Washington State Health Care Authority

# Washington State Health Technology Clinical Committee Meeting

Hyaluronic acid/Platelet-rich plasma

July 21, 2023

DISCLAIMER

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| Josh Morse (HCA) | The Health Technology Assessment program I think we have a couple people that are attempting to log in via teams, we'll give them a moment to get over here into Zoom and then Dr. Rege, when you're ready we can then get going. |
| Sheila Rege | Hello this is Sheila it's 8:01 it. |
| Erika Brodt | Sorry I was talking, and I was muted. This is Erika Brodt from Aggregate Analytics. Good morning, everyone. |
| Laurie Mischley | Good morning. |
| Sheila Rege | Good morning, this is Sheila Rege. Are we doing roll call? |
| Josh Morse (HCA) | Yes, we'll start with the roll call. Val, do you have a list? |
| Val Hamann (HCA) | Yes, just give me a second my computers. |
| Sheila Rege | And this will help us test everybody's audio, the panelists. |
| Val Hamann (HCA) | OK Dr. Bramhall, which he did say he may be half hour late as he did have a conflicting meeting so, Clint Daniels? We couldn't hear you. |
| Clint Daniels | Still can't hear me? |
| Val Hamann (HCA) | We can. |
| Clint Daniels | OK. Are you wanting us to comment on disclosure and things like that as well or just say here? |

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| Sheila Rege | Yes please, please roll call and just tell us your position on the you're on the committee member or career position and if you have any conflicts with today's business or the previous business also the SBRT because we're going to approve that. |
| Clint Daniels | Gotcha so I'm Dr. Clint Daniels. I'm the chiropractic section chief at VA Puget Sound I had no conflicts with the last meeting. For this one, I work with colleagues that offer these procedures, but I don't have any conflicts myself. |
| Val Hamann (HCA) | Okay, Janna Friedly. |
| Janna Friedly | Hi, I'm Janna Friedly. I'm a professor in the Department of Rehabilitation Medicine at UW and a committee member and I have no conflicts for the previous SBRT topic and just like Dr. Daniels, I also have colleagues that perform these procedures, but I have no, no conflicts myself. |
| Val Hamann (HCA) | Chris Hearne. |
| Chris Hearne | My name is Chris Hearne. I'm a nurse practitioner. I work with Swedish Hospital Medicine, and I have no relevant conflicts to this close. |
| Val Hamann (HCA) | Conor Kleweno. |
| Conor Kleweno | Oh yeah, thanks Conor Kleweno, Associate Professor of Orthopedics at University of Washington and Harborview. No conflicts with the previous topic. And similar to what's been stated, I do have colleagues within my department, or within our institution, that do deal with these medications, but I do not personally have any direct conflicts with this or perform these procedures. |
| Val Hamann (HCA) | Christoph Lee. |
| Christoph Lee | Yeah, Christoph Lee. I'm a diagnostic radiologist at the University of Washington and Fred Hutch Cancer Center. I do not have any direct conflicts at the top. |
| Val Hamann (HCA) | Laurie Mischley. |
| Laurie Mischley | Yeah, present. I'm a naturopathic physician at a private practice, Seattle Integrative Medicine and I do epidemiology research at Bastyr in metabolomics research at University of Washington, all related to Parkinson's and I have no conflicts to disclose. |
| Val Hamann (HCA) | Sheila Rege. |
| Sheila Rege | I'm here. This is, and, I have a declared a conflict with the prior topic, the SBRT, only because of some committee positions within the College of Radiation Oncology sector that drafts some guidelines. I have no conflicts for todays. I'm a radiation oncologist in private practice in Eastern Washington. |

Val Hamann (HCA) Jonathan Sham.

Jonathan Sham Good morning, Jonathan Sham. I'm a surgical oncologist at the Fred Hutch Cancer Center, University of Washington. I have no disclosures.

Val Hamann (HCA) And Tony Yen. And so that's all we have.

Sheila Rege All right. Well, welcome everybody. I am going to just let everybody know we are gonna be a little out of order. Currently according to our agenda between 8:15 and 8:40, we are going to be approving the previous minutes, meeting minutes, and the SBRT draft findings and decision which Janna will chair. We're gonna postpone that. Remind me what time we are gonna postpone that because one of the committee members that was present for that discussion could not be here this early. So remind me what time we're gonna postpone that to?

Val Hamann (HCA) 12:30.

Sheila Rege 12:30. But the rest everything will stay so everything will move forward. By that timeframe so we are going to now, I have another question the scheduled public comment can we keep that at 9 am and kind of work around that in case somebody was planning to comment publicly? Question for staff.

Josh Morse (HCA) We can do that.

Sheila Rege Okay, perfect. So, with that, you know, this is an important role for all of the committee members because I think the agency relies on this committee just by law and Josh is going to explain more about the program updates and kind of our responsibilities, but thank you for coming today. Josh, over to you.

Val Hamann (HCA) It does look like we have a hand raised. From Dr. Kleweno.

Conor Kleweno Yes, Sheila, just in terms of, nuts and bolts, I did notify somebody, with committee. I can't remember who that I did need to leave today. Probably 1:30 at the latest. Apologize for that. Just a hard conflict that I have. If there's any way I can work with you with the rest of committee for participation for voting or not, I'm happy to be flexible with that. Just wanted to notify you and I did notify somebody of your email previously.

Sheila Rege Okay, thank you for letting me know. And yeah, if you don't mind, we may call on you if, something happens to make sure that we have a way to reach you in case we come to an issue and have a quorum problem today.

Conor Kleweno Yeah, definitely something I can step out of if needed. I just have a hard conflict later this afternoon.

Sheila Rege Oh. Any other items? Discussion? Otherwise, we will go to program updates.

Josh Morse (HCA) Yeah, thank you here. Working on. Let's see how do we do this reverse this. Okay, are you seeing the main side screen here? Excellent.

Sheila Rege Yes, yes, I am.

