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

Health Technology Clinical Committee Public Meeting

June 12, 2020

DR. SHEILA REGE: Welcome and thank you again for your patience while we're getting up and getting used to this. The only people in case you want to be on or not Mika and John we can see your smiling faces and I actually like it. So hello. And I am actually going to turn it over to Josh for HTA program update.

JOSH MORSE: OK. Good morning thanks you for joining this morning thanks Dr. Rege. And we will do a roll call here in just a moment and I'll get the first side presentation setup. Brit can you do a roll call for members.

BRITT REDICK: Yes, I can. Just one moment. OK. So Dr. John Bramhall?

DR. JOHN BRAMHALL: Yes, I'm here.

BRITT REDICK: Dr. Janna Fridley?

DR. JANNA FRIEDLY: I'm here.

BRITT REDICK: Dr. Chris Hearne?

DR. CHRIS HEARNE: I'm here.

BRITT REDICK: Dr. Conor Kleweno?

DR. CONOR KLEWENO: I'm here.

BRITT REDICK: Dr. Laurie Mishley?

DR LAURIE. MISHLEY: Present.

BRITT REDICK: Dr. Sheila Rege?

DR. SHEILA REGE: Yes.

BRITT REDICK: Dr. Seth Schwartz?

DR. SETH SCHWARTZ: I'm here.

BRITT REDICK: Dr. Mika Sinanan?

DR. MIKA SINANAN: Here.

BRITT REDICK: Dr. Kevin Walsh?

DR. KEVIN WALSH: Here.

BRITT REDICK: And Dr. Tony Yen?

DR. TONY YEN: Here.

JOSH MORSE: Great. Thanks Brit. Thanks everyone. OK so good morning.

A little housekeeping here: It's always a good idea to have other windows closed during the webinar to I think minimize the burden on your P.C. If you're participating by phone, there's some instruction here about how to mute and unmute yourself and enter the audio pin if you haven't done that. Webinar Controls - I think most of us may be familiar with it. Those should be on your screen. You can raise your hand or send us a message by chat. If you have any questions. All right.

Today's agenda includes the topic of stem cell therapy for musculoskeletal pain and previous meeting business today will be limited to the minutes from the May 15th meeting. The consideration of comments on the two topics that were decided as draft decisions on May 15th are currently out for public comment and the committee will have those comments and those final decision questions on their agenda for July 10th.

So meeting reminders; this is being recorded, a transcript of the proceedings will be made available on our website at some point after the meeting. It does take a few weeks for us to develop that transcript. When participating in discussions please try to remember to state your name and of course speak into whatever microphone you are using today. And to provide public comment during today's meeting we will announce the public comment period and ask for people to let us know if they wish to provide comment and we will take some time to ask for your names, we get spellings correct and any conflict of interest you might have.

So a little background about the program, multiple state agencies participate in this program and work to identify topics and implement the policy decisions that come from this program. These programs include the uniform medical plan and the Medicaid program and both of these programs are managed through the Health Care Authority. Also participating is the Department of Labor and Industries and the Department of Corrections participates and uses the decisions from this program. These agencies implement the determinations from the Health Technology clinical committee within their existing statutory frameworks. So again, the HTA program is administered through the Washington State Health Care Authority. It was created in 2006 through legislation and it designed this program to use evidence reports in this panel of clinicians to make coverage decisions for selected medical procedures and

tests based on their evidence. The evidence available for safety, efficacy and cost effectiveness. The purpose of this program is to help ensure that medical treatments, devices and services that are paid for with state health care dollars are safe and proven to work.

The program provides a resource for state agencies that are purchasing health care, we develop scientific evidence based reports on medical devices procedures and tests and we facilitate this independent clinical committee of practitioners to determine which medical devices, procedures and tests are appropriate for coverage. There are many ways to participate in the program, the HTA program has a website on the Health Care Authority web pages shown here the U R L is on this slide. Anyone can sign up to receive notifications from us via email using what's called our gov delivery system and you can find information about that on the Health Care Authority Web site. Anyone may provide public comment on topics that are proposed for review, on key questions as they're developed for each topic, on draft and final reports and on draft decisions. And here at these public meetings attendance at the HTCC public meetings is open to anyone and anyone may present comments directly to the committee. Additionally, anyone may petition for a review of a health technology.

Here is the calendar for 2020, we are meeting today June 12th to consider stem cell therapy for musculoskeletal conditions. On July 10th, there will be a short meeting of roughly an hour typically to complete the review of the draft decision from today in the draft decisions from May 15th. And we have September 18th reserved for a committee retreat and if you have questions you can contact me at any time or visit our web pages again on the Health Care Authority Web site we have program contact information there as well. Thank you.

DR. SHEILA REGE: Thank you Josh. This is Sheila Rege. And since we can't see each other if when we start if we could just, if you comment, we could just put our name and whether we're HTCC committee member or you know kind of how we're here. Josh has brought us up on schedule, I am going to go around the room again alphabetically just get introductions. Just giving a one sentence about ourselves and as a warning. Josh and Britney went into this view and I'm gonna ask any agency medical directors I see Jason's on, Gary's on also to introduce so be prepared. John would you be willing to start?

DR. JOHN BRAMHALL: Yes of course. So I've been a member of this committee for a few years now. I have a day job as an anesthesiologist, one of the associate medical directors at UW Medicine Harborview campus. It's a pleasure to be here this morning. Thank you.

DR. SHEILA REGE: Thank you. That's John Bramhall. Janna would you like to go?

DR. JANNA FRIEDLY: Sure. I'm Janna Fridley. I am a physiatrist at the University of Washington my clinical practice is at Harborview Medical Center and this is my second year on the committee.

DR. SHEILA REGE: Thank you. Chris.

DR. CHRIS HEARNE: My name is Chris Hearne. I'm a nurse practitioner. I work in little medicine for Swedish.

DR. SHEILA REGE: I hear Chris. Conner... And tell us how you say pronounce your last name? Klewano it's what I think, but I'm not sure.

DR: CONOR KLEWENO: Sure. Yeah. My name is Connor Kleweno . I'm an orthopedic trauma surgeon at the University of Washington Harborview campus and this is my first year on the committee.

DR. SHEILA REGE: Thank you Conor. Laurie?

DR. LAURIE MISHLEY: Yeah. My name, I'm Laurie Mishley. I am a naturopathic physician and a nutritional neuro epidemiologist.

DR. SHEILA REGE: And then we have Paul Manner today. Paul would you mind introducing yourself? I'm just going alphabetically.

DR. PAUL MANNER: Sure. I'm an orthopedic surgeon at University Washington. I specialize in hip and knee replacement and I also served as an editor of "The Orthopedic Journal, Clinical Orthopedics and Related Research".

DR. SHEILA REGE: Right. Seth Schwartz would you mind going?

DR. SETH SCHWARTZ: Yeah, I'm Seth Schwartz, I'm a neurologist at Virginia Mason here in Seattle. I've been on the committee forever - for about nine years.

DR. SHEILA REGE: Like you said. Mika?

DR. MIKA SINANAN: Hi, Mika Sinanan. I'm a general surgeon based at UW Medical Center Mob Lake and I've been on the committee for two and a half years.

DR. SHEILA REGE: Kevin?

DR. KEVIN WALSH: Hi, I practice family medicine at a community health center in Ellensburg Washington.

DR. SHEILA REGE: Tony, would you mind going next Tony Yen?

DR. TONY YEN: Sure. I'm a hospitalist at Evergreen Health in Kirkland Washington. I'm also the Chief Medical Information officer of there as well. And I've been on the committee for several years, I've kind of lost count.

DR. SHEILA REGE: And I think I've got all the committee members. I'm Sheila Rege, I practice in Eastern Washington Tri-Cities, regional medical director Northwest cancer clinic, auto radiation oncologist and president of the College of radiation oncology. Josh Do you mind if I put you on the spot.

JOSH MORSE: Not at all. Thank you. This is Josh Morse. I'm the Health Technology Program Director. I've been with the program since 2011 and I'm a section manager as well here at the Health Care Authority in the fee for service side for Medicaid. Thank you.

DR. SHEILA REGE: Thank you. Britney. Would you mind just a short introduction because it's weird not to know who was on the phone.

BRITT REDICK: Oh yes. So this is Britt Redick. I am a relatively new addition to the program. I am the program manager and happy to be here. Thank you.

DR. SHEILA REGE: I know Jason you're gonna be presenting, would you mind starting with an introduction.

DR. JASON FODEMAN: My pleasure. I'm Jason Fodeman, I am internist, primary care doctor and I'm an associate medical director at L and I and have been there for a little over a year. Thanks.

DR. SHEILA REGE: Thank you. I'm not gonna call on but if anybody from the agency would be willing to provide just a one sentence would you mind going. I'm looking at the list here.

(CROSSTALK)

DR. JUDY ZERZAN: I'm the chief medical officer at HTA. Hello. Good morning.

DR. SHEILA REGE: Thank you Judy. Anybody else?

BRITT REDICK: I have to go and unmute them. I'll unmute Dr. Franklin.

DR. GARY FRANKLIN: Gary Franklin, L and I. Thank you.

DR. SHEILA REGE: Britney, are we done?

JOSH MORSE: We also have Christine Masters our HTA program specialist. She is on the webinar as well.

DR. SHEILA REGE: Thank you Christine would you like to say something. You've been with us a long time and I know you're behind the scenes magic with Josh and Britney.

CHRISTINE MASTERS: Well that's awfully sweet of you Dr. Rege. I'm Christine Masters. I've been here almost as long as Josh and I am excited to be working in this new environment...of virtual meetings.

DR. SHEILA REGE: Britney or Josh anybody else that we missed on introductions? I have just been the first meeting after meeting that I know of here virtually.

DR. GARY FRANKLIN: This is Gary Franklin. Joel McCullough, another one of our associate medical directors is also on.

BRITT REDICK: And I can unmute. One moment.

DR. JOEL MCCULLOUGH: Yeah. This is Joel McCullough. Like Gary said I'm Associate Medical Director at L&I.

DR. SHEILA REGE: Welcome. Thanks, Joel. Alright. Well, I'm sorry if I missed...we missed anybody. If we could pull up the May meeting minutes and we've all have a chance to look at this and so absent any corrections, I would take a motion to approve these minutes?

DR. JANA FRIEDLY: So moved.

(Inaudible.)

DR. SHEILA REGE: All...Josh is it OK with you if we just take anybody who opposes these minutes please pick up now?

Is that OK or do you need to take roll call?

JOSH MORSE: I...no I think we're OK doing that as we did last time. We'll assume everybody is approving unless we hear a "nay" or an "abstain"... "abstention" and...

DR. SHEILA REGE: So, any names? Any names, now? Any abstains? Josh back to you.

JOSH MORSE: OK, and BrItt will be recording the votes today so she may be asking for clarity around the vote count as we move forward on the more complicated votes.

DR. SHEILA REGE: Thank you. And now we're entering the stem cell therapy for musculoskeletal pain.

Before we begin, we have a clinical expert, Paul Manner. Would you mind...I'm going to give you just a spotlight again on your expertise with this and thank you for being with us. Anything you wish to say a minute before we start just on your expertise, not on data or anything like that.

DR. PAUL MANNER: Sure. OK, so I'm an orthopedic surgeon that specializes in hip and knee replacements so, my area of expertise is arthritis. As...in my younger years, I was also at the NIH at the cartilage biology branch of NIAMS. I was there for about five years and I was specifically looking at cartilage biology and in fact, working on stem cells in the lab to build cartilage. I also did some research while...when it came to University of Washington where we were looking at various matrices and substrates for stem cells specifically for rebuilding cartilage. And then as in my later guise, as an editor, obviously, I see a fair number of manuscripts that focus on arthritis, joint replacement and cell biology specifically cartilage biology.

DR. SHEILA REGE: Thank you. Thank you very much and we are lucky we also have Conor Kleweno, who is an orthopedic surgeon who is also on our committee. And Conor feel free you know, to pipe up as we go on in discussion. Right on time if it's OK I'd like to turn it over to the state agency...the agency representatives.

JOSH MORSE: Great. Thank you and Jason Fodeman will be making the presentation.

DR. JASON FODERMAN: Alright, let's hope you guys are handing over to me. Perfect. Can everybody or somebody at least see that?

UNIDENTIFIED: Yes.

UNIDENTIFIED: Yes.

UNIDENTIFIED: Yes.

DR. JASON FODERMAN: Oh, perfect. Right, I just wanted to...just wanted to make sure. And everybody can hear me OK?

JOSH MORSE: Yes.

DR. SHEILA REGE: Yes, very clear. Thank you.

DR. JASON FODERMAN: Alright. Perfect. Thanks so much. We had to do several dry runs of this so I'm so glad it paid off.

So, alright. Thank you so much, Josh and Dr. Rege. And thank you so much for everybody's time today. So, I'm Jason Fodeman. I'm an Associate Medical Director. And today we're going to be talking about stem cell therapy for musculoskeletal conditions. The safety and efficacy of stem cells from peripheral blood or bone marrow for hematopoietic reconstitution in conditions such as leukemia and lymphoma has been well established. This is not what we will be talking about today.

What we will be talking about today is this. The number of US businesses marketing direct-to-consumer stem cell therapy has increased rapidly in recent years. A 2016 report found that nationally, 351 businesses were advertising stem cell therapy treatments at 570 clinics across the country.

