at least six weeks is fine.
Josh Morse	Do you wanna?
Conor Kleweno	And then I do I I I did think we're gonna end at 1:45, so I did. I need to leave soon. I didn't know if we're gonna have a vote. I do wanna make sure I vote.
Sheila Rege	Yeah, I'm gonna do a vote. Let let's do a vote first on. People just type in if they would prefer any prior treatment or most recent just type in what you'd like.
Josh Morse	You want language about the episode.
Sheila Rege	No. So so it's just, you know we right now have with prior any prior treatment but just on that not Janna just no no, six weeks most recent. OK. Thank you, Janna. Janna. Jonathan, you're gonna stay with it prior. Does everybody kind of opined that's here? So based on that, we're gonna remove prior and make it most recent. And then I think everybody was fine, but at least six weeks was there a desire to change that or is that OK?
Conor Kleweno	I just meant that if you say at least you can't have a range, that's all I was saying. Six weeks is great.
Sheila Rege	OK. Any further discussion before the final vote? OK. If everybody is good at but this

	language just say approve type in approve or they more discussion. I think that is it correct.
Josh Morse	I think so. There are still two questions to answer after you vote on this about Medicare coverage.
Sheila Rege	Correct and, but I think this is the most one. Anybody who has to leave. I'm really sorry we ran overtime. Let's do the two questions. Let's go through our decision guide. Go back to that now that we have the language.
Josh Morse	But you will do that after you do a final vote here. Can we do a quick final vote?
Sheila Rege	Yes.
Josh Morse	Val, can you show the vote screen?
Val Hamann	Yes. Do we wanna breakdown again?
Sheila Rege	Yes. So we're gonna do. Let's do a MDD.
Val Hamann	OK. Uh John Bramhall.
John Bramhall	I've lost my screen, sorry.
Sheila Rege	MDD covered with conditions or not covered. Unconditional.
John Bramhall	Yes, covered it's covered with conditions. Sorry. Lost my screen covered with.
Sheila Rege	Actually, John Bramhall, why don't you do all of it?
John Bramhall	The whole thing.
Sheila Rege	But yeah, so then go to the next one, GAD.
John Bramhall	So GAD not covered smoking not covered, TMS for repeat, TMS has to repeat treatment MDD that was covered with conditions, TMS for OCD not covered and PTSD not covered.
Val Hamann	And SUD.
Sheila Rege	So everything else was not covered, OK.
John Bramhall	Not have it also correct.
Val Hamann	OK.
John Bramhall	OK. Sorry, sorry.

Josh Morse	Yeah, and Val, we don't need to vote on the repeat piece. That's all. All of one. Yeah. No, that's OK. Thank you.
Val Hamann	OK, Clinton Daniels.
Clinton Daniels	Covered with conditions MDD.
Val Hamann	OK.
Clinton Daniels	And the rest will all be not covered.
Val Hamann	OK.
Val Hamann	Janna Friedly.
Janna Friedly	Covered with conditions for MDD and the rest are not covered.
Val Hamann	Chris Hearne.
Chris Hearne	Covered with conditions for MDD and the rest is not covered.
Val Hamann	OK, Conor Kleweno.
Conor Kleweno	Same, covered with conditions for MDD and the rest not covered.
Val Hamann	OK.
Val Hamann	Laurie Mischley.
Laurie Mischley	The same cover with conditions for MDD and not covered for the rest.
Val Hamann	OK.
Val Hamann	Sheila Rege.
Sheila Rege	Uh, covered with conditions for MDD and not covered for the rest.
Val Hamann	Okay. Jonathan Sham.
Jonathan Sham	Same covered with conditions for MDD not covered for the rest.
Val Hamann	And Tony Yen.
Tony Yen	Same, uh, covered with conditions for MDD, not covered for the rest.
Val Hamann	OK.
Sheila Rege	Do you pull out a decision aid up? We have just a little more the the document you'll

pull up. We just have a little more checking against other guidelines, and there's one more thing I can't remember. I'm trying to pull it up.

Josh Morse Medicare coverage.

Sheila Rege Right.

Josh Morse So I'm sharing my screen here. You guys did not have this teed up.

Sheila Rege So what we do is after we come up, based on the evidence, we look at other carrier decisions and making sure that we are still comfortable. Conor, this won't take long.

Josh Morse So the clinical practice guidelines are in the report on page 100 by a true page count or 76 if you're looking at the page numbers.

Sheila Rege And I think when I saw this in the packet, we were pretty, I think what we did today was consistent. Does anybody have any comments on this? I will take a motion to move on.

Conor Kleweno 2nd.

Josh Morse Thank you.

Sheila Rege I can't make. OK go on to the next one.

Josh Morse And there is no Medicare national coverage determination. So you do not need to review a national coverage determination to see if your policy aligns with that or not.

Sheila Rege OK. Do we have anything else we need to do?

Josh Morse No, you have voted. You've made an excellent decision. Thank you very much. I think you have covered all the bases here.

Sheila Rege Thank you, everybody. Happy Saint Patrick's Day and take care. Bye.

Janna Friedly Thank you.

Josh Morse Thank you all.

Clinton Daniels Thanks.

Gary Franklin See you later. Thank you.

Josh Morse Thank you, Doctor Burns.