Josh Morse (HCA) Okay, so, as you know, today we're talking about a large report on hyaluronic acid and platelet-rich plasma for knee or hip osteoarthritis. And, if you're able to see the screen, then as you know, you are successfully in this webinar. We are recording as we usually do this meeting today. A transcript of today's meeting will be available on our website. We ask for a help and identification that you please state your name when you're speaking and use your microphone. So as noted on today's agenda, we have previous meeting business. We'll start with the minutes from the last meeting, we will, then look at the draft decision and the comments from the June meeting and we'll do that about midday to accommodate a member's schedule. We'll start the morning with the technology review for hyaluronic acid and platelet-rich plasma. Was there a question? The reports for both these topics SBRT from the last review and for today's are available on our website. You can navigate there by going to the Health Care Authority's web page if you need to. So, some background on the program, the health technology assessment program is administered by this Washington State Health Care Authority here in Olympia. This program brings evidence reports to the Health Technology Clinical Committee to make coverage decisions for selected medical procedures and tests. And these are reviewed based on their evidence for safety, efficacy or effectiveness and cost effectiveness as well as other factors. Multiple state agencies are participating in this process to identify topics and implement the decisions from the Health Technology Clinical Committee. These include the Health Care Authority, the Department of Labor and Industries, and at times Department of Corrections at times does participate actively and does actively use the decisions from this process. State agencies implement these determinations within their existing statutory frameworks. In each program, as noted, is operated by different agencies here, so they have different laws to follow. The purpose of this program and this process is to ensure that the medical treatments, devices, and services that are paid for with state health care dollars are safe and proven to work. This program provides resources for the state agencies that purchase healthcare. We develop scientific evidence based reports on the medical devices, procedures, and tests that are selected for review. And our team here supports the HTCC in their process to make determinations for these medical devices and procedures. For anybody interested, there are multiple ways to participate in this process. I've noted the website here where you can get all the information about the program and upcoming dates and comment periods. There is a sign up ability to receive HTA program notifications by email from the Health Care Authority and our program. Anyone may provide comment on topics when they are proposed, on the key questions as the process the topics are being developed, on draft and final reports, and on draft decisions. Anyone may attend the HTCC public meetings and present comments directly to the clinical committee and we will have a comment period here in about an hour on today's topic. Additionally, anyone may nominate a topic for review or for rereview. So regarding public comment, attendees wishing to provide comment, we do have some scheduled to provide public comments. They

will temporarily be reassigned as a panelist in Zoom, the technology we're using today and given the option to unmute and turn on their camera if they wish to. You can see here that a pop-up window will ask you to rejoin the meeting as a panelist. There's a small delay as that happens. We ask that you please limit your comments to 4 minutes, when you are finished providing comment your role will change back to an attendee. There's again a brief pause as that happens. If you're not signed up in advance, please indicate your interest by providing a comment using the chat function. Prior to the comment period the volume of sign-ups will determine it available time for each person. Please disclose any potential conflicts of interest prior to making your comment. So, in the interest of the record here, please clearly state your name, declare any conflicts during the public comment period. We will be sharing this slide at that time. So again, a little bit more detail on the agenda here for today, we will address the minutes from the last meeting and address the draft decision at the middle of the day. The technology review has the standard format here will start after this presentation with the agency medical director's presentation and take on the HA PRP topic. We'll then move to the public comment period. We'll hear from our evidence reviewers with the report presentation. The committee then has time for questions and answers regarding that evidence. The committee that moves into a discussion and decision framework time. After each decision meeting and after today's meeting, the program will publish the draft determination. These determinations are open for public comment for a 2-week period. And our next meeting is November 17th. It's currently scheduled as far as topic meetings go. This is for a review, a rereview of spinal cord stimulators. And if there are any questions, please let me know. That concludes our presentation. Dr. Rege, I can turn it back to you.

Sheila Rege Thank you. And as, as per the law and our prior meetings we do have a, a panelist or a committee member who is non-voting who is an expert. Have we introduced our clinical expert for today?

Josh Morse (HCA) We have not.

Brian Liem Good morning, everyone. That would be me. My name is Brian Liem. I'm a Clinic, a Clinical Associate Professor here in the Department of Rehab Medicine within the UW. I perform hyaluronic acid and PRP injections for multiple joints and different regions here. Primarily at the Husky Stadium Clinic here at the University of Washington. I have no conflicts of interest.

Sheila Rege Thank you very much. Thank you for joining us. And so, just, you know, where we've had some technical issues in terms of voting and stuff. You are a full member, but are not a voting member. So when the polls come up, please make sure you do not, you know, kind of participate in those polls. Appreciate it. Now I will turn it over to the Washington state agency utilization and outcomes presentation.

Azadeh Farokhi (L&I) Good morning, everyone. Let me just share my screen. Okay. Okay, are you guys able to see the presentation?

Sheila Rege Yes.

Azadeh Farokhi (L&I) Okay, not my notes? Just the slides?

Val Hamann (HCA) No, it is in.

Sheila Rege No, I can see the notes too.

Val Hamann (HCA) Yeah.

Azadeh Farokhi (L&I) You can. Alright. Let me stop sharing then. And redo this. Okay. And is it good now?

Val Hamann (HCA) Yes.

Azadeh Farokhi (L&I) Okay, alright, then we can start. Good morning, everyone. My name's Azadeh Farokhi. I'm Associate Medical Director at Department of Labor and Industries and I will be presenting on HA and Platelet-rich Plasma for knee or hip OA. So, starting just kind of with the background information first. So, osteoarthritis is one of the most common disabilities affecting people in the US. About 32.5 million Americans are currently affected and this is projected to grow with estimates as high as 29.5% of US adults over the age of 45 by 2032. So osteoarthritis most commonly occurs in the knee and hip. So, knee OA is the most common form of OA with about affecting about 40% of men and about 47% of women. Hip OA is the third most common form of OA, and it affects about 18.5% of men and 28.5% of women. So, it is a progressive disease that often leads to joint failure, can cause pain, fatigue, disability, general limitations to daily life activities. And since there's really no cure, treatment can become considerably expensive long term. So, healthcare costs due to OA in the US are estimated about 45.5 billion dollars per year. And then there's the reduced ability to work, which results in additional wage loss. So, in terms of treatment management, conservative management commonly includes exercise and physical therapy. These can benefit both pain relief and maintenance of functionality. However, it can be difficult for overweight or obese individuals. Use of NSAIDS or acetaminophen are another common form of conservative management. They're very easy to access, very low cost, but long term use increases risk of potentially serious adverse events. There are supportive devices that can be used as well. And then moving on to sort of the next step, which is inter-articular corticosteroid injections. So, these are very effective at reducing pain in the short and medium term. Risk of adverse events though such as pain flare and rapid destructive osteoarthritis of the joint as well as increased risk of post-operative surgical infection exist. And then as a final last resort is really joint replacement surgery. Of course, this is invasive, has surgical complications and you know it's typically you know, last resort, to do, so. All right, so kind of talking about hyaluronic acid first. Viscosupplementation with intraarticular hyaluronic acid, most commonly provided to individuals who are unable to utilize or don't respond well to other frontline or preferred treatment. So, HA actually occurs naturally in connective tissue joints and other place where extracellular matrix is present. It's native function of hyaluronic acid in the joint is to increase joint cushioning and fluid retention. So theoretically it really carries no risk of immune response when injected due to its non-specificity to any tissue or species. So, it's thought that HA inhibits inflammatory mechanisms and nociceptor firing is what's responsible for