Some of these clinics specialize while others take a broader approach offering stem cell therapy for up to over 30 diseases and injuries. Commonly marketed conditions include degenerative disorders, neurological conditions, spinal cord injuries, pulmonary disease, heart issues, urological pathology, and cosmetic use. Orthopedic disorders and pain were the two most commonly marketed conditions. So, why are we here today? Why review stem cell therapy? Stem cells are being targeted for a large broad range of conditions. These disorders have a high prevalence and there is controversy and uncertainty about the role of stem cells in treatment. Yet despite this, there is aggressive marketing and promotion of these products and patients may be vulnerable to this direct marketing. Agency medical directors have concerns. We have concerns about safety...

Dr. SHEILA REGE: I just lost...this is Sheila Rege, I just lost Josh...Jason, sorry. Jason, Yeah. He's away from the microphone probably.

DR. GARY FRANKLIN: Jason, are you there? He's still talking.

UNIDENTIFIED: No. He's still talking?

DR. GARY FRANKLIN: He is. He doesn't know it yet. I don't think. Let me see.

DR. GARY FRANKLIN: I'll text him.

UNIDENTIFIED: He's offline. It says he's offline.

DR. JASON FODERMAN: November 27...What?

JOSH MORSE: Jason, we lost you about two slides ago. Your audio went out.

DR. JASON FODERMAN: Oh.

JOSH MORSE: Back on the readings slide.

DR. JASON FODERMAN: Oh, really. I had no idea. Can you hear me now?

JOSH MORSE: Yes.

DR. JASON FODERMAN: Alright. Can you tell me what slide to go back to? I'm so sorry. I'm not sure what happened.

JOSH MORSE: It's back to the safety, efficacy...yes, that slide.

DR. JASON FODERMAN: This one...did you...do you want me to start with the beginning of the slide? You didn't hear anything?

JOSH MORSE: I think we got about halfway through.

DR. JASON FODERMAN: OK. Thank you for letting me know. I'm sorry for the inconvenience.

So the Agency Medical Directors have concerns. Concerns about safety at a high level, we have concerns about efficacy at a high level and we have concerns about cost high as well. The Food and Drug Administration, the FDA has concerns as well.

In March 2017, the New England Journal of Medicine FDA leadership "Outside a few well-established indications, the assertion that stem cells are intrinsically able to sense the environment into which they are introduced and address whatever functions require replacement or repair is not based on scientific evidence.

In November 2017, the FDA released two comprehensive policy documents to provide additional clarity to industry and other stakeholders and layout its current thinking.
In light of this new guidance, the FDA has given lower-risk products 36 months of enforcement discretion. The FDA has incorporated new concepts and tools to help small investigators and firms and the FDA is encouraging investigators to engage

early on in the process with the agency.

As far as regulations of human cells, tissues, and cellular and tissue-based products HCT/Ps, the FDA utilizes a tiered risk-based regulatory framework and I...and we included an overview of that framework below for your convenience. Irrespective of the regulatory framework, what we need to know is does it work. Here's the evidence. The evidence report looked at four key questions.

What is the evidence of the short and long-term efficacy of autologous or allogenic stem cell therapy?

What is the evidence regarding short and long-term harms and complications of autologous or allogenic stem cell therapy? Is there evidence of differential efficacy, effectiveness, or safety of autologous or allogenic stem cell therapy compared with conventional treatment options, surgery, or no treatment/placebo? And then finally, what is the cost-effectiveness of autologous or allogenic stem cell therapy? According to the evidence report, there are currently not established guidelines or standard protocols to isolate stem cells, to concentrate and process them, and the number to inject. The evidence report found 14 RCTs across the spectrum of musculoskeletal conditions.

Most of these, 12 were for knee osteoarthritis, one was for lumbered degenerative disc disease and one was for Achilles tendinopathy.

Overall, the quality of evidence was deemed poor. RCTs predominantly had a moderately high risk of bias. The majority of studies were for knee osteoarthritis with limited research beyond that and in general, studies did not abide by the proposed standards for reporting of clinical stem cell studies. As far as efficacy and effectiveness, there was significant heterogeneity. There was heterogeneity as far as patient populations, stem cell sources and preparations, use of adjunctive biological components, and heterogeneity as far as pre and post-injection therapy is.

The sample sizes were small. There was variable reporting of co-interventions and post-treatment rehabilitation protocols that could impact outcomes. Follow-up rarely exceeded a year limiting the ability to assess the long-term impact of stem cells on pain and function and the need for subsequent interventions was usually not assessed.

As far as safety, overall the quality of evidence was poor as well. Adverse events were poorly specified and poorly reported. Small sample sizes in the majority of studies are likely too small to identify anything but common side effects and most studies had follow-up of less than one year likely preventing the ability to evaluate long-term risks of stem cell therapy such as neoplasm or other long term consequences. The MMWR published a case series of cases of serious infections from clinics in Florida, Texas, and Arizona in patients after they received injections with stem cells. The injection sites included the knee, the shoulder, the cervical, and lumbar spine. The infections were severe infections including osteomyelitis, septic arthritis, and epidural abscess.

Eight out of 12 of these patients became bacteremic and all 12 patients were hospitalized. The causative agents included E Coli, Proteus, Enterococcus, Enterobacter, and Citrobacter.

The article concludes "this investigation highlights the serious potential risk to patients of stem cell therapies administered for unapproved and unproven uses other than hematopoietic or immunological reconstitution." In December of 2019, the FDA issued a public safety alert on stem cell and exosome products. The alert highlighted serious AEs among multiple patients treated in Nebraska with exosome products. According to the FDA, other potential safety concerns of stem cells include the cells moving from the injection site and changing into unintended cell types and or multiplying, the cells not working as expected, and tumor growth. With the current use of stem cells, the FDA warns that adverse events are likely more common than recognized given there is no reporting requirement of AEs when these interventions are performed outside of clinical trials.

In September of 2019, the FDA warned "the US Food and Drug Administration is concerned that some patients seeking cures and remedies are vulnerable to stem cell treatments that are illegal and potentially harmful. And the FDA is increasing its oversight and enforcement to protect people from dishonest and unscrupulous stem cell clinics while continuing to encourage innovation so that the medical industry can properly harness the potential of stem cell products." The FDA advises patients to be sure that if they are considering stem cells, the stem cells are either FDA approved or in
a study under an investigational new drug application in IND. For key question number three, differential efficacy, effectiveness or harms, no evidence was identified by the evidence report.

And for key question number four, cost-effectiveness, no evidence was identified as well.

So how much does this cost? In the United States, treatment protocols vary based on the clinic and the treatment provider. A one-time stem cell intervention utilizing blood drawn from the patient can cost $1,500. Other protocols involving stem cells from bone marrow or adipose tissue can cost as much as $15,000 to $30,000. To learn more about the costs of stem cell therapy, researchers contacted 273 out of 317 US centers offering direct-to-consumer stem cell therapies for musculoskeletal conditions. Using a simulated 57-year-old male with unilateral knee osteoarthritis, the authors found the mean price of a unilateral stem cell knee injection was $5,156 with a standard deviation of $2,446 and the prices ranged from $1,150 to $12,000.

CMS, the Centers for Medicare and Medicaid Services does not have a national coverage determination for stem cell therapy for musculoskeletal conditions, and the payers deem it investigational and experimental. The Agency Medical Directors' Group recommend that stem cell therapy for treating musculoskeletal conditions is not a covered benefit. And we base this recommendation on insufficient evidence of efficacy and effectiveness, safety concerns, and a very high cost especially if use

lightens as well as commercial payers deeming it investigational and experimental. Any questions? And again, sorry for the technical difficulties (AUDIO DISTORTS).

Thank you. Any questions?

DR. MIKA SINANAN: Hi, Mika Sinanan. Can you tell me what the prevalence of direct-to-consumer marketing in Washington State is? Is it...is that something that's growing? Big issue? I personally haven't seen the advertising but I haven't looked for it.

Excellent question. So, as you may know, I've only lived in Washington for a little over a year but in that time I have seen advertising for this. I think there's been some significant advertising in the Seattle Times. I've seen I believe several of those and I honestly I just haven't been looking for it just come across it but there definitely have been some prominent advertising in this area.

Mika, I can tell you this...I can tell you that patients ask about this all the time. This is out there. Patients will often come in with printouts from websites. There are several centers in Seattle that market this pretty excessively.

DR. CONOR KLEWENO: Yeah, this is Conor Kleweno. I agree with Paul. This is on major local news stations with advertising as well as local newspaper releases. I've seen both and I've seen it frequently and increasing.

Yeah, that's exactly what happens on news segments on this as well, on this topic.

DR. JOHN BRAMHALL: Jason, this is John Bramhall. Thanks for your presentation. It's very very enlightening.

Can I ask you if someone...if a patient, a potential patient or consumer is persistent they see these advertisements in the Seattle Times and they go to a facility and perhaps that's not going to be covered by any financial management organization. Is other opportunities in let's just say the Seattle area for someone to be enrolled in a trial? Are there any locally functioning trials?

DR. JASON FODERMAN: So, that's a great question and I think this issue has come up before as far as our decisions and how it impacts trials and I don't want to you Know, misspeak Josh or perhaps you can add on but my Understanding is that you know, or any decision that we were to make as far as the HDA today that that wouldn't impact the ability to participate in a trial and their separate policies for that.

Is that correct, Josh?

JOSH MORSE: Hi. Thanks, Jason. Yes, that is correct.

DR. JOHN BRAMHALL: Right. Thank you.

DR. JASON FODERMAN: Great question. Thank you.

DR. SHEILA REGE: Any more questions? This is Sheila Rege. Any more questions for Jason about utilization outcome? Thank you, Jason. I think we will now go to the open public comment. Are there any scheduled and...

I'm gonna turn it over to Britney to unmute and direct us.

BRITT REDICK: Yes, thank you. So we have one so far. Christine if you can confirm (INAUDIBLE) Leslie Emerick?

CHRISTINE MASTERS: I'll go ahead and let you know. Yes, Leslie Emerick.

DR. SHEILA REGE: If you could tell us intro...in your introduction tell us you know, why you're here, if anybody's paying for your way here before...and your full name for the record and thank you for coming or thank you for virtually coming.

LESLIE EMERICK: Sure. My name is Leslie Emerick.

I'm the Public Policy Director for the Washington Acupuncture and Eastern Medicine Association and they do pay me as their public policy director. So, thank you for the opportunity to speak this morning. My public comment isn't related to the stem cell therapy because this is an open public comment period.

So I just wanted to make sure that the committee was aware that our association has sent a letter to the members of the health technology clinical committee as well as the health care authority and the Washington State legislature about concerns that we have about a data bias against non-pharmacological alternatives. And I'm not gonna spend a lot of time talking about the details of the letter but I just wanna make sure that all the members of the committee are aware of the letter and have seen it.

Also, I just wanted to make you aware that our association has petitioned the health care technology committee for re-review of acupuncture for migraines. We've submitted 36 new studies to be reviewed and I really would like the commission to please consider how you are making non-pharmacological opportunities or options available for patients.

We fully support evidence-based medicine and when we meet the standards of safety and effectiveness and cost-effectiveness but yet are not allowed to re-review some of the decisions it creates a lot of frustration and we just perceive that there is a bias towards pharmacological options as opposed to ones that aren't. So that's all pretty much I have to say today but I'd like to know how we can get this on your radar screen. Is this something that can be brought up during work session in the future?

Is there a way that we can have the committee review how you are looking at these different options because it has a huge impact like for instance the migraines one regions quit paying for acupuncture provider and headaches. You know that's affected thousands and thousands of patients in Washington State and it's very

disconcerting and even when we're asking for a re-review we have concerns that you know, the standards that you use and the studies that you get from pharmaceutical companies which are extremely well funded tend to overshadow decisions that are being made.

So basically I'm just trying to get this on your radar screen and trying to figure out a way we can have a discussion about this in the future. Thank you.

DR. SHEILA REGE: Thank you, Leslie.

Thank you. Thank you. Thank you for bringing that to our attention and we...you know, I know our agency staff are very very vigilant and so we will...we will talk about that and thank you for bringing it here today. Any...any other comment? Will we...this is a question for staff. Do we have a way to monitor the lines in case somebody comes in with a public comment if we move on earlier than 9am to the evidence report?

Yes, we do have a way to monitor people joining the webinar either by phone or online.

OK, so we then we'll be you know, make sure we monitor that even while we go to the evidence report. And Erica and your team since we have ten minutes if we...if you wouldn't mind introducing your team or have your team members introduce each other and Brit you can unmute Erica starts since I think you're presenting and then if Andrea's here or Shelby. So I'll let you direct us, Erica. Just a one-minute introduction on who you are and just trying to get to know people since we can't see you or see each other in-person. Thank you.

I think Erica might be just getting set up. Andrea or Shelby did you wanna introduce yourselves?

ERICA BRODT: Hello, This is Erica. Can you hear me?

Yes.

Yes, and that's a cute picture.

Oh, goodness that's my little boy who's not so little anymore. Let me see. I need to fix my screen here but real quick I'll just...Yeah, I'll just introduce myself. Erica Brodt. I am Vice President and a Research Associate here in Aggregate Analytic and I'll be giving the report on stem cell therapy for musculoskeletal conditions today. We're honored to be a vendor (INAUDIBLE) here we...starting with (INAUDIBLE) research back years ago and we're one of the first evidence centers. So we're just very privileged to be part of this process.

DR. SHEILA REGE: Thank you, Andrea are you there and is Brit...Will you be able to unmute Andrea?

DR. ANDREA SKELLY: Hi, thanks Brit and Dr Rege. This... Can you hear me?

DR. SHEILA REGE: Yes, this is Sheila. Yes, I can.

DR. ANDREA SKELLY: OK, great. Yeah. Yeah, this is Andrea Skelly. I'm President of Aggregate Analytics. I'm an epidemiologist by education and as Erica mentioned we have been an evidence vendor since 2007 and we're happy to be able to present our findings today.

(CROSSTALK)

SHELBY KANTNER: Yeah, I'm Shelby. I am the Research Assistant with Aggregate Analytics.

And Mark is our statistician and he's not gonna be here.

DR. SHEILA REGE: And Christine and Brit you will let us know if anybody comes on the line for a public comment but if it...will go ahead Erica.

ERICA BRODT: OK, great. And I wanna make sure everyone can hear me and they can see the full slide correct.

DR. SHEILA REGE: Yes.

(CROSSTALK)

ERICA BRODT: OK, great. So we'll get right into some background here. So musculoskeletal diseases are common and can lead to chronic pain, disability, and reduced quality of life. In 2015, more than half of US adults reported having a musculoskeletal medical condition and for many of these people it affects their ability to work.

The most common conditions leading to disability are back or neck pain and arthritis and chronic joint pain. Many musculoskeletal tissues have a limited capacity for endogenous repair and for many with repeated conditions effective non-surgical treatment options are limited. So there has been a lot of interest in and research on the use of cell-based therapies including the use of stem cells to stimulate repair and regeneration of tissues for these kinds of conditions.

And as Jason explained and showed previously there's been a dramatic increase in the number of clinics offering such therapy. So a very basic introduction to stem cells.
I think most of us probably understand that stem cells are the basis of all tissues and organs. They have three general properties which distinguish them from other cells in the body as defined by the National Institute of Health. This is the ability to self-renew in order to ensure a steady supply of replacement cells for those lost to disease, injury, and age. They are unspecified and they have the ability to differentiate into diverse specialized cell types.

So beyond these three critical properties or abilities those stem cells vary widely in what they can and cannot do and in the circumstances under which they can and cannot do certain things.

So in the next slide, I'll go into more detail regarding types of stem cells. But in general stem cells are often described as embryonic but these exist at the earliest stages of development. Tissue-specific also referred to as adult or somatic stem cells. And on this slide, that term is highlighted because these are the types of stem cells most commonly described for the treatment of the conditions in this HTA. And recently induced pluripotent stem cells which are engineered from specialized cells.

So stem cells sources maybe autologous. That is comes from the person themselves and is re-injected or allergenic which are cells from a donor. The biological activity may differ between these two general sources. So you'll notice that throughout the report we have stratified our data according to these sources.

So let's table on this slide provides an overview of kind of a classic type of stem cells that have been described and is organized from top to bottom according to the degree of cell potency. So those cells at the top of the table turns totipotent and pluripotent have the highest potency. They are undifferentiated with the ability to generate all cell types. So they're really the only types of cells that meet the NIH definition of a stem cell described on the previous slide. At the very bottom of the slide, unipotent cells on the other hand are technically not even stem cells so they can only differentiate into one cell type.

So in the middle and it's like (INAUDIBLE) taking up most of the slides. These are multipotent cells and these are the types of cells of interest for the purpose of this HTA.

As mentioned on the previous slide, tissue-specific or adult or somatic stem cells are the types of stem cells used by the trials in this report. They are a type of multipotent stem cells meaning they have already differentiated into specialized cells but they do have the potential to produce some or all of the mature cell type contained in a specific organ of tissue such as musculoskeletal tissues. There are two ty...basic types of tissue-specific stem cells. Hematopoietic which give rise to all types of blood cells and non-hematopoietic which are circled there in red on the slide which are also...they're commonly harvested from bone or adipose tissue and demonstrate an ability to make bone cartilage in fat cells.

So these non-hematopoietic stem cells are what is being used in the trials included in this HTA. Collectively they are referred to as mesenchymal stem cells though its important to note that the term mesenchymal stem cells, mesenchymal stromal cell, and mesenchymal multipotent cells are broadly used in the literature and maybe and accurately applied. We'll talk a bit more about terminology later as well.

Also of note, the concentration of truth stem cells contained in an extracted sample regardless of source may be small. So culturing them could be important to increasing the quantity of stem cells to a therapeutic level. For the US Food and Drug Administration regulate tissues and human cells intended for implantation, infusing, or transplantation via the Center for Biologics Evaluation and Research.

And there's more information on this process in the full report. To date, it talked

about previously the only stem cell therapy explicitly approved by the FDA for use in the United States consists of hematopoietic or blood stem cell transplantation from bone marrow for the treatment of leukemia, lymphoma as well as specific blood-related disorders. And as mentioned on the previous slide because there is low concentration of stem cells and tissues they likely need to be expanded in order to have a quantity that may be therapeutic. However, there are no established therapeutic level and culture expand itself for orthopedic applications are not FDA-approved at this time. The exception would be if the treatment was part of an FDA-approved clinical trial.

By contrast, minimally manipulated cells for homologous use and not combined with another substance are not regulated in this way and do not require FDA approval for use. So these minimally manipulated cells are generally the type of cells described as being used by many of these stem cell therapy clinics. Again, because of the distinction between culture expanded and nonculture expanded cells. We've also stratified our results based on those two types of preparations. So given the properties described previously stem cells have the theoretical potential to facilitate repair and regeneration of tissue. They are further thought to have anti-inflammatory properties and may support and stimulate other cells to enhance the repair process.

Some have referred to the use of stem cell therapy as part of quote regenerative medicine. These properties make them very attractive and promising approaches for the treatment of a variety of medical conditions for which non-surgical treatment options are limited. However, stem cell therapies have the potential to create some unique and serious risks depending on the processes for obtaining, manipulating, and reinserting them into a person whether from autologous or allergenic sources. And the potential for adverse events is influenced by multiple patient factors such as comorbidities, medications, age, and disease processes for example.

So some of the potential safety concerns in addition to the potential failure of cells to work as expected include and again, these are mentioned by Jason administration site reactions or infection, abnormal immune reaction, undesirable bone formation, the ability of cells to migrate and differentiate into inappropriate cell types or even the excessive multiplication of cells which may cause or promote tumor growth.

So although the safety of stem cells derived from peripheral blood or bone marrow or hematopoietic reconstitution is well established the extent to which this would carry over to other applications is unknown. Conventional treatments for musculoskeletal conditions vary by ideology. Common treatments include conservative strategies such as physical therapy, exercise, weight reduction or pharmacological management as well as minimally invasive injection.

These treatments may improve some burden and facilitate natural innate healing processes but are not considered curative. Surgical options are a current standard. Excuse me. For many, however, they may not be feasible in all patients. So we identified two clinical guidelines both of which essentially concluded that there is a

lack of evidence from high-quality clinical trials to recommend the clinical use of mesenchymal stem cell therapies for joint or tendon regeneration. The American Society of Interventional Pain Physicians limited their guidance to low back pain only and basically suggested that biologics follow the FDA-recommended draft guidelines. The Australasian College of Sports Physicians evaluated mesenchymal stem cell therapy for various other musculoskeletal conditions listed there.

And recommended that their use be limited to...rigorous trials or individual therapy. So we also identified two expert consensus and research statements one put out by the American Academy of Orthopedic Surgeons and the National Institute of Health as well as the International Society for Stem Cell Research and both suggest that stem cell therapy may have potential but that further research is needed and clinical recommendations cannot be made at this time. Regarding coverage policies just to reiterate what Jason said previously there is no national coverage determination from CMS and across the four bellwether payers you see there mesenchymal stem cell therapy is considered investigational and not medically necessary for any orthopedic application.

Just wanted to take a minute and talk about some of the challenges we encountered in trying to interpret the stem cell literature and the studies included in this report. So first, the terminology is imprecise, inconsistent, and sometimes is inaccurate. The consensus opinion is that the term stem cell has been overused to encompass uncharacterized minimally manipulated cell preparation as well as tissue-derived culture-expanded cells. And in fact a 2018 AAOS NIH consensus statement I mentioned on the prior slide recognizes that stem cells have unique properties not met by this minimally manipulated mixed cell preparation and they actually suggest the term "cell therapy" be used instead. So meeting the International Society for Cell Therapy criteria must be cultured in the laboratory and cultured cells are not currently FDA-approved.

There are no established guidelines or standard protocol for how to isolate, concentrate or process stem cells or on the number to inject. And this is reflected in the inconsistent and inadequate reporting of these types of variables in the literature. Lastly, some processes for curing and expanding mesenchymal stem cells may be proprietary. So the bottom line is that this leads to a lot of heterogeneity making it difficult to compare across trials and you'll hear me say that more than once throughout this report. So our key questions are pretty standard and ask what is the evidence of short and long-term efficacy and effectiveness, harms and complication, differential efficacy and effectiveness or safety and cost effectiveness of stem cell therapy compared with common treatment options.

And as mentioned previously we found no studies that met inclusion criteria that address key questions three or four so all the results that follow will pertain only to key questions one and two. We included adults with the musculoskeletal conditions listed here to receive autologous or allergenic stem cell therapy in an outpatient or office setting compared with conventional nonoperative and surgical treatment as well as placebo or surveillance.

Our focus was on the primary outcomes you see listed here and on our safety data when available. I would like to note that we did not include comparisons of different cell types, concentrations, preparations, or procedures for efficacy and effectiveness. We did include them for safety when applicable.

And for a list of all the inclusion and exclusion criteria you can see table six in the full report. So as usual all comparative studies that we identified were assessed individually for risk of bias using this criteria. The top three are specific to randomized control trials and shortcomings in any of these areas can introduce bias.

So Appendix E contains the risk of bias evaluation for all the studies if you're interested. And of note, P series were all considered high-risk bias. So while the previous slide indicated what we do for individual studies this slide shows what we do across all studies and I think most of you are fairly familiar with our process of grading strength of evidence which is based on HRQ's recommendations and our application of grade. So the overall strength of evidence is assessed separately for each primary outcome.

After assessing across all studies reporting that outcome these five criteria. So risk of bias, consistency, directness. For this report, all outcomes were considered direct. Decision and publication bias. For this report for the individual outcomes, it was difficult to assess publication and reporting bias given the small number and the type of studies identified though we considered it unknown. And again just to reiterate, SOE is not set for any secondary outcome.

So to recap a systematic review process we identify eligible studies via a formal systematic search of the literature, assess the risk of bias of individual studies, synthesize and analyze the data and come to a consensus regarding the strength of evidence across comparative studies by primary outcome.

The final strength of evidence rating for each primary outcome represents how confident we are that the evidence reflects the true effect. So from a total of almost 26,000 citations identified by our search, 51 studies across 56 publications met inclusion criteria form the evidence base to this report. As part of our hands searching we looked at prominent cell therapy...a prominent cell therapy website and cross checked all study cited with our search results and our inclusion-exclusion criteria. In addition, we identified two trials on clinicaltrial.gov that provided results.

So getting to the results.

So this table gives an overview of the evidence-based by condition and key question addressed. There were a total of 14 RCTs identified across 16 publications as shown there with the green circle. 12 of these were in Knee OA and one each in degenerative disc disease and tendinopathies specifically Achilles tendinopathy.

Evidence for the remainder of the conditions came primarily from case series, those are the red diamonds. Case series of single arm registry study as well. Or poor quality cohort studies, which is the yellow square.

For this presentation, I'll be focusing on those three conditions at the top of the table, for which we have RCTs. And on primary outcomes, common across the RCTs within those conditions. I'll spend most of my time on evidence where we have low strength of evidence. If you're interested, data for secondary outcomes and cohorts or case series can be found at the very end of this slide presentation in an appendix.

Beginning on slide 50.

So I will begin with knee osteoarthritis for which we have the most data by far and by way of orientation for this and all conditions, I'll be presenting the data first by stem cell source autologous, then allogenic and within each of those categories by non-culture-expanded followed by culture-expanded cells.

Five small trials were identified that evaluated autologous, non-culture-expanded stem cells. Four used bone marrow derived cells and the fifth used adipose-derived cells. The total sample size across all trials was 200. So I just want to point out, we're talking about pretty small trials here.

I'd also like to draw specific attention to the fact that the grade of Knee OA varied across the studies and in some cases between groups within studies. Comorbidities were not reported, which is a problem as I talked about the effect it might have on safety. Neither were concomitant medications. The extent to which studies verified specific types of STEM cells and the cell characteristics also varied as did the total number of cells injected. Most trials included other biologics such as PRP and post-treatment care varied from nothing to structured physical therapy.

So again, we just would like to underscore the fact that there's a lot of heterogeneity between these studies and it's unclear to what extent some of these additional factors could have impacted outcomes.

So beginning with function, so autologous, non-culture-expanded stem cells. The only outcome we could pull was the 12 month change score for the KOOS across only two small trials with a total of 83 patients. Comparing bone marrow derived cells with hyaluronic acid, there were no differences between groups with the exception of one of the subscales, the KOOS spot, which slightly favored stem cells, though the confidence interval was wide and approach zero. That's the third row down in the figure. However, all the data was considered insufficient.

Just before I move on to orient you to these spots part, we do with the risk of bias of each of the studies, the specific intervention, whether it's bone marrow, adipose-derived, et cetera. And what the comparator treatment is. So that's all there for your information.