the neurological pain sensation within the joint as well as temporarily restoring a portion of the joints natural hyaluronan producing mechanisms. It requires clearance from the FDA and currently there are 12 FDA approved HA products available in the US. Now platelet-rich plasma has become increasingly popular for use in OA management. But mechanism of action and effects are still not entirely clear. It's derived from a patient's own blood by separating the plasma platelets and other cells other and other cells from the red blood cells in a centrifuge or via filtration and then injecting the resulting compound into the intraarticular space. So this is not regulated as a pharmaceutical product due to its autologous nature and therefore lacks some standardization. So PRP is thought to lubricate the joint, while also suppressing several anti-inflammatory mechanisms and increasing cartilage production. So, this suggests that it may not only, you know, help reduce pain in the short-term but can be capable of repairing damage within the osteoarthritic joint. Okay, so going back to our previous review. So, this is for hyaluronic acid. The initial review that was done on HA was back in 2010. So at that time, it was, covered with conditions, however, those conditions were much more liberal than they currently are. So, it was covered for patients who had not had an adequate response to non-pharmacological conservative treatment and simple analgesics. Now in 2013 it was rereviewed and again determined to be coverage covered with conditions. However, these conditions became much more restricted, and it was really for patients who had a medical contraindication to other forms of non-surgical care. I've included both of those links to those reports for you guys to review if you need to do that. Now for platelet-rich plasma. So autologous blood and PRP injections were reviewed back in 2016 and determined to not be a covered benefit. At that time that review actually included osteoarthritis as well as a range of other musculoskeletal conditions as well. And again, there's the link for if you need to review that. So really why are we, you know, why was PRP and HA selected for rereview? So in terms of PRP, there's a growing evidence base on PRP. So back in 2016 there was only 5 RCTs for various musculoskeletal disorders. But with the 2023 HTA report for knee and hip OA report, for Knee and hip OA we have 34 RCTs, you know, just, for knee and hip OA. So significantly more evidence, than we had back in 2016. In terms of HA, one of the reasons for rereviewing it, as I mentioned, you know, the, coverage decision, from 2010 to 2013, became more restrictive and that definitely presented some challenges in implementing that coverage decision. So we rereviewed it. Okay, so looking at the agency medical director concern so overall fairly similar in terms of our concerns for HA and PRP. With PRP, minimally higher concern for efficacy, but overall, pretty similar. This is our current state agency policies on hyaluronic acid for treatment of knee OA, it is covered with conditions. And current state agency policies for PRP, it is not a covered condition. Okay, so looking at some of the utilization information. So this is agency utilization of hyaluronic acid and related procedures and services. This is combined data for cost and encounter from 2019 to 2022 and you can see you know over the 4 years the number of encounters with HA have been fairly, stable, and similar over each year. The amount paid for HA. You can kind of see the totals about over 2 million. And then the amount paid for HA and related procedures that's over a little over 9 million. This shows the utilization comparison of HA and related procedures and services by state health programs for Medicaid PEBB and L&I and you can see a number of average encounters per individual pretty similar. You know, interestingly

looking at the average total payments per individual, L&I pays significantly more. Alright, and then this is agency utilization of PRP and related procedures and services. Again, combined data for cost and encounter from 2019 to 2022. And you know, of course there aren't as, you know, as much data here because it's not covered procedure but it's also not 0. All right, so moving on into some of the data. So just to kind of mention, Andrea and Erika from Aggregate will, you know, present all the data in comparison. So I've only selected a few of the comparisons for a review here just to not be redundant. So the ones that I, you know, felt were most important. So this first one is a comparison of hyaluronic acid versus placebo for a knee osteoarthritis. So you can see in the data table that there's moderate evidence that HA was associated with a small improvement in function, short-term. But no difference between treatments at intermediate term. And moderate evidence really that there was no difference at short or in your intermediate term on pain score or likelihood of achieving a clinically meaningful threshold for pain improvements at either short or intermediate term. So overall, when you compare HA and placebo for knee OA, really no significant difference. So next one is a comparison of PRP versus placebo for knee OA. So this table you can see PRP was associated with improvement and function at all time points measured based on the WOMAC physical function and IKDC scales. But no difference between PRP and placebo on the KOOS ADL and sport and recreation sub scales. Similarly, PRP was associated with moderate improvement compared to placebo based on the WOMAC pain sub scale at short and intermediate term. But no difference between groups at any time on the KOOS pain scale. All right, and then this is a comparison of HA versus PRP for knee OA. So you can see it intermediate and long term, PRP was favored over HA for the likelihood of clinically meaningful improvement based on the WOMAC physical function sub-scale. At intermediate term PRP was associated with higher likelihood of treatment response and with small improvements in pain on both WOMAC and VAS pain scores. An improvement really favoring PRP persisted into the long term based on WOMAC pain scores. So just to kind of summarize the evidence for knee OA, for hyaluronic acid, really no difference when compared to placebo, when compared to steroid, when compared to NSAIDs, and when it was compared to PT, there was actually small improvement that favored PT. And most of these studies were industry funded. So for platelet-rich plasma, there was moderate improvement in function and pain compared to placebo, small improvement in pain but not function when compared to steroid. Improvement and function and pain when compared to analgesics and no difference between PRP and exercise. So moving on to, the evidence for hip osteoarthritis. So this is a comparison of hyaluronic acid versus placebo for treatment of hip OA. And there really was no, differences between HA and placebo on measures of function or pain across to our RCTs short or intermediate term. And then, for PRP, so this is comparison of HA versus PRP for treatment of hip OA. There's one RCT that found basically no difference between HA with PRP on measures of function or pain. So in summary, when looking at hip osteoarthritis, no difference between HA and placebo or steroid use and no difference between HA and PRP on measures of function or pain. So briefly, kind of to talk about the safety, this is for hyaluronic acid. So for knee OA, there was a substantial heterogeneity regarding how adverse events were categorized and described. Serious adverse events were uncommon following HA injection. Treatment related adverse events, very variably defined and