So for pain, results according to the VAS and the KOOS pain scales were pooled across at most four trials with a total of 182 patients, and there were no differences between groups. So the main change from baseline at any time point. The strength of evidence for this outcome is low.

So moving on now to autologous, culture-expanded stem cells, for which there were also five trials to using bone marrow, derived mesenchymal stem cells, and three, using adipose-derived mesenchymal stem cells. Total sample size is 183. So again, small trials.

There's differences in sex distribution and osteoarthritis grade. Comorbidities again were not reported. And with the exception of one trial, neither were concomitant medications. The extent to which studies verified specific types of stem cells and stem cell characteristics, again, varied as did the total number of cells injected. In this case only one trial used another biologic hyaluronic acid. And post-treatment care, again deferred. So we just, again, would like to underscore the heterogeneity across some of these trials.

So this slide shows functions success or their proportion of patients meeting a predefined cutoff for improvements, usually considered clinically meaningful. Three RCTs reported this outcome, but defined success differently. Measured it at different time points and the results were inconsistent across the trial.

Only two of the trials reported statistical significance between groups for some of the outcomes, not all, at 12 months as shown here on the slide, which did favor stem cells. However, the evidence was rated as insufficient for the reasons cited below.

Function was also evaluated using the WOMAC total score across at most five RCTs evaluating autologous, culture-expanded stem cells. There was a total of 173 patients, when these were all pulled together. We found low strength of evidence of no difference between groups in the pool of estimates. That is the mean difference in follow-up scores up to 12 months. But as you can see, there was substantial heterogeneity.

So the exclusion of one outlier trial of Lamino Espinosa which compared bone marrow mesenchymal stem cells with hyaluronic acid. The exclusion of this trial did result in somewhat larger effect sizes. Though still wide confidence interval which favored stem cells at three and six months. At 12 months, the testicle heterogeneity was still high and there remained no difference between groups.

The clinical significance of these findings is unclear as we could not identify a published minimally clinically important difference for the total WOMAC score in patients with Knee OA. One of the included trials, SITO, reported an MCID of eight points, but did not provide a reference for how that MCID was validated.

Again, the source of heterogeneity is unclear here. It could be that Lamino Espinosa is dealing with different severities of OA. He also injected hyaluronic acid with the stem cells. So those are some possibilities, but we're still unclear. And the evidence that 48 months kind of hiding down there, some once small, poor quality trial was considered insufficient.

Similarly pooled results for the WOMAC physical function scores reported by up to

four RCTs with a total of 144 patients showed no difference between groups at any time point. The strength of evidence was low at three and six months and insufficient at 12 months.

Again, the exclusion of Lamino Espinosa, the outlier trials at three and six months did reduce statistical heterogeneity and resulted in larger effect sizes, which favored stem cells at three, but not at six months. The clinical significance of these differences, again, it's unclear, although an MCID of 9.1 has been suggested to be clinically significant and a population of Knee OA being treated with NSAID.

So moving on to pain outcomes, and we're still talking about autologous, culture-expanded stem cells for Knee OA, starting with pain success. Like function success, this was defined differently across two very small RCTs, which reported differing results. And again, the strength of evidence was considered insufficient for this outcome.

So the main difference in pain scores according to the VAS. Patients reported less pain with stem cell therapies versus the comparator treatments at six and 12 months. There was no difference in the earlier three months pooled in estimate. The strength of evidence at these time points was considered low and differences may be clinically important.

The minimally clinically important difference cited for the VAS was 1.9. Again, for patients with Knee OA chewed with NSAID that was the only population for which we can find an MCID for VAS. And longer-term follow up at 48 months from one small poor quality trial was considered insufficient.

So still talking about pain, but now WOMAC pain scores. There were no differences between groups in the pool to estimate at any time point for this outcome. Strength of evidence was low at three and six months and insufficient at 12 months.

The final two RCTs identified for Knee osteoarthritis evaluated allogenic, culture-expanded stem cells. So coming from a donor, different person. Again, these are very small trials with different stem cell sources and concentrations, as well as different comparators. Again, there was a lack of reporting of comorbidities and medication.

So only one of the RCTs reported on function using two different measures, the WOMAC and the Lequesne. Though the results may suggest improved function in the intermediate term with bone marrow, mesenchymal stem cells compared with hyaluronic acid, were unable to draw conclusions because the strength of evidence was considered insufficient.

Regarding pain, there were no differences between groups at any time point for the VAS pain scores as reported by both RCTs. Or for WOMAC pain scores as reported by one RCT. Again, this data was considered insufficient.

So turning now to safety for Knee osteoarthritis, beginning with autologous, non-

culture-expanded stem cells. This is the first of two slides for this group.

So there's low strength of evidence from RCTs and case theories suggesting that pain and/or swelling at the injection site and a fusion may be common. Pain, swelling was the most common adverse event in the registry studies, single arm registry study, which accounted for two-thirds of all the adverse events reported in that study. And that registry is the one we have the most numbers for, the highest sample size.

And I'd just like to mention before moving on that for these and all safety outcomes, really we have to interpret these results cautiously given the study limitations and the very small sample sizes that we're seeing. The latter especially makes some of these percents a bit misleading.

The evidence was considered insufficient to draw conclusions for all of the adverse events you see listed here. Again, talking about autologous, non-culture-expanded stem cells.

While mortality and serious adverse events may be rare based on limited data from included trials and the registry study, sample sizes were small and likely inadequate to identify serious adverse events, especially uncommon or rare events.

Follow-up was also short, with the longest being 12 months for the RCTs and 18 months for the registry. The registry study which looked at bone marrow concentrate plus PRP with and without lipoaspirate, so it was doing a bunch of stuff there. Did evaluate a variety of other outcomes. Listed kind of the bottom half of the table there. But these were poorly described and adjudicated. And again, with a small sample sizes, the percent may be misleading such as for serious non-infections shown by the one RCT there.

So now this is the first slide of two slides showing the safety results for autologous, culture-expanded stem cells for Knee Osteoarthritis. Again, beginning with those outcomes for which we have low strength of evidence. So the frequencies of any non-serious treatment related adverse events and joint pain maybe common following stem cell therapy across three RCTs and potentially more common than some compared to treatments. However, the number of patients again are very small and percents are a bit misleading here.
I did want to briefly mention that the two RCTs that looked at different numbers of injections or different doses. So that's the RCT comparing stem cells with usual care and the one comparing stem cells with hyaluronic acid. They suggest there may be more complications with increased doses of stem cells, however, they are isolated studies and need to be interpreted cautiously.

So again while mortality and serious adverse events may be rare based on limited data from included trials, sample sizes were small and again, likely inadequate to identify serious adverse events and uncommon or rare events. The longest follow-up available was 12 months in the RCTs. And again, percents are a bit misleading given the small number of patients and many of these outcomes are just poorly

described in the studies. Therefore the strength of evidence for these outcomes is insufficient to draw firm conclusions.

Regarding safety for allogenic, culture-expanded stem cells. One child reported that no serious adverse events occurred and pain fusion and/or swelling at the injection site was common across those trials. However, the data was insufficient to draw conclusion.

So now we'll talk about degenerative disc disease for which we only identified one RCT, and there will be only one slide related to efficacy for this condition. So the one RCT which evaluated allogenic, culture expanded stem cells found no difference between bone marrow mesenchymal stem cells and sham in either function or pain at any time point. However, the data was considered insufficient. Again, a very small study, 24 patients.

Similarly for tendinopathy, we identified only one RCT in Achilles tendinopathies specifically. So one of the function measures and VAS pain did show some limited improvement with stem cells. That's the bolded data you see there. At earlier time points only. However data from this one small, poor quality trial was insufficient to draw conclusions regarding the use of adipose-derived stem cells compared with PRP for Achilles tendinopathy.

So safety for both of these conditions, degenerative disc disease and tendinopathy. All safety data was considered insufficient to draw conclusions. For degenerative disc disease, no serious adverse events were reported across any study, one RCT and five case series. For tendinopathy, one RCT and one case series reported that no adverse events occurred in their population.

So this slide just shows all the various other conditions for which we had primarily non-competitive or single arm data and all were considered higher at the bias and the evidence was considered insufficient. The vast majority were autologous, non-culture-expanded stem cells, primarily bone marrow concentrate.

Briefly regarding effectiveness, they all reported improvement from baseline and function and pain with stem cells and they reported no serious adverse events, although minor complications, similar to those stated previously such as pain and swelling at the injection site and skin reactions were common. However, again, the data was considered insufficient for all of these conditions. And please see the full report for details.

So this slide is here just as a reminder that case series do not answer the question of comparative effectiveness and safety, which should be somewhat obvious I suppose. In the absence of the control arms from the same underlying population, it's not possible to know the extent to which an intervention is truly effective. So that is to what degree a given treatment results in an incremental benefit compared to a relevant comparator.

So as this figure shows, there's some proportion of a treatment response that likely

would have occurred in the absence of any treatment, such as the natural history of a disease. And there's also the effect of the placebo response. So as a result, most case series simply helped to generate hypotheses, but just don't answer clinical questions of efficacy or effectiveness.

This slide provides a high level summary of the three conditions for which we had evidence from RCTs. So here we're talking about efficacy and effectiveness, primarily function and pain. The conditions are listed to the left as is the category of stem cells consistent with how I presented the results.The light gray and dark gray cells indicate insufficient or no evidence respectively.

For autologous, non-culture-expanded stem cells, for Knee OA, we could not say anything about function, but there was low evidence of no difference between groups in pain, according to the VAS and the KOOS over 12 months. And this is indicated by the yellow or orange shaded cells. And just for your reference, any orange, yellow cells, indicate low strength of evidence of no difference.

For autologous culture-expanded stem cells, there was low evidence of no difference between groups in the WOMAC total and the WOMAC physical function of KOOS up to 12 months.

For pain, actually we had some low evidence of an improvement in pain according to VAS. VAS only, and sorry, not the WOMAC, as you can see there. Differences were significant at 6 and 12 months and maybe clinically important. The difference at six months was 1.9 and at 12 months was 2.3. And again, an MCID of 1.9 has been suggested as clinically relevant for the VAS. However, some people may or may not consider these differences clinically meaningful. So that's why I have the question mark there.

For allogenic, culture-expanded stem cells for Knee OA and the other two conditions, all evidence was insufficient or not reported.

Some of the challenges to drawing conclusions regarding efficacy or effectiveness. This is kind of an overview or reiteration of many of the things I said previously. There was substantial heterogeneity in the patient populations, in the stem cell sources and the preparations.

The characterization of the injectate cellular composition and stem cell concentration was inadequate, particularly for autologous, minimally manipulated stem cells. Many studies use adjunctive, biological components, such as PRP and many use pre or post injections as well. Inadequate reporting of co-interventions such as NSAID use, or post-treatment rehabilitation makes comparisons difficult.

Small sample sizes and no long-term follow-up as well as poor quality studies and the potential for publication bias were all concerns here for us.

So turning now to safety. This slide shows a summary of the safety data against the three conditions for which we had RCT data. The only condition for which we had at

least low strength of evidence, again, was Knee OA.

As you can see for both autologous, non-culture-expanded and culture expanded stem cell, pain and/or swelling at the injection site may be common as reported across the studies. A fusion may also not be uncommon as reported by two trials of autologous, non culture-expanded stem cells. And treatment, injectate and/or procedure related adverse events were reported frequently across three RCTs, but these were really poorly described and adjudicated, and it was difficult to make sense of them to be honest.

So again, looking at some of these percentages, I just want to reiterate the small sample sizes and the fact that many of these percentages are a bit misleading.

Again, reiterating challenges to drawing conclusions regarding safety. The adverse events were variably defined and adjudicated, as I've mentioned previously. Studies did not describe potential treatments, specific adverse events or priority.

So give us a little bit of pause regarding possible reporting bias. There is no differentiation between the adverse events that could be due to the injection procedure versus the injectate component or both, follow up with short twelve months or less, precluding evaluation of important long term consequences such as Neoplasia. Again sample sizes were very small and likely inadequate to detect all but extremely common event.

Are there any questions?

DR. SETH SCHWARTZ: Yeah I had one question just I think regarding the autologous injection for Knee OA. There was one study you excluded as an outlier. Tell us a little bit more about why you excluded that study.

ERICA BRODT: Sure, let me find that. Let me see here. Yeah.

So. these slides as you can see all the point estimate pretty much are favoring stem cells. There are all kind on the left side of that line. Some might be over to left more than others but they're all kind of in the general, same general direction except for Lamo-Espinosa, He's just way over favoring the control. So and you can see the heterogeneity here.92% ,89%, 96%. So really high.

So we had to we felt it was worth excluding that outlier and see what the evidence showed. It did change the pooled estimate a little bit there. So and again I think as I stated you know, it's unclear why some of these studies why there's so much heterogeneity. This study in particular this was not a well done study. The comparator with hyaluronic acid and they also gave patients in the bone marrow group an injection of hyaluronic acid at the same time. So you know, I don't know what impact that could have had on the stem cell injection. You know there's many variables that could have impacted it why this is an outlier. Then here you know same pattern. The other two studies here are on the left side the line Lamo-Espinosa is on the right. So does that help answer your question?

DR. SETH SCHWARTZ: Somewhat, I mean, I think just excluding it if you think that the quality that study was significantly poorer than the others that makes sense. If you're just because it has a different finding that doesn't make so much sense. So I'm just trying to understand whether it was because it altered the outcomes of the pooled analysis that you excluded it or was it because that study seemed of lesser quality than the others that you're including.

DR. ANDREA SKELLY: Let me briefly speak to that when we do meta-analysis. It's very common for us to see to explore the heterogeneity and excluding an outlier such as Lamo- Espinosa is part of sensitivity analysis to see what happens to the heterogeneity from a statistical standpoint. We also attempt to look at from a biological or pathological standpoint, is there a potential reason for that. So it's a part of a matter of completeness for evaluating the heterogeneity but also to point out that it's unexplainable in this case. And so that you have the complete data before you. If that adds to the discussion.

DR. SETH SCHWARTZ: Well I think that makes a lot of sense if you're looking at 10 studies and you have one outlier. If you have three studies and you have one outlier, is it really an outlier? I guess what I'm getting at…

DR. ANDREA SKELLY: And you're right. You know and we have so few studies. It's very difficult to really ascribe meaning to some of that. Nonetheless, again we felt that it was important for transparency to do that.

DR. SETH SCHWARTZ: Thank you.

DR. CONOR KLEWENO: This is a Conor Kleweno, I have one question and just a comment to the panel. The use of hyaluronic acid for the competitor definitely shouldn't be considered as a standard of care comparison group. So I agree that that's a potential confounding variable. My question is, were there any aspects of the discussion methodology that explained why this small sample sizes given the high prevalence of Knee OA in particular.

ERICA BRODT: That's a great question. Not that I can remember. I would have to go back to the studies themselves.

DR. ANDREA SKELLY: I don't believe that they really gave a rationale for the small sample sizes.

ERICA BRODT: Yeah. Nothing.

DR. ANDREA SKELLY: Frequently it's not done.

DR. SETH SCHWARTZ: Theoretically you would include a power analysis in a well-designed study. So I guess that's another way of asking the question of you know, were there studies appropriately powered based on their prior power analysis or not.

DR. ANDREA SKELLY: We would have to go back and look and see if any provided power analysis

DR. MIKA SINANAN: Hi, Mika Sinanan. I wanted to thank you for your slides 45 and 47 those summary slides which I think really are a helpful way to present this kind of information. I had a question which I think really may go best to Dr. Manner. How does this actually work. Does a patient come into the clinic and get if it's a tally guess, does the clinic do the actual processing or is it done by a commercial firm? Does a commercial firm come into the clinic and do it or is it shipped off? What's the process?

DR. PAUL MANNER: Thanks. Because you know it's a good question and you know the short answer is it's a little bit of the Wild West out there. And you know, I don't do these injections, we don't do them at UW but you know, it could either be done you simply take a large needle poke it into a body part that is potentially a rich source of whatever cell it is you think you're injecting and you know you take it into the back room process it a little bit and go ahead and re-inject. You can also have it done commercially. You can have it send out commercially so there really are a number of different ways that you can do this. And the stem cell world is very entrepreneurial. Let's put it that way. And so there are any number of ways that that that this can be done.

There are a couple of companies out there that advertise fairly aggressively. Regenexx is one and they typically will contract with a with a provider to give the services and then essentially take a cut of the of the fee... of the reimbursement.

DR. SHEILA REGE: You know we used to have somebody standing at the microphone but let's have questions in the evidence report first and then we can go around the room with a round robin before or after the break depending on how much time we have and discuss you know our feeling about this. But any questions for Erika and her team on the evidence?

DR. PAUL MANNER: I actually do have a question where I did take a brief look at the journals involved are these open access journals? what's the level of peer review with these and within these journals? do we know anything about impact factor for example or you know sort of what their editorial processes are.

DR. ANDREA SKELLY: This is Andrea; we don't usually look into that. The journals are listed. One could look up what their impact factor et cetera are. I think that at least from our experience in the last 10-15 years looking at Orthopedics journals, sometimes and I don't mean this derogatorically really but we've actually recently published a systematic review of systematic reviews. Some of the highest impact journals do not necessarily publish the highest research quality. But we don't we don't routinely, systematically look at the quality of the journal or their editorial process but realize that's a very important thing.

DR. PAUL MANNER: Yeah. Your point is well taken. You know the reason I'm concerned about this is that I look at a number of these journals and I don't recognize a number of them and I wonder if some of these are sort of the open access large predatory journals that really have very little in the way of peer review or in the way of you know sort of editorial oversight.

DR. ANDREA SKELLY: That may be. We do to the extent possible try to rely on things that are indexed in PubMed National Library of Medicine.

DR. PAUL MANNER: Sure.

DR. ANDREA SKELLY: That said there still is a lot of variability in the quality of journals that are indexed.

DR. PAUL MANNER: OK. Fair enough. Thank you.

DR. MIKA SINANAN: Can you talk a little bit about the 93 excluded articles which left you with what are not apparently great quality 56 publications you actually reviewed.

DR. ANDREA SKELLY: Do you have the big question about the excluded articles?

DR. MIKA SINANAN: They were excluded for a number of different reasons from the full text review or at full text review.

ERICA BRODT: Sorry Andrea, in the appendix we do with all the studies excluded and the reason why and most likely they did not meet a prior inclusion or exclusion criteria. I believe a lot of them were excluded because themselves were used in conjunction with surgery for instance which is just not the population that we're looking at. I know a lot were excluded because they were in conditions like osteonecrosis or avascular necrosis which were excluded. And some may have looked at different cell population or cell preparations and things like that which were excluded. So but you can you we should have and I'm positive in the appendix we've listed the reasons why they were excluded.

DR. ANDREA SKELLY: Yeah. Appendix C is the listing of things excluded at full text and the reasons.

DR. MIKA SINANAN: OK. Thank you.

DR. SHEILA REGE: Anymore questions on the evidence report? Thank you Erica. We're about. We thank you. We're about 10 minutes early. Were there any other public comments that call them that we missed because we went 10 minutes ahead of schedule.

BRITT REDICK: No. Dr. Rege, I'll just note that this is Brit Reddick. I will send a message to the entire audience and let them know that they can email me if they'd like to make a comment. Because I do see it there might be a few people that have called in but they're not able to use the question box function. So if they're just on the phone or so we just may need to take that up after the break but I will contact the group and let them know how to do that.

DR. SHEILA REGE: OK. I know people are having a little trouble with the hand raise. If you have trouble I think what I'm hearing from Brit is use the question mark to send a message to her and that's what Brit, you were monitoring. Correct? In case somebody feels that they're not being heard or has technical problems.

BRITT REDICK: Yes, that would be good. Thank you.

DR. SHEILA REGE: Maybe, we could do our break now and come back at 10 which is 10am and we would start then with what we've done before kind of a round robin around the room on the evidence report. Just our thoughts on the strength, the evidence and what they feel about it. So be prepared. And just as a warning I'll start at the bottom of the alphabet this time. Tony you would be a great first…absent any objections we will take a break. OK. Break for 10 minutes. I would recommend staying on because and just muting your phones or your computers. Thank you

DR. SHEILA REGE: Sheila Rege here. I believe everyone should be unmuted. Tony, would you mind just round-robin on your thoughts on the evidence report.

DR. TONY YEN: Sure. I think of… I really appreciated Seth's comments before about why that one study was excluded on page, I think 25 and 26 of the evidence report. And I think those are the slides that I tend to focus on because if anything that would be probably the most compelling in terms of showing that this therapy actually works because that's a culture expanded stem cell therapy. And at least in terms of my own thinking I think that's probably the type of intervention that would give this therapy the best chance of working. Even by excluding outlier therapy by Loma Espinosa, it appears that the pooled results still don't show a significant difference. Now by, I think mentally adding back Loma Espinosa study that the pulled results would still cross zero ,which I think shows no significance in the intervention. So my general feeling about this intervention is that it doesn't incur any benefit.

Thank you, Tony. Kevin, if you wouldn't mind sharing your thoughts at this time.

DR. KEVIN WALSH: There we go. Now can you hear me?

DR. SHEILA REGE: Yes.

DR. KEVIN WALSH OK, thanks. First, I want to say I'm really enthusiastic about the possibility of this technology. I care for a lot of patients who whose mobility and function is impaired by their knee osteoarthritis, and I'm excited about this as a potential therapy for them, but also for me because I have very debilitated knees personally. In terms of safety, I don't think any of the studies raised issues of concern. I'll choose to speak to the knee studies only because I don't think that the other studies at other locations were sufficient to consider. In terms of autologous non-expanded therapy I didn't find any benefit in either pain or function. However, there was some improvement in pain at 12 months in the autologous expanded therapy group.

To me, I want to say that as someone who cares for a lot of people with chronic pain, and has to manage patients who have come with significant opioid burden, I don't feel that treating to pain is nearly as important as treating to function. So while there is an improvement in pain at 12 months in that autologous expanded group, there is no change in function. So I don't think that there is a benefit to the technology for that specific technology. And then finally for the allergenic, I don't think that there is appreciable difference for function or pain. So I don't think that this technology has demonstrated sufficient benefit to be covered at this point.

Lastly, I noticed Dr. Bramhall sporting some new facial hair, and I really liked the look, John. If you can hear me, I've lost video. I've lost the audio to everybody now.

DR. SHEILA REGE: I can hear you.

DR. KEVIN WALSH: Now I can hear people. Thank you. There was a prolonged silence I thought I was gone.

BRITT REDICK: Hi, this is Britt Reddick. The audio seems to be having some mishaps here. So if you could just because bear with us and might have to go through it manually and mute each committee member as you speak, but then after that hopefully you'll have the freedom to speak as you as you wish. Dr. Rege, are you able to speak now?

DR. SHEILA REGE: Yes. Thank you. Mika Sinanan is next. We could unmute him first.

DR. MIKA SINANAN: I think I'm unmuted. Can you hear me?

DR. SHEILA REGE: Yes.

DR. MIKA SINANAN: Good. Thank you.

So I look forward to hearing what Paul Manner has to say about this in the context of his experience more broadly. And that may or may have some influence on my opinion. I'm surprised that what appears to be a very prevalent problem has been so poorly studied with low quality studies, and poor comparaters. It seems to me this is not being dealt with as a sort of serious medical intervention but more as a marketing opportunity very often. And clearly there are a lot of people out there who gravitate to what sound to be more natural, more organic, more lower risk types of interventions than often surgery as the option.

And so taking advantage of that concern and fear there's a whole market for this type of intervention. Having that perspective and seeing what the available evidence is the very small numbers, and the low response rates across the board don't seem to support, at this point, supporting this. It just doesn't seem that that the value of any types of stem cell therapy, autologous, cultured, non cultured, expanded, or allergenic has been proven, I think. I would agree that function is probably more important than pain, but somebody who has chronic pain might have a different opinion about that. But even in those cases it doesn't appear that it's been particularly effective. The evidence even in those cases is pretty low.
Thank you.

DR. SHEILA REGE: Seth, would you be willing to give us your opinion next?

DR. SETH SCHWARTZ: Yeah. I don't think my perspectives are all that different. I think I pull out knee osteoarthritis first and say that I would agree that with regard to everything else there is insufficient evidence to make any comment. Was initially impressed to see 12 randomized trials on something. That's that's unusual for us to get that. But then I was quite disappointed at the quality and size of those trials. I think it's right that

the pool don't show a significant effect of this technology. I think that was challenging as what we've seen as the heterogeneity of the trial. So I don't know that it's hard to group these studies when it seems like slightly different things were done to all these patients. And it's really hard what exactly was happening.
I sort of mirror Kevin's point which is that I think there there's a lot of patients are very excited about this potentially deadly less invasive technologies that could be regenerative. So I think there's a risk of sort of over excitement for something that I'm not seeing adequate proof of yet, but I will admit I'm guessing that if we had better quality. But I really want to know what that's going to look like. So I guess to summarize I think that there's really not a lot of evidence here to support its use in the (INAUDIBLE) tests, but I certainly want to see more.

DR. SHEILA REGE: Thank you.

I think alphabetically I would go next, and I would echo others, and also surprise because so different in the cancer world where there is evidence, and I'm just also not seeing it. And our principle is, you know, determinations need to be evidence based for further the criteria of safety, effectiveness, and providing some value improving health outcomes. So echoing similar comments. Laurie, would you be willing to go next ?

DR. LAURIE MISCHLEY: Yeah. This is Laurie. So I agree with everybody else. And you know, I think that the heterogeneity of these data simply prevents us from drawing any meaningful conclusions here. And the data that we do have suggests that it's not as effective as we would probably all like it to be.

In addition to these data I do put some weight on my clinical experience, and what patients have told me and seen. As a naturopathic physician I have certainly had my share of patients who have gone this route, and I have not been impressed with anything that I've seen. I've not personally had anybody ever come to me saying it made a meaningful long term difference. These aren't referrals of mine, but things patients have just done on their own and told me about. So between, you know, the data that we're seeing here, and what I've seen personally in clinic, I can't see. Unless the expert has something compelling to say otherwise, I don't see myself voting in favor for this.

DR. SHEILA REGE: Thank you, Laurie. Paul, actually alphabetically you would go next. if you do not mind commenting, or you could wait till the last. It's your choice.

DR. PAUL MANNER: Sure. Yeah.

So I would I would put out a few points to mention. So you know my experience with the basic science of stem cells and goes back about 20 years. And our work at the NIH was predominantly looking at getting stem cells to become chondrocytes which are the cells that are found in cartilage. And the cartilage is a little bit of a unique structure in the sense that the only cell that's in cartilage is the chondrocytes. So the chromdrocytes is responsible for making the matrix. It is responsible for repair. It is responsible for maintaining that tissue for the lifetime of the patient.