not specified as serious. These were more common. But really no difference between HA and the comparator groups. And for hip OA, there was one serious treatment related adverse event, which was arthralgia in the saline group. Now, safety for platelet-rich plasma. Again, substantial heterogeneity regarding how, adverse events were categorized, reported, and described, if they were described at all at all. So many of the trials simply stated that there was no serious events that occurred. Evidence on safety harms was considered insufficient due to generally poor reporting of serious adverse events and small sample sizes. So 2 studies reported serious adverse events as defined by the authors. So 3 of the leukocyte rich, PRP cases experienced swelling and mild fever with one requiring arthroscopic debridement and one leukocyte poor case of severe inflammation with swelling and stiffness. And then for hip OA, really insufficient evidence to draw conclusions. So in terms of the cost effectiveness, there were 3 US based studies comparing HA with various forms of conservative care. So they've determined that HA was cost effective at a willingness to pay of 50,000 per QALY. One poor quality US based study compared HA with PRP, found that PRP injections were not more cost effective than HA. There were 4 economic studies that were conducted outside of the US. Those might not be, you know, relevant to, to what we do in the US. Studies in the US again, we're mostly industry funded, with high risk of bias. And then conclusion regarding really cost effectiveness of HA were difficult. Alright, so just to kind of show you some of the other payer's policies, this is on intraarticular hyaluronic acid injection for knee and hip OA. So the Center for Medicare Services, CMC, does not have a national coverage determination on HA for knee or hip OA. As you can see, the majority of private payers do cover HA when conditions are met except for Premera Blue Cross which finds it not medically necessary for the knee and investigational for other joints. And this is for PRP. So again, CMS does not have a national coverage determination on PRP injections and private payers do not cover PRP. Okay, so just to kind of share a little bit of the guidelines on the use of HA, for knee or in hip OA. So, of interest this is or the orthopedic in the rheumatology groups both recommend not covering HA for knee OA. And this is guidelines on the use of PRP. So, this ortho, orthopedics recommends that PRP may be helpful, while rheumatology recommends against PRP use. Okay, so this is our final recommendations. So, for hyaluronic acid injection is not a covered benefit for the treatment of knee osteoarthritis and hyaluronic acid not a covered benefit for the treatment of hip osteoarthritis. And for PRP, platelet-rich plasma injection is a covered benefit with conditions for the treatment of knee osteoarthritis. So, some of those conditions' adults over the age of 18 with symptomatic knee OA treatment after failure of conservative treatments, question of repeat injection, whether that should be covered or not. Overall, really there was no difference between single versus multiple injections and then of course we have concerns for lack of standardization and heterogeneity. So really no FDA guidance here. And PRP injection is not a covered benefit for the treatment of hip osteoarthritis. And just to make a brief note, autologous blood injection is still not a covered benefit, that was part of the prior review. But was not included in the scope. So that would remain and not a covered benefit. And I believe that is it.

Josh Morse (HCA) Excellent. Thank you, Dr. Farokhi.

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| Azadeh Farokhi (L&I) | Sure. Would you like me to stop sharing or? |
| Sheila Rege | We'll ask if there's, any questions for Dr. Farokhi from the committee members? That was excellent, Dr. Farokhi. |
| Azadeh Farokhi (L&I) | Thank you. |
| Sheila Rege | And normally after this we would go to the public comment, but we're gonna hold off. And we will begin the evidence report if there are no questions. Please let me know. |
| Janna Friedly | Sheila. Sheila, Conor and Chris. Conor was first and then Chris has his hand up. |
| Sheila Rege | Thank you, Janna. Go ahead, perfect. |
| Conor Kleweno | Yeah, if you could put back your conditions slide. |
| Azadeh Farokhi (L&I) | Yep, this one. Okay. |
| Conor Kleweno | Yeah. Okay, and this is sort of the working document you have at this point, right? |
| Azadeh Farokhi (L&I) | Yes, yes. |
| Conor Kleweno | Alright. Thank you. |
| Janna Friedly | And Chris? |
| Chris Hearne | Thank you for the presentation. I just wanted to clarify it. I understood from the beginning of the presentation that PRP is autologous platelets and so if I don't know if autologous blood injection isn't a covered benefits, how is that, how would that be implemented? |
| Azadeh Farokhi (L&I) | So, are you talking about this the final note here the autologous blood injection is still not covered? |
| Chris Hearne | Correct. Correct. |
| Azadeh Farokhi (L&I) | Yeah. So yeah, this was part of the previous review. It was autologous blood injections and PRP. So this would still remain not covered. It would be, I mean, PRP, yes, I know it's, it's autologous injection, but for PRP, it would specifically, you know, we would recommend, covering that, but not other, not other forms of autologous blood injections for it for anything else. |
| Chris Hearne | Gotcha. Gotcha. Thank you. |
| Azadeh Farokhi (L&I) | Yeah, yeah, I just wanted to make a note of that, because it was part of the previous review. So just keep those 2 things in mind. |