And so as a consequence our work really focused on taking these incremental stem cells and driving it down the chondrocyte pathway.

So there are a few issues. First of all, whatever cell you're working with has to be clearly characterized with markers. So you have to know that the cell that you're that you're using is in fact a stem cell. And there are ways to do that there are various cell markers that you can use. So there are certain populations that you know that are stem cells. In a test tube if you take those cells and provide a very specific chemical (INAUDIBLE). Meaning cytokines, Dexamathasone put it into a bioreactor so you get the gravitational force just right. You can get those mesenchymal stem cells to become a chondrocytes in small quantities. Sort of on the order of about maybe the size of a pea, if you're really, really good at it. The problem is that as soon as you take those cells out of that (INAUDIBLE) the cells tend to revert back to an undifferentiated state. So they tend to revert back to being at best a stem cell, and more commonly what they become is a fibroblast. So the basic science simply isn't there.

When you move on to the clinical world. There's a lack of quality control. We have no idea what people are injecting. If we assume that they've got it right, and this is a stem cell that they're injecting, there is the assumption that the cells stay where you put them as opposed to being taken up by a macrophages or being by broken down. And then there's an assumption that those cells and cells remain either stem cells or the differentiated cell that you want them to be, and don't turn them into something else.

So then the next thing is the idea that simply injecting cells into a, whatever type, into the structure that you want them to be makes biologic sense. And I would put it to you that does not make sense. The body already has these mesenchymal stem cells in the bone marrow immediately adjacent to an arthritic joint. And so my thought on this would be if those stem cells were going to magically work in the joint they would have done it already. We would not have to get somebody to pull it out with a syringe and re-injected it. The stem cells would simply migrate to the area of damage and take care of things themselves.

When you look at the studies that have been done on this. First of all, all of the assessments are short term. They're almost all under a year. Some of them go up to 12 months. But almost anything is going to work for a few months if you can convince the patient that it's working. There is no objective evidence in the sense that there is no histologic data, no cell marker data, no imaging data other than an X-ray. And what you are reporting on is essentially subjective outcomes which are pain and function. And those can be influenced substantially by the fact that you have a patient that's a sunk cost. They put $5,000 into injecting this knee. They are going to be very motivated to think that it's working even when it's doing very little. And then there is the idea that you want to please the provider know so you don't want to tell that nice doctor that what she did didn't work at all. You want to go in there and tell her that it's great.

A final point that I would make is that when you're discussing coverage there is an opportunity cost because the resources that you have available for health care are finite. And every dollar that you spend on a useless therapy is one dollar less that you spend on things that work. And you know, it's one thing if you're looking at something novel for something that's relatively benign, OK? if you have a kitchen spill you know why not use the Shamwow ,OK? It's cheap. The ads for it are fun. It's probably no worse than anything else. But this is different, you know. We're not talking about a small amount of resources here. We're talking about $5,000 per joint on average. That's not a small amount of money. And to do that with no objective evidence to me sound seems like a bad idea. And that would be my take on this.

DR. SHEILA REGE: Thank you.

Conor Kleweno, would you mind sharing your thoughts on the evidence report and the agency presentation which is kind of our discussion?

DR. CONOR KLEWENO: Can you hear me?

DR. SHEILA REGE: Yeah.

DR. CONOR KLEWENO: OK, great. Yeah. Thank you, and thanks Paul. I thought that was a very elegant explanation of the basic science background on this.

And first, I just want to… I'm just glad that we are bringing this up to this committee. As we've mentioned this is a very hot topic that as providers we see come up often. You know, whether you're talking about prevalence, or dollar spent the disease burden for degenerative joint diseases is massive. And these people are somewhat a vulnerable population because they're miserable. An often-quoted study just because of the conclusion was so ironic that if you look at physical function, quality of life the only thing worse in this study from a degenerative joint disease of an ankle from high energy trauma was, you know, end stage congestive heart failure, or spinal cord injury. So in the study the degenerative joint disease of the ankle was worse than chronic coronary artery disease, chronic diabetes, chronic asthma in terms of their ability to function.

So this population is desperate, they're miserable, and they're looking for solutions. And when I hear the direct to consumer advertising for the unregulated stem cell therapy, it's quite disturbing because I feel like it is taking advantage of the somewhat vulnerable population with their disease burden. I am not surprised by the data presentation today some of which I've reviewed myself for my clinical practice. Although not in its entirety. I don't see that it is something that is supported by the data at this point. Granted, it's something that if we are able to some point inject something into a joint and cure, or change the natural history of the disease the benefits of which would be huge. You look at something, an analogy would be rheumatoid arthritis which used to be, you know, somewhat of an orthopedic surgery disease due to its natural history of end stage joint destruction. Now with DMARDs it's relatively controlled with medications. And it's completely changed the clinical course for patients.

So obviously everyone that sees patients with degenerative disease would be excited by a much smaller intervention that could improve function, improve pain. A comment about function versus pain. I agree with what's been said, and also about the quality of literature. Although this is an orthopedic condition. So to speak, I don't think that all of the literature presented was necessarily orthopedic literature. As Paul said that a number of these journals we've never even heard of. So I think that I would agree that at this point based on the evidence available not a compelling data to support coverage.

DR. SHEILA REGE: Thank you, Connor. Chris, would you be willing to go next?

DR. CHRIS HEARNE: Yeah. I don't have much to add to what's already been said. It seems that the evidence that this is effective is just not that compelling to recommend covering it right now. I am in agreement with what's been said thus far.

DR. SHEILA REGE: OK. Janna, would you be willing to share any thoughts?

DR. JANNA FRIEDLY: Yeah, I agree. At this point, I don't have anything substantial to add to what's already been said. And I have said I really appreciate the perspective of Dr. Manner, and understanding the basic science and the biologic plausibility. And I think if so many ways in which this can go wrong when translating from basic science to clinical application, to even controlled trials, to then out into actual clinical practice. So I I did not think that the evidence supported the intervention for any condition, or any of the types of stem cell treatment.

When you drill down to the actual individual studies as well, and look at them carefully the methodology this from a research standpoint is is quite poor. And there's such a high risk of bias in terms of reporting of pain and function outcomes. I really appreciate the comments about for people who are investing personal money into these treatments that there is a strong desire to show that they work for this. And so I think that may not influence the results of these trials because I imagine these patients were not paying for the treatments in these trials. But certainly that is is true in clinical practice.

DR. SHEILA REGE: Thank you. And John, you're going to be our final words on this our round-robin.

DR. JOHN BRAMHALL: Yeah. It's a futuristic sounding therapy that's designed to help people who is, Dr. Kleweno mentioned, are probably pretty desperate by the time they go this route. The sort of poor cousin of this is, in a way, is platelet rich plasma injections, And a couple of our own trainees from the university system, you know, they earn a living doing that in one in Vegas, one somewhere else. They earn a living doing that. And I'm not here to criticize PIP injections, but this is a much more sophisticated sounding injection.

It offers a therapy which sounds very futuristic. And, you know, looking at this slide 45 this before us, there's nothing there that stimulates excitement about the validity of the intervention. I'll reiterate what Mika said, I appreciate this format from the Aggregate Analytics company. I think this is a this is a slide that

encapsulates a pretty significant amount of information in a very succinct way. So thank you for that . The only question in your mind for the future.

So the present status is is dismal for anyone who really wants to try and make a case for the the the honest effectiveness of this intervention. In the future, it could be that many of the grey boxes or the black boxes on this slide could be filled in with green by providing evidence. You know, studies that are done appropriately, and properly, and sufficient power structure, and done with injector rates that are characterized in a sophisticated manner. It may well fill in some of the boxes, and may well demonstrate an effect.

But here and now, I agree with everyone else I think. I don't see that there's anything rewarding here at all. And coupled with the the sort of comments that Dr. Manner made about the… I'd say psychological. The situation that desperate patients are in who can afford to spend $5,000, or $10,000, or $15,000 on a intervention that they really want something to happen. They really want something to be beneficial to them. And perhaps they aren't ready to go for a total knee replacement or something like that yet. But that that obviously is going to distort subjective assessments of success.

So I'm saying what everyone else has said. This slide here encapsulates very little evidence in support of the therapy and certainly doesn't excite us and excite me to want to spend public money on this...this intervention.

DR. SHEILA REGE: OK, thank you. Any...any other comments? Actually, I would like right now for us to go and maybe we could project on our safety criteria so we make sure that we are...have everything listed and that would be page...page 30... Page five just for discussion document to make sure that we have listed everything before we start talking about (INAUDIBLE) and for the discussion. So that on my PDF is page 91.

JOSH MORSE: Sheila, are you looking in the report?

DR. SHEILA REGE: Correct. I'm looking in the report just under discussion document and it's serious treatments related just to kind of make sure that we don't have any gaps before we you know, kind of help us guide us in our discussions since it seems like we're...Most of us have the same thought.

So I just kind of wanted to make sure we were in agreement with what's been listed in our report on safety, efficacy...So we have alluded to this during the evidence report. It's page five but on my PDF it's page 91.

JOSH MORSE: I'm looking at the Word version I apologize and...

DR. SHEILA REGE: It's on the...I'm sorry it's the analytical tool. It's on the (INAUDIBLE)

JOSH MORSE: Oh, gotcha. OK.

DR. SHEILA REGE: I should have made that clear.

JOSH MORSE: Not a problem. My apologies.

There we go. And Conor and Paul who possibly have more expertise on this or any of the surgeons serious treatment-related outcomes. You know, neurologic events, nerve damage, allergic...I don't see graph versus host issues but is that not seen in orthopedics like it is in cancer? And this is open for anybody to add or comment on.

DR. PAUL MANNER: Yeah, this is Paul. You know, I would say if you're dealing with autologous cells it's unlikely. Couple reasons for that. First of all, you know, you're...you're dealing with an immune...immune incompetent patient. You have not suppressed the immune system with various and sundry awful things. There are...there is some thought that the...that the articular joint is a little bit of an immune-privileged area in the sense that you don't typically get an immune response within the joint in the absence of something like rheumatoid arthritis. I don't know if that's necessarily true or not.

My sense is that most of the stuff that's been done clinically tends to be autologous cells. So it would be unlikely to see a graft versus host reaction.

DR. CONOR KLEWENO: Yeah, I agree. Another thing I would add on here is that I've seen clinically is adhesive capsulitis. So no severe joints stiff...stiffness after injection of these and that may not be related to the actual you know, quote-unquote stem cells or just the process of injecting into a joint which is not necessarily benign.

DR. SHEILA REGE: OK, so do we agree with this list about neurologic events, nerve damage, allergic (INAUDIBLE) embolism, sepsis infection, joint effusion as being a comprehensive list we haven't missed anything and then we have all cause mortality? Any discussion on safety issues?

DR. PAUL MANNER: Yeah, this is Paul again. For me, infection would be the probably the biggest worry in terms of these treatments. I mean I would say that's true with any form of injection therapy but at least with other modalities there...there is some documented benefit. With this where there's really at this point no documented benefit you know, you can't really do a cost-benefit decision on whether to inject somebody if there really is no benefit. And an infection in a joint is basically game over when it comes to treatment.

DR. JOHN BRAMHALL: Now, this is John here. Paul is it an appropriate time if we just ask a question about not really directly the safety issue but...I assume the hypothesis is that the injectate contains cells that then remain in the joint region where they're not distributed systemically that would be a safety issue obviously and presumably that's a function of the architecture of the anatomy of the joint capsule itself. But what I'm wondering is the hypothesis the cells that are injected that are relevant cells? Are they...Do they organize themselves into a structure into a sheet or do they simply sit in the quote joint you know, secreting collagen or something of that sort that the (INAUDIBLE) laid down in sort of a chemical fashion?

I'm a bit uncertain about how to imagine what's going on or what's thought to be going on.

DR. PAUL MANNER: I'd say that's because there is no obvious explanation of what's supposed to be going on other than...other than (INAUDIBLE) You know, you could...you could I suppose do this one of two ways. One is to put the cells into some form of matrix whether it's a collagen matrix a you know, a artificial constructed scaffold where the cells are happy and decide that they're actually in car...in cartilage and start to become chondrocytes. You know, and certainly you know, there's...there's a lot of work on scaffolds and putting cells into those scaffolds and seeing how they behave but you're quite right. The idea of inject...just taking a bunch of cells randomly and injecting them into the joint I don't know what they're supposed to do. I assume the idea is that they...some (INAUDIBLE) will seek out a spot where...where there's no cartilage sit down and start...and start making matrix but I have no idea biologically how that would ever happen.

DR. JOHN BRAMHALL: I mean if I could just do a follow-up question. A lot of the excluded 93 articles dealt with the combination of stem cell therapy and surgery. Is there a role in your mind for that any efficacy?

DR. PAUL MANNER: Well, again I don't really know what it is they're doing with these cells. You know, if...if they're simply opening up the joint and kind of making a paste and putting it into an affected area you know, again there's no guarantee that the paste won't simply detach from...from the area of interest as soon as you close the joint and as soon as the patient starts moving. So I...you know, I don't really know what it is they're doing with these stem cells. Part of the problem is that you know, in some ways you know, the surgeon is the method. So, I would you know, even when we're doing very well described operations that are routine you know, everybody does them a little bit differently. What they are doing in these combined treatments I quite honestly have no idea.

DR. JOHN BRAMHALL: Thank you.