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| Janna Friedly | And Brian? |
| Brian Liem | Yeah, I think to clarify the difference between PRP and what we consider autologous blood here in a clinic is in the autologous blood when we take the blood from someone's vein at acute vein, we don't manipulate it so we don't centrifuge it at all. It includes red blood cells and, and you don't want to inject a product that has red blood cells into a joint because essentially red blood cells can cause inflammation and damage. So PRP is basically the centrifuge form isolating out simply the platelets, which gets rid of the red blood cells. So I think that might clarify the difference. |
| Conor Kleweno | Maybe having the word whole in there, autologous whole blood, Brian with it. |
| Brian Liem | Yeah, I think that might be to clarify. A little bit because it can keep confusing if the word autologous blood is used synonymously with PRP. |
| Azadeh Farokhi (L&I) | That makes sense. Thank you. |
| Sheila Rege | That is a good idea. So, we'll just remember that when it comes up for discussion. Any other hands raised? I'm having trouble seeing hands raised. |
| Janna Friedly | Nope, I don't see any. |
| Sheila Rege | Okay. You know, we normally do a break after public comment. If everybody's okay since we've just started, I would like to move to the evidence report. |
| Josh Morse (HCA) | That sounds good. Sheila, Erika, Andrea, are you ready with the evidence report? |
| Andrea Skelly | Yes. The plan we have is I will run the slides and Erika and I will be a tag team for presenting. And so, I may need a reminder how to share the screen so you can see the slides, but I can see the notes. So, I just share the presentation? Is that it? |
| Josh Morse (HCA) | That should be it. I'll be honest and I have to sometimes experiment with zoom and this screen side, but right screen correct, if you have multiple screens. |
| Andrea Skelly | Okay. |
| Josh Morse (HCA) | Not doing this frequently enough. |
| Andrea Skelly | Oh yes, I do. Yes, I do. You and me both. Okay, well let's give this a try and we'll see, we'll see how this works. Alrighty, so you can see my slides? |
| Josh Morse (HCA) | We are seeing. |
| Andrea Skelly | But I can't see my notes. And if I go to slideshow? |
| Erika Brodt | Yeah, our presenter mode is there. I think that's usually an option. |

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| Andrea Skelly | Oh, I'm sorry. Where do I find the center? Placental mode, yeah, right. Presenter mode. I'm also having a little trouble with the. |
| Janna Friedly | You can go on to the slide show. |
| Erika Brodt | Yeah, you could. |
| Janna Friedly | There you go. And then you can, you can do that or, or there's a presenter mode. Somewhere. |
| Andrea Skelly | Oh, there we go. Now we're cooking with gas. All righty, well. On behalf of Aggregate Analytics, I'd like to thank you for the opportunity to present our work on this. |
| Janna Friedly | Andrea, sorry, we're still seeing, we're not seeing the, the slide we're seeing the, the notes and the, yeah, not |
| Andrea Skelly | All right. The notes? Okay. Okay, so I'm gonna end the slideshow. And. How do I stop sharing? Stop sharing. |
| Erika Brodt | What, what if you hit the little slideshow icon up at the? |
| Andrea Skelly | Or, oh, like up here. |
| Josh Morse (HCA) | The sharing you need to remove screens. |
| Erika Brodt | Yeah, see if that I don't know share that. |
| Andrea Skelly | Yeah, I've got I've got a dual screen. I mean, if I don't, and don't have the notes, it's okay. Is that better or you can still see the notes? |
| Janna Friedly | No, we're still seeing, we're not seeing the slides show version. We're just seeing the PowerPoint. |
| Andrea Skelly | Okay. |
| Janna Friedly | That's, version. |
| Andrea Skelly | So let me see. I'm sorry, go ahead. |
| Laurie Mischley | In the bottom. On the bottom right, there's a monitor that you can click and that'll, that's another way to do it. If you go back to the screen, you were just on. |
| Andrea Skelly | Screen I was just on. Okay. |
| Laurie Mischley | Share again. |
| Andrea Skelly | I'm sorry? Oh, share again. Okay, sharing again. Then there's |

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| Erika Brodt | Sure. |
| Laurie Mischley | Go back. |
| Sheila Rege | Are you, are you on a MAC? or on a PC? |
| Andrea Skelly | PC. |
| Sheila Rege | Okay, so the PC people please help her. I'm on a Mac, so I'll stay quiet. |
| Andrea Skelly | So I can share my screen. But I don't think that's what we want. |
| Sheila Rege | Can you do a slide show, you know, how they'll let you do that? And then share your screen, after you do that maybe that'll help? |
| Laurie Mischley | So down on the bottom right, see where it says 60%. Go, slide left a little bit. It's that first icon to the right. No, to the right, to the right, to the right, to the right, to the right, to the right, right there. |
| Andrea Skelly | Right. |
| Laurie Mischley | Click that. |
| Andrea Skelly | Okay. |
| Sheila Rege | There we go. |
| Andrea Skelly | Interesting. I wonder why it worked that way and not. |
| Janna Friedly | Well, we're still seeing the…okay. |
| Val Hamann (HCA) | So. |
| Sheila Rege | Well, we're still seeing notes. |
| Laurie Mischley | Okay. |
| Andrea Skelly | Yeah, okay. Well. |
| Erika Brodt | That's better. |
| Clint Daniels | So, you know, changes swap the monitors. Like there should be a way at the top. To like a little pop up where it says you can swap which is on which screen. And I think probably you're seeing the slides on one. |
| Andrea Skelly | Display settings. Okay, display settings swap presenter and slideshow. |
| Clint Daniels | And then I think it'll show us the slides and you'll still see that other screen. |