DR. CONOR KLEWENO: And John to your question and maybe Paul can even comment more. The...when you actually when people have tried to actually graft stem cells or differentiated chondrocytes into cartilage deficits and then cover them with a biofilm or an allograft you know film, the mechanical environment is so challenging that they sort of shear off and have lost their home base to some degree. So, even when you attempt to place those things in the area of question it's a difficult mechanical environment for them to actually stay there. So to suppose that then they'll find their way themselves is an additional leap.

DR. JOHN BRAMHALL: That's interesting. Thank you and I just...Is it....Is it…Do you understand...Do you know whether there are a number of studies where perhaps the arthroscopy after the injectate has been allowed to sort of develop and do what it's supposed to do? So six months later if a surgeon went in with an arthroscope do you think that there's any evidence in the literature that relates to observations that they might

make about the integrity of the capsule and the collagen deposition? I'm asking you to speculate I suppose because I don't think the data is there.

DR. PAUL MANNER: So there are a number of studies that have done sort of a second look you know, after some treatment whatever that treatment is.

You know the problem with that is that when you just simply look at it you kind of go yeah there's...there's something there, OK? What we don't have is a biopsy or histology or cell markers saying this stuff that's been laid down is what you would find in a normal...in normal articular cartilage. That is to say, we see a lot of type 2 collagen, we see small amounts of type 9 and 10 and type 11, and we see it in an organized structure that mimics what we would see in a native joint. The few studies that have done a biopsy typically show type 1 collagen which is essentially a scar. So, what...what's probably happened is that you've had a few cells that have become fibroblasts they have laid down some scar tissue which not functionally equivalent to normal articular cartilage.

DR. JOHN BRAMHALL: It's interesting. Thank you.

DR. SETH SCHWARTZ: And this is Seth. I guess I would have a question in that regard. I mean we never looked at animal literature but I think (INAUDIBLE) animal models (INAUDIBLE) that work?

So, you know, there's always a problem with an animal model. You know, there are a number of models out there. I would say the main problems we have with them are animals walk on four legs for the most part people walk up two. The ration of studies tends to be short because it is expensive and difficult to keep an animal alive for years to watch them. The model of inducing of arthritis tends to not be particularly good. They tend to not be really clinically applicable and then lastly most of the time that animals are used they tend to be young animals. Meaning either the equivalent of an adolescent or at best the equivalent of a teenager where the growth plates are closed but you know, the biologic capacity of a young animal is substantially better than the biologic capacity of an old animal in which group by a less categorize myself. So there is a lot of trouble with animal models because in arthritis simply because we don’t have a great animal model.

DR. SHEILA REGE: Any other discussion on safety outcome? And my suggestion and please feel free to suggest a better alternative would be for us to imagine we were all in the room and still had our yellow cards. Next time maybe we'll have some a slab of yellow cards where on safety we go to a straw poll on stem...stem cell therapy compared to placebo in terms of safety is proven to be better more and some equivalent less and some or unproven. So I'm looking at if you say proven that it is safer compared to a placebo is how I would interpret it and if everybody is OK with that then we would start with John but please let me know if anybody thinks of a better way.

DR. JOHN BRAMHALL: No, I think your approach is correct. It's what we would do in the room and I think if I was gonna hold up a card for safety I would hold up my “Unproven” card.

DR. SHEILA REGE: John goes “Unproven”. Janna, would you mind going next?

DR. JANNA FRIEDLY: I think I'll say “Less” for safety.

(INAUDIBLE) (CROSSTALK)

DR. SHEILA REGE: Staff are you OK with this? Can we go on. To Chris?

BRITT REDICK: Yes.

JOSH MORSE: Yeah, I think we're OK. There is not a “Less/ Some” option. I don't think it's less...There is a “More” and “Some”, but there's I think they’re just different.

DR. SHEILA REGE: I can’t remember.

JOSH MORSE: Yeah.

DR. SHEILA REGE: Do we have “Proven’? Tell me what we have Josh? I couldn't remember.

JOSH MORSE: Can you see...Is my screen showing? I'm showing the vote. The non-binding vote which is page six. So “Unproven”, “Less”, “Equivalent”, “More in some” or “More in all”. And you're voting on safety of the technology.

Did you say for all conditions or for knee osteoarthritis? Are you breaking this apart or doing altogether?

DR. SHEILA REGE: I was going to do all together unless somebody wants us to break it apart. John what did you...When you said “Unproven” were you thinking of “All”?

DR. JOHN BRAMHALL: Yes, I was. Yes, I was looking at the cohorts of evidence that we have all cases.

DR. SHEILA REGE: OK, thank you.

DR. CONOR KLEWENO: Sheila, this is Conor. Just a clarification question. When you say placebo are you implying someone's gonna inject like saline into the knee or you...as opposed to doing nothing or what's our comparison for safety? Because that would change, I think, whether you do nothing - versus doing a sham injection into a knee in terms of safety 'cause you can still get an infection of a knee if you just inject saline from the needle introduction.

DR. SHEILA REGE: I guess I in my mind was thinking of doing nothing but I'm open to a suggestion.

OK, let's go with placebo being no intervention because we said safety issue was infection.

So John did you wanna revote? Good question.

DR JOHN BRAMHALL: No, I mean hypothetically I can imagine that there's an increased risk but I don't think it was demonstrated in the literature that we were presented. So I'm gonna stick with “Unproven” for safety.

DR. SHEILA REGE: Janna, I'm sorry I misled you. If you would vote again.

DR. JANNA FRIEDLY: It's OK. I'm still gonna say “Less” and “Some”.

DR. SHEILA REGE: Chris?

DR. CHRIS HEARNE: I would also say “Less” and “Some”.

DR. SHEILA REGE: Conor?

DR. KEVIN WALSH: Excuse me. I just wanna remind you that Josh told us that “Less” and “Some” is not a category. So you can choose....

DR. JANNA FRIEDLY: I am sorry. I apologize. “Less”.

DR. CONOR KLEWENO: Yeah, this is Conor. I'd say ‘Less”.

DR. SHEILA REGE: Paul I know you don't officially have a word but I'm kind of curious what you would vote it if you were to vote.

DR. PAUL MANNER: For safety I would say “Unproven”. I simply don't think there's enough proof one way or the other for safety.

DR. SHEILA REGE: Laurie?

DR. LAURIE MISCHLEY: I'll say “Unproven”.

DR. SHEILA REGE: Sheila, I would say “Unproven” also. Seth?

DR. SETH SCHWARTZ: I'd say “Less”.

DR. SHEILA REGE: Mika?

DR. MIKA SINANAN: “Unproven”.

DR. SHEILA REGE: Kevin?

DR. KEVIN WALSH: “Less”.

DR. SHEILA REGE: Tony?

DR. TONY YEN: “Unproven”.

DR. SHEILA REGE: Shall we get a summary of our thoughts on safety?

BRITT REDICK: So, this is Brit Redick. There were five votes for “Unproven” and five in “Less” for the last category.

DR. TONY YEN: Sheila, this is Tony. Can I ask you a quick procedural question over here? Because underneath “Unproven” it says “No” and underneath it “Less” says “Yes”.

DR. SHEILA REGE: And I had not noticed that till Tony. So I would ask Josh why?

Josh is reflecting on the form and those questions. Let me get back to you on that.

DR. TONY YEN: Yeah, The reason why I'm asking Josh is that it seems like my my general sense is that the folks who may have stated ‘Less” is that they feel that it is less safe. It sounds to me like a “No” rather than a “Yes” for (INAUDIBLE)

JOSH MORSE: I agree with you. I would...I don't think we've referred to those parentheticals in a while so it's a good question and again I'm gonna reflect on what the meaning is there. I think you've identified your use of the terms “Unproven” and “Less” are pretty clear.

DR. TONY YEN: Yeah.

JOSH MORSE: You're doing a comparison I'm not exactly sure how we apply a yes or no to the question you're asking yourselves.

DR. TONY YEN: OK, thank you.

DR. JOHN BRAMHALL: Well, I think it…Josh I think it's...I mean the way I had read it in the past is that the answer no....So the question is is there sufficient evidence and then the answer is well if you don't think there's any evidence or sufficient evidence you would say “no” and if there is sufficient evidence to make a decision you would say “yes” and then the question is what is the decision that is supported by the technology?

JOSH MORSE: There you go Dr John Bramhall.

(CROSSTALK)

DR. JOHN BRAMHALL: It does make...it does make some sense if you look at it that way. To me.

DR. TONY YEN: That helps. That helps thank you.

DR. SHEILA REGE: Any other discussion on safety? If not...If we could go back and I'm sorry I'm going back and forth to page five on “Efficacy” because that's the next one. We're gonna do the yellow cards on and we have a list here. Function, pain, objectivity. Is that pretty comprehensive or any discussion on that - on terms of the evidence?

(CROSSTALK)

DR. MIKA SINANAN: It seems to me that those are all potential categories. Many of them were not addressed in many of the studies. Function and pain seems to be the most commonly addressed ones.

DR. SHEILA REGE: And I...based on that Micah I wonder if we should only kind of because that's all we got was discussed. We should not be looking at the others. Medication, use, return to normal activities, time to recover because we didn't really have data on that and you know, everything below that.

DR. MIKA SINANAN: I agree. We don't have data on those.

So I think unless any...any discussion on that that all the evidence that we reviewed was function and pain.

DR. JOHN BRAMHALL: Yes, I agree Sheila. I mean again I take this as a little worksheet for each of us individually if we were using a file you know, a three-ring binder and we would each of us then I think make our own decision about whether we thought the time to recover is the most important thing or quality of life or patient satisfaction and we would just sort of rank those subjectively independently of whether there's evidence to support or deny. That's the way I take it.

So I would...I would say well OK the most important thing is to get back walking function is the big thing and then I would ask the question is there any evidence that the intervention supports or detracts from function? That's what I would take from this is a little worksheet to help us sort of come to a coordinated conclusion in the end.

DR. SHEILA REGE: I agree. So any...any more discussion on that otherwise we'll pretend we're back in a room and all the voting members have our yellow cards and again it is going to be unproven, less, equivalent, more and some, more and all and this time I'm going to go with Tony if you would not mind.

DR. TONY YEN: Sure. “Unproven”.

DR. SHEILA REGE: Kevin?

DR. KEVIN WALSH: “Unproven”.

DR. SHEILA REGE: Mika?

DR. MIKA SINANAN: “Unproven”.

DR. SHEILA REGE: Seth?

Dr. SETH SCHWARTZ: “Unproven”.

DR. SHEILA REGE: Sheila, “Unproven”.

DR. SHEILA REGE: Laurie?

DR. LAURIE MISCHLEY "Unproven".

DR. SHEILA REGE: Connor?

DR. CONOR KLEWENO: "Unproven".

DR. SHEILA REGE: Chris?

DR. CHRIS HEARNE: "Unproven".

DR. SHEILA REGE: Janna?

DR. JANA FRIEDLY: "Unproven".

DR. SHEILA REGE: John?

DR. JOHN BRAMHALL: "Unproven".

DR. SHEILA REGE: If we could get a tally of the voting members on efficacy/ effectiveness.

BRITT REDICK: Ten votes for "unproven".

DR. SHEILA REGE: OK. On cost or cost/ effectiveness any...any discussion on whether the data...I did not see much in the data but open to discussion before we a the straw vote.

OK, John would you like to go first as a voting member on pulling up your yellow card, "Unproven", "Less", "Equivalent", "More in some", "More and all"?

DR. JOHN BRAMHALL: I think there's no evidence that the technology is cost effective. Because there's no evidence that it's effective physiologically, so "Unproven".

DR. SHEILA REGE: Thank you. Janna?

DR. JANNA FRIEDLY: "Unproven".

DR. SHEILA REGE: Chris?

DR. CHRIS HEARNE: "Unproven".

DR. SHEILA REGE: Conor?

DR. CONOR KLEWENO: I guess always depends on what we're comparing, but yeah, "Unproven".

Because there is evidence that it costs money, but not evidence that it provides efficacy. (LAUGHTER) So depend, you know, depending on how we're interpreting. But if we wanna say "Unproven", that's fine with me.

DR. SHEILA REGE: Laurie?

DR. LAURIE MISCHLEY: The way I understand the question, I would say “Less”, based on lack of effectiveness and the cost price tag attached to it.

DR. SHEILA REGE: Sheila, I go “Unproven”. Seth?

DR. SETH SCHWARTZ: “Unproven”.

DR. SHEILA REGE: Mika?

DR. MIKA SINANAN: “Unproven”.

DR. SHEILA REGE: Kevin?

DR. KEVIN WALSH: “Unproven”.

DR. SHEILA REGE: Tony.

DR. TONY YEN: “Unproven”.

DR. SHEILA REGE: OK, would you like, can we get a summary?

BRITT REDICK: Yes. There were nine votes for unproven and one vote for less, for cost.

DR. SHEILA REGE: OK. Let's move on to the next page. We kind of just a little more time for discussion, see if there's any differences of opinions. And remember, we are charged with using evidence for a coverage decision. And so, open to discussion at this point. Any questions? It's a really quiet group this morning.

DR. MIKA SINANAN: Sheila, Mika Sinanan. Question. I am worried a little bit about the internal inconsistency of saying that effectiveness is “Unproven” and cost effectiveness is “Unproven”. And yet, for a significant portion of our group, “Safety” is “Less”. Do we, in fact, have enough data to say that safety is “Less”? If we're saying the data is insufficient, to say the other two are “Unproven”?