| | |
|---|---|
| Andrea Skelly | Okay. So, are you seeing anything? I think I stopped sharing. That's why. Are you seeing anything? |
| Erika Brodt | Nope. |
| Andrea Skelly | Okay, alright, so let me go back. And now I can't see you all. There we go. Okay, so. I'm going to share. I'm going to do the PowerPoint. And share. |
| Erika Brodt | There it is. Nice. |
| Sheila Rege | Yes. |
| Andrea Skelly | Okay. All right. Well, I can't see my notes, but that's okay. Let me. |
| Erika Brodt | Oh. They're not on the other screen? |
| Andrea Skelly | Yeah, it's on it's on my small my little computer small computer screen. I'm sorry y'all. I think after several years of doing all this, we'd all have it down. But that is not the case. Let me try this. And if this doesn't work, I'll just go without notes. Does that work? |
| Brian Liem | Hey, Sheila, do you have 2 screens? |
| Andrea Skelly | I do. |
| Erika Brodt | Yeah, I can see. Yeah. |
| Brian Liem | Okay, so maybe try, yeah, so we can see the slides now. If you need the notes, sometimes at the top part of the of one of the screens. Right by the X, you know, when you can X out the, presentation where the top quarter of the presentation right next to it is like a like a little 2 boxes squares double over each other. If you click on that, sometimes you can just move one of the screens. The note screens to one of the screens and then the presentation to the other screen, so can swap them. |
| Andrea Skelly | Yeah, I'm sorry. |
| Josh Morse (HCA) | Alternatively, Andrea, I'm happy to present from my screen if you want to follow with your notes. |
| Andrea Skelly | I think it's okay. I think it's okay. I'll have Erika back me up. She's probably more important for her to have the notes. And for me to have the notes. So why don't we go ahead and if you can all see what's going on, we'll start from the very beginning. How's that? |
| Sheila Rege | It's back to the problem. |

Andrea Skelly I'm sorry? This is a problem.

Erika Brodt No, it's we don't see the full slide again. What if you go down to the. There it is.

Sheila Rege There we go.

Andrea Skelly Okay, we're cooking with gas now?

Sheila Rege Yes.

Erika Brodt Yes.

Andrea Skelly Okay. All righty then. All right. Let us move forth. So again, thank you. And I just would like to acknowledge all of the people that help put this together. Most of whom are listed here. We did have Eric Latzka who was at the University of Washington serve as a clinical expert and assisted with topic refinement as well as with a peer review and he was available to answer questions as we went through the report. So I'm going to actually, I believe, turn it over to Erika now who will give the reader's digest condensed version of the prior reports. Dr. Farokhi actually covered most of this. So, take it away Erika.

Erika Brodt Yeah, good morning everyone. My name is Erika Brodt and yeah, on behalf of Aggregate Analytics, I'll be presenting, tag teaming with Andrea. As some of the results here. So, we're gonna start the next 2 slides just give a brief overview of the previous reports. And I'll try to go, I, we recognize there's a lot of slides and so we are gonna try to go fairly quickly through a lot of them. Especially the background because Dr. Farokhi did do an excellent job summarizing a lot of that. So I don't think there's a need to kinda rehash that. So starting with the prior report on hyaluronic acid, it was published in 2013 and it actually updated a prior report from 2010. Looking at HA specifically for Knee OA. That review relied mostly on summarizing evidence from published systematic reviews. So it was kind of interesting to, to work through. It did incorporate some new evidence but again most of the data came from SRs. Most of the evidence was HA compared with saline. There was limited evidence for other comparators. The authors found that there was some benefit in paying function compared with saline for HA, moderate quality of evidence, but that those differences were small and likely not clinically relevant in their opinion. Yeah, evidence showed comparable efficacy to NSAIDs but that HA was inferior to corticosteroids. They did look at different formulations of HA, but really didn't come to any conclusions about their differential efficacy. For safety they only had safety in the short term data which showed that HA was fairly safe in the short term, but they had no longer term data. So moving on to the PRP report, which was published in 2016. As a Dr. Farokhi mentioned that report included you know not only various musculoskeletal conditions no longer applicable to this review out of scope. So other than knee or hip OA there were also interventions that were included that are now out of scope for this review and that includes autologous whole blood, autologous conditions serum, platelet-rich growth factors things like that so the focus again is simply on knee and hip OA. That report found that there was short and intermediate term improvement in pain and

function versus saline. When compared with PR or HA, there was no difference short term, but over the longer term, PRP was favored regarding pain and function improvements. PRP had comparable efficacy to exercise and somewhat superior efficacy to corticosteroids. And most of those results at that time were based on low quality or insufficient evidence. Regarding safety, PRP and more adverse events then saline but comparable to other treatments. And the results of our rereview are pretty consistent with the results of these prior reports. So the rationale again is Dr. Farokhi said, we have a lot more evidence, both on hyaluronic acid and PRP to include more comparison so different treatment options. The new review again is specific to osteoarthritis of the knee and hip and specific to hyaluronic acid and platelet-rich plasma only as the primary forms of treatment. So moving on to some background. So again, osteoarthritis as we've talked about. It's a progressive degenerative joint disease. It's currently not reversible. It's not curable and the knee and the hip are the most affected joints. It's very prevalent in the American population and it's very costly to treat. So, osteoarthritis is classified radiographically via some validated scales, the most common of which is the Kellgren-Lawrence. And most of the studies included in our report use the Kellgren-Lawrence. The Ahlback scale is another scale that is often used in a couple of studies did use that as well. Those 2 scales are fairly similar. And the higher the grade, the higher the degree of degeneration. There was a third scale used just by one study. It was very different, MRI based and looked more at cartilage changes. So the management of osteoarthritis is talked about previously. You start with conservative management, including, you know, exercise, physical therapy, pharmacological treatments, also intra-articular corticosteroids, and all of those are in the hope of delaying or, obviating the need for a total joint replacement surgery. But that is kind of the last, last option and each treatment is associated with disadvantages and advantages. So again, briefly, hyaluronic acid does occur naturally in our bodies and connective tissue joints and other places where extracellular matrix is present. The pharmaceutical versions of HA which we're talking about here are made either from avian sources so they come from rooster combs or from bacteria, through bacterial fermentation. And they are injected into intra-articularly and as said previously there's a low risk of a immune response given it's non specificity to any tissue. Thought to provide anti-inflammatory and conjure protective effects. The FDA has approved 12 different products for use in the knee. However, there's a lot of variability in, the compositions sources and formulations of these products as well as the treatment regimens. So, it's not standardized. Platelet-rich plasma again, is derived from a patient's own blood. And I said before separating the plasma from the platelets and other cells and compounds like leukocytes and growth factors. And what you're doing is you're basically concentrating the platelets within the plasma. So, it generally creates about 3 to 5 fold higher plate the account than you normally see in the whole in in whole blood. But there's no widely accepted. A quantified value of platelet concentration in PRP. The mechanism of action, again, not entirely clear, but, evidence supports lubricating and anti-inflammatory effects within the joint. So the FDA does not regulate PRP as a pharmaceutical product given it's autologous nature so it's used off label. But there are a wide range of devices used to process PRP so like centrifuge machines and PRP kits that are cleared by the FDA for use. Again, you know, and you'll hear us talk about this a lot, there's just currently no

standardization in how these are made or delivered. So indications for both PRP and HA are similar. We're looking to relieve pain for patients who aren't responding to other treatments. Contraindications are similar as are common adverse events such as injection site pain, joint swelling, which can be expected with these treatments. Serious adverse events can include severe swelling, severe or serious infection and sepsis. So our key. Sorry, was there a question? Okay. So our key questions we have to the first key question is focused on hyaluronic acid. And it's subdivided into, looking at what the effectiveness, the harms and complications, differential effectiveness or safety, and cost effectiveness of hyaluronic acid compared with either placebo, sham, other common conservative treatments to include PRP, or no treatment. Key question 2 is focused on PRP and is, runs in parallel with key question one, so asks the same questions. I do just wanna point out that for the comparison of HA versus PRP that is covered under key question one. So under sub A here, we, said that we weren't comparing PRP with HA, simply because that's covered in the prior key question. So our inclusion criteria, we looked at adults who were symptomatic with knee or hip OA. The interventions again just PRP or HA and for HA it had to be FDA approved formulations. They could not be used in conjunction with other interventions not listed for inclusion such as, arthroscopic or minimally invasive surgery and we did not include combinations of HA and PRP together or with use with biologics. Common, so competitors again are listed here. And our primary outcomes of interest are pain, function, and the need for invasive surgery and harms. So, we only did strength of evidence on these primary outcomes. We looked at a number of secondary outcomes and they're available in the full report. And then of course we looked at economic impact. So given the chronic nature of the disease, our intent was to focus on outcomes that reported data at least one month post treatment. We did of course support what we were given though. And study design was focused on RCTs since they have the, least potential for bias. And of course, English, studies published in English and peer-reviewed journals. So our methods, we do strength of evidence, which is based on AHRQ, so the agency for healthcare research and qualities recommendations and our application of grade. Which I believe most of you are, pretty familiar with at this point. We grade the overall strength of evidence separately for each primary outcome. So function, pain, that kind of thing. Using the domain shown here. So risk of bias is just one of those domains. Then we look at consistency across studies, directness all of outcomes in this report were considered direct, precision the level of certainty around the effect estimates and publication bias is difficult to affect and for this, or sorry difficult to assess. And for this report, we could not, assess it given, the few number of studies, for each outcome. So, our systematic review process again when we go as we go through and identify studies for inclusion, do the synthesis and analysis. Then across each outcome, we rate the strength of evidence. And we come to a rating, okay, that reflects our confidence that the effect is true or accurate. So that's high confidence, moderate, low or insufficient. So, getting to the results. So, our literature search, we, searched for studies published since the prior reviews, so we didn't go all the way back and we did include any relevant studies that still met our inclusion criteria for this. So, we check them for accuracy and carry them forward into this review. So we looked at over 2,000 citations and ended up including 61 unique RCTs across 64 publications. So throughout this report, we have classified the magnitude of effects

based on a system we've used often in our AHRQ reviews on pain. And you can find, you can find this in appendix J as well of the report. So, in general an improvement of 5 to 10 points on a hundred point scale is considered a small improvement. Greater than 10 to 20 is moderate and greater than 20 is large. And I just wanna note that, even if something is to statistically significant, but the effect falls below a threshold for small we categorize that as no effect, since that's kind of a clinically meaningful cut off. So just some quick notes about the organization. So. This report focuses again just on function pain. The need for invasive procedures and safety. We're going to go through all of key question one first, which Andrea will present. And then I will present key question 2, which is PRP. Okay, if you need to refer to the full SOE tables, you can find them in section 7 of the report and we've noted some key here that could be helpful.

Andrea Skelly Okay, well I guess this is my cue. So.

Josh Morse (HCA) Good. Just check in with Dr. Rege here since we're at a possible good check in point. Sheila, do you wanna check in for public comments? At this point since it's not a little bit after 9.

Sheila Rege I think we should and then Josh, maybe make an announcement since if there's not, you know, we If we don't take up the full time of a mechanism that they can let, the committee, the staff know, that they want a public comment in case we finish early. Go ahead. Okay.

Josh Morse (HCA) Yes, so we don't have anybody signed up in advance to provide a public comment. We have 13 attendees, a number of which are part of our process or part of our agencies, but If there's anyone else attending, if there's a public attendee that would like to provide comment at this point. Can you raise your hand or indicate that in the chat? I think I'm gonna have to check in with Val though about the technology here if we have the chat function on or what the proper way

Val Hamann (HCA) We, yeah, we don't have the chat function on, but there should be a QA that they can put a question. Just or simply something stating they would like to present a comment.

Josh Morse (HCA) So, let's do that here for a few seconds. If there's anybody that would like to provide comment, please use the QA function to let us know. Okay. Sheila, I think we are good to move on. I do not see any indication of an interest to do a comment right now. If you'd like, we can change it again at the end of this presentation?

Sheila Rege Yes, that would be good. Let's, let's make sure to check again. Actually I'd like to check again in 10 min in case somebody is late. But they can always use the QA if they come on so thank you keep going

Josh Morse (HCA) Okay, thank you.