DR. JANNA FRIEDLY: This is Janna. Since I voted “Less”, I guess, I can at least share what I was thinking. I think if there is, in my mind, reports of adverse events that you wouldn't expect with a comparison to no treatment. So things like in infection around the injection site or things like that, that you would not expect from no treatment or from alternative treatments like physical therapy or other things. Then I think, in my mind, you can still say that there is less safety, even if you have unproven outcomes and cost effectiveness. At least that’s the way I was interpreting it.

DR. MIKA SINANAN: So, thank you. Just to be clear, one safety event would be sufficient evidence under that analysis. Is that right?

DR. JANNA FRIEDLY: Well, one isolated one, I probably wouldn't. But that wasn't necessarily the case here.

DR. MIKA SINANAN: O.k. Thanks.

DR. JANNA FRIEDLY: But I'd also feel fine, saying “Unproven” as well, but that was my rationale for the “Less”.

DR. CONOR KLEWENO: Same here, if we're comparing like, as I said earlier, for comparing versus placebo. And if you assume a placebo is a injection of saline, then I would say “Unproven”.

If you're comparing to nothing, then I think that even if it's a you know, case reports of injection-related infection versus sort of what the baseline population risk of spontaneous arthritis from bacteremia or that kind of thing, you wouldn't expect them to be related there. So that's why I went with less, if we're assuming that what we're comparing to is nothing. If we're comparing to a placebo injection, then I think I would say unproven.

DR. MIKA SINANAN: So, Conor, thank you. Mika Sinanan again, I'm just not sure we have the data on the untreated population to say all. We have is the data on the treated population, but we don't have the untreated population data. So I don't see that we can actually say we have a, we can assume. Yes, I understand, but we don't have the data to say that.

DR. SHEILA REGE: Mika you're correct because I was using more just the fact that this had to be injected. And that's why I compared it to a placebo based on our safety profile we had outlined.

Any other thoughts on that, any discussion?

JOSH MORSE: Well this is Josh and I would, I would… I reflect on that question and think about is it, is this safe? Is it safe versus the ben, you know, in context of the benefit? I don't know if that helps. Presumably, if you're doing this to my painful knee, there is some assumed likelihood of a benefit.

DR. CONOR KLEWENO: Well, I think, back to Mika's point, I don't think we were presented with a baseline incidence of knee infection. But you know, back to what Paul said earlier or maybe Paul can comment, if you have an injection and get an infection from that, that is less safe than not getting an infection, even if you still get arthritis. Because the complication, which will change your natural history of what kind of knee replacement and when, etc. And so, there is clearly some sort of incidence of a general population for risk of getting knee arthritis or knee infection, septic arthritis of the knee. I mean, I don't know if those presented today, obviously, but there is some baseline incidence level that you would compare to.

DR. MIKA SINANAN: I mean, my take on this would be, you know, if you're looking purely at cost effectiveness, if something is ineffective, you know, and there's any cost to it clinically, then it's not cost effective. And it would be less effective than doing

nothing, but you know, that's you know, that might be more semantics than anything else.

DR. SHEILA REGE: Mika, would you like to go back and look back or re-vote on the straw poll on the yellow card, based on this discussion or?

DR. MIKA SINANAN: No, I did. Thank you for the question. You know, so much of this is dependent on whether there's any benefit. And since we have, I think essentially agreed that the efficacy is “Unproven”, I don't think we can actually say, there's a cost effectiveness. If it's “Unproven”. if we said it was “Less”, then yes, we could vote on cost effectiveness. And if we said, it was “Less” for advocacy, then we could vote on safety. But if it's unproven for efficacy, it, I think, internally requires to - at least the way I'm thinking about it that, that we can't say that it is proven to be less safe or proven to be less cost effective. We just don't have the…

DR. KEVIN WALSH: Can I offer an opinion? I wanna… I think we're way down a logic rabbit hole. I feel like we're meant to just look at each question separately, and not apply the degree of logic to which this is leading.

DR. SETH SCHWARTZ: Yeah, and this is Seth, I think, you know, we are getting a little deep. I think when I used to recall these questions, we would say, is this technology less safe under any circumstances? And that's why when we went for more for, when we talked about effective, we had more, and some and more in all. Because it seemed like a very blunt instrument to say, well, if it's more in like one random condition, then we have to rate it more overall. So we made that differentiation. We haven't really done that for the less. So it's more broad. So if we're saying, could this be less than some circumstance, then the answer may be yes. It may require, I mean, but I agree that data's really soft on this, and it's hard to extrapolate. I think part of the other reason I interpreted this, and I'm one of the people that said less, is because the studies were so small. And there's so much potential for harm in this that may, some of it may be theoretical.

But it's significant, and when we're looking at studies that have 20 people in them for our safety data, it's true, it's unproven.

But the fact that there is even some suggestion, and that limited of a data set would suggest to me that there's the real potential for this to be more harmful. So that was the way I voted. I don't know that we need to be any more specific because we're not looking at precise data on safety. We catch a much, much wide cast, a much wider net, and are willing to look at much lower quality evidence to show safety outcomes in this situation.

DR. CONOR KLEWENO: Right, they weren't phase one trials as you say.

And then to go one step further, you know, given where we are on effectiveness and cost effectiveness, I'm not sure that we need to beat this dead horse. I think we kind of all know which direction this is heading at this stage.

DR. MIKA SINANAN: Yeah, Mika, again. Sheila, I don't think we need to re-vote on it. I was just giving you my thinking about why I voted the way I did.

DR. SHEILA REGE: No. And it's important because you know, we just need to make sure we're all comfortable with moving on from our straw vote.

So now we would need to go to our vote, which would be a second vote based on the evidence and the technology safety, efficacy and cost effectiveness. It is either the choices are not covered; unconditionally; or covered under certain circumstances. And I cannot remember how I went last time. So Tony, I'm gonna have you in the spotlight first, if that's OK.

DR. TONY YEN: Would you like me to give you my vote right now?

DR. SHEILA REGE: If you are comfortable, and if everybody's OK with doing a vote.

DR. TONY YEN: Sure, I'm comfortable. I would actually vote to “Not cover”.

DR. SHEILA REGE: OK, Kevin?

DR. KEVIN WALSH: “Not cover”.

DR. SHEILA REGE: Mika?

DR. MIKA SINANAN: “Not cover”.

DR. SHEILA REGE: Seth?

DR. SETH SCHWARTZ: “Not cover”.

DR. SHEILA REGE: Sheila? “Not cover”.

Laurie?

DR. LAURIE MISCHLEY: “Not cover”.

DR. SHEILA REGE: Conor?

DR. CONOR KLEWENO: “Not cover”.

DR. SHEILA REGE: Chris?

DR. CHRIS HEARNE: “Not cover”.

DR. SHEILA REGE: Janna?

DR. JANNA FRIEDLY: “Not cover”.

DR. SHEILA REGE: John?

DR. JOHN BRAMHALL: “Not cover”.

DR. SHEILA REGE: OK, if we could have a summary of our vote.

BRITT REDICK: This is Britt. And there were ten votes to “Not cover”.

DR. SHEILA REGE: OK. Any further discussion? But then we need to also go to any identified Medicare decisions, expert guidelines. It seems like we're all consistent.

So if we would move on to identify Medicare coverage and guidelines, and that's been projected that there's no national coverage determination. And then clinical practice guidelines. And I know that's been discussed in our evidence report. Anybody wanna add anything? And we're projecting from the Interventional Pain Physicians, 2019.

And I do recall, and I don't know, Josh, help me here. The FDA also had some cautionary on some of the on you know, because on some of the treatments that were potentially harmful and some unscrupulous. And I don't know if that's something we've often added or if that's appropriate to add in for discussion.

JOSH MORSE: Thanks, Dr Rege. I don't know. I think related to the professional society guidelines, the FDA doesn't fit under that umbrella. But I don't think once you've concluded on the society guidelines and the national coverage determination. If you'd like to add that to the record, I think that wouldn’t be harmful.

DR. SHEILA REGE: So we'll go through, keep going on the interventional. And this is all in the PDF we have. And Conor, we look for you to kind of make sure we're not missing any guidelines, keep going. And it's all in our package too. And I think I reviewed this before, and I thought we were pretty consistent. But any discussion on this?

DR. JOHN BRAMHALL: No. But I would just comment that I've come across this discipline in the professional society of anesthesia domain previously. And I've been struck. I may be a cynical person, but I've been struck by the sort of disconnect between the ASA. So the American Society of Anesthesiology will have a sort of position statement and will often defer to subgroups. And there's a subgroup referenced here in our table, the interventional pain subgroup. But who knew it there's an interventional pain subgroup, subgroup, which is the society for spinal injection? And I have been struck in the past by the disconnect between there's a consensus view of the overarching specialty and the specific view of these subdivisions, where you know, it's like, it's what we do. And therefore, we want to have freedom to do it and we'll constrain it with the usual sort of rubric about selection of patients and aseptic therapy, and what have you without necessarily having a reference to the effectiveness.

So that's not, it's just a comment that in the anesthesia world, there are subdivisions of subdivisions of people that do this apparently for a living, and are reluctant to

have constraints put on by the national society in its entirety. Maybe the same thing is in subdivisions of the orthopedic world, I don't know.

DR. PAUL MANNER: It is.

DR. JOHN BRAMHALL: And I'm sorry if I sound disparaging of the well, you know, there's no evidence, right. I sound disparaging and that there's a venal sort of a side to all this, but this seems like it's a little, a little bit strange disconnect.

DR. SHEILA REGE: Very true. I think our state should be commended on trying to you know, have physicians and just healthcare providers do what we're doing. I think just looking at the data and looking at the evidence and trying to discuss these issues. So I must commend Washington State and HTCC.

Any anything else? Anything that would make us change our mind or have a comment regarding our decision? And if not, I would take a motion that we are comfortable with having reviewed the national guidelines, since we're not in the room together.

MIKA SINANAN: So moved. Mika,Sinanan.

DR. SHEILA REGE: Second?

DR. TONY YEN: Second, Tony Yen.

DR. SHEILA REGE: Then all in favor that we are comfortable that we have reviewed the national guidelines.

(VOTING)

Anybody is a nay, please speak now? So that means that we are feel that we are consistent with Medicare decisions and expert guidelines.

Josh, if you would let us know. Well, actually, before the next step, I wanted to bring up the fact that I know that the FDA has had some warnings about you know, some unscrupulous providers, stem cell products that are both unapproved and unproven. I actually did find some in Seattle and they on their websites have IRBs that I tried to track and I was having trouble. And I also have patients that have really paid out of pocket, out of their savings, because this is debilitating, knee pain or any kind of joint pain, musculoskeletal pain.

So, I will forward a Josh kind of something from the STA website, but it's just a consumer update. Any other discussion on that before we go to next steps?

Josh, I will turn it over to you.

JOSH MORSE: OK, thank you all very much. That concludes the stem cell topic for today. The only update I have for you is it relates to the July meeting. It is scheduled for, staring at

my calendar, Friday, July 10th. We'll be meeting at 9:00 in the morning. And if you haven't already, I think, Brit sent out invites for that earlier today. We'll be using the same technology. We'll be doing a webinar.

The decision that you've made today, the draft decision to non-cover stem cell therapies for musculoskeletal conditions, will be published early next week for a two-week comment period before that July meeting.

And then on the agenda for the July meeting will be the minutes from today, the decision from today, and the two draft decisions from May 15th. So we'll have a little bit more than usual for the July meeting. And if you have any questions or suggestions for me you wanna bring up right now, I'm happy to consider them or you can email me after the meeting, if you have any thoughts. So that's all I have for you today.

UNIDENTIFIED: Great, thank you so much.

DR. SHEILA REGE: We have a little time. I would like to ask this committee, and we've discussed. We've gone back and forth about audio versus having video. And there was some talk about whether the presenters should have their video on. Would members of this committee feel very strongly that that would be helpful or it doesn't or it's not as important. And you've seen, I mean, I got disconnected at one point too, kind of with this virtual meeting format. So I just like a discussion on that. Because depending on what we communicate, then our next meeting, our staff is gonna try and ask, you know, do we want ours? Do we want it optional? What would we like? And John and Mika, you were on. And now, I don't see you, so. (CROSSTALK)

DR. SETH SCHWARTZ: And I would just say that while John looks beautiful, I think we should avoid video until hairdressers are open around the country.

DR. SHEILA REGE: So for the July meeting, then it'll be the same and format. Is any anybody with a strong feeling about that?

DR. JOHN BRAMHALL: I think this is fine. I mean, Sheila, we spend a lot of time looking at the actual data, presentations. And you know, that takes up, I mean, just in terms of real estate on this on the screen, the slides are the important thing. I think, and a lot of the Zoom meetings that we all attend, it's automatically uses video if people wish to use it. But this was fine, this was a nice way of doing it. And I think we recognize each other from our voices quite nicely.

DR. MIKA SINANAN: Agreed.

DR. LAURIE MISCHLEY: This is Laurie, I agree.

DR. SHEILA REGE: OK, anybody else? So it sounds like we're all in agreement. Thank you everybody. And again, if there's any other suggestions, thank you for letting me pick on people. And next time, I may try and go from the middle, which I think Laurie is gonna be you and me or Seth. So we'll try and figure that out for next time.

DR. JOHN BRAMHALL: Very clever.

DR. SETH SCHWARTZ: Thank you.

DR. SHEILA REGE: O.K., thank you. Bye-bye now.