Andrea Skelly All right, thanks. So we'll start with key question one which focuses on how hyaluronic acid and if you consider both generic and approved brand names there are 15 I believe listed in appendix K and as you already know there are various

compositions sources formulations, molecular weights, and there really is no standardization. In the studies there was a broad range of doses and treatment schedules so again, no standardization. For the question of HA versus some other comparator we had a total of 30 RCTs, 33 publications and you can see most of them were concentrated in HA versus placebo or HA versus PRP. Most of them were industry funded for the HA versus placebo and you know kind of split then for the HA versus placebo and you know kind of split then for the HA versus PRP, but most of them did not receive any funding. One thing to note is that some of the RCTs did, did contribute to more than one comparator. So let's look at the effectiveness for knee OA first. So we had 9 RCTs, 7 of which were industry funded across 12 publications, fairly reasonable sample size as you'll find with all of the studies both for HA and PRP most of them were in an age range of sort of mid to late fifty's to early mid sixty's, most of them were in females and most of them were grades 2 or 3 on the Kellgren-Lawrence severity. And again, you're gonna see this throughout, but. And again, you're gonna see this throughout, but the HA injections, you can see we've got to see this throughout but the HA injections you can see we've got some used single one used 3 injections one used 5 injections usually it was weekly if there were multiple injections. And again, the distinction between high molecular weight and low molecular weight isn't really clear. Most of these labeled themselves as high molecular weight. There wasn't reported in one of the studies and again we had a range of doses per injection. And for saline injections in general they mimic the frequency seen in the HA injections. So looking here at WOMAC function, we can see that at short term, there was a small improvement that favored HA over the saline, but there was no difference at intermediate term and we considered the strength of evidence for this to be moderate. If we take a look at pain success or that clinically meaningful important difference and percentage of patients that may have met that you can see that there's no real difference between the HA versus the PRP at short or intermediate term. And, yeah, you, you can see that that's the case and the strength of evidence was moderate.

Sheila Rege Okay.

Andrea Skelly If we take a look at the pain scores individually, either on a WOMAC, 0 to 20 scale or VAS 0 to 20 scale or VAS,0 to 10 scale. Again, the bottom line, a short term was that there was no difference. That was based on the highest quality study. We do have a range of quality of studies and so, we felt that it was best to focus on the highest quality study this low risk of bias study for our final determinations and strength of evidence of moderate. When you look at 6 months, again, no difference. The pain scores for the WOMAC scale were below our threshold so that's although, I, it's although it's statistically significant that's why we made a determination of no difference and there was insufficient evidence that long term. Looking at responders using the OMERACT-OARSI criteria, which was you know as sort of a multi component criteria having to do with pain and function. There was no difference at any time period. The Strand study was a fair study, a moderate risk of bias, so we gave that stream of evidence low, but the Farr and the Gomoll are the same RCT different time frames and they were both very core so the strength of evidence was, considered insufficient. Moving on. When we look at HA versus PRP,

we had a 11 RCTs across the same number of publications. 2 were just industry funded, others were not. One interesting note at is that all but one RCT was conducted outside of the United States. And again, we see similar demographic information for this set of studies. And again, heterogeneity across the numbers of injections, the molecular weights that were used and the dose, dose ranges. And turning again to again a clinically meaningful change, a success if you will, in physical function. The first study, Tavassoli did not give us information by patient only by percentage in terms of knees and they found that no HA recipient met the thresholds for a response for this comparator. And one then moderate quality study, we have low strength of evidence that at intermediate term hyaluronic acid was associated with a lower likelihood of treatment response versus the PRP. So PRP was favored and that also was true long term and strength of evidence was low. If we turn our attention now to the scores. This is the plot showing all of the available studies. We made our determination of strength of evidence and etc. based on excluding the one study that was an outlier that reported on knees. At intermediate at short term and there was no difference. In intermediate term there was evidence of a small improvement that unfavored PRP not the HA for low strength of evidence. And then at long term, again, small improvement with PRP over HA for low strength of evidence and that excludes the outlier trial that you see here. And then when we take a look at some of the other measures of function like the IKDC, the Lysholm, it depends a little bit on the scale. What the, what the range of outcomes was but basically there is no difference at short term across the 2 same studies that looked at the Lysholm and the IKDC. An intermediate term, maybe a small improvement when you look at the IKDC versus the Lysholm. But we thought that the evidence for the live show was insufficient because of the quality of the studies and basically, the same story long term. So insufficient evidence when you consider the Lysholm based on poor quality studies and in consistency and in precision, but low strength of evidence if you want to consider the IKDC and small improvement. So moving on. Looking at the pain success again, using different cut offs, the one study, again, reported them patient knees suggests that, you know, there was a very different response in the PRP group, but again, insufficient evidence. The good, the high quality study showed that substantially more PRP patients received that, substantially more PRP patients received achieved the 20% decrease. Yeah, in pain scores relative to the HA group. If we take a look at scores again, we see a bit of a similar pattern to what we've seen before. Excluding the outlier there was no difference short term for HA versus PRP again part of the issue is meeting a clinically important threshold an intermediate term there was small improvement. At a longer term, again small improvement. A string of evidence was low for all of these time frames. And again, we did exclude, the extreme outliers. If we go on, now we're going to HA versus steroids. Unless did I hear a question? Okay, hearing none. So again, similar demographics.

Sheila Rege Let's, let's have everybody mute, unless you're speaking.

Andrea Skelly Oh, okay, that'd be a good idea. Yeah.

Josh Morse (HCA) Hey, sorry, since we're in a pause here. The chat is currently open to anyone for a few minutes if you'd like to make a comment. And have not been able to indicate

that, you can use the chat function at this point to let us know you'd like to make a comment. Thank you.

Andrea Skelly

Okay. So moving on to HA versus steroids for knee OA, still in knee OA, in similar demographics. Similar story, different injection protocols for the HA, as well as the steroids. There was a fairly reasonable correspondence if one group got, in one study if they got single injection of HA, they also got single injection of corticosteroid. Variety of different steroids were used and again doses ranged for both the HA injections as well as the steroid injections. Looking at WOMAC physical function. Looking at the scores for WOMAC, KOOS, and KSS you can see that there's no difference between HA and the steroids and that's based on a good quality RCT. And the pooled KSS across 2 studies, that were very poor quality, we didn't feel was a good way to consider the strength of evidence for that. So it's the low is based on, no difference between HA and steroid injection based on the good quality RCT. For KSS, again, poor quality studies and the evidence was insufficient. And you can see plotted out here the WOMAC pain scores, not a lot to write home about, both not is significant at either time frame and the strength of evidence was considered moderate. But we don't have a lot of studies. Although we have one fairly large study. Moving on pain scores using the VAS again, no difference in any time frame. We felt that was insufficient at long term because of the poor quality, one single score quality RCT. And moving on to NSAIDs, this is an interesting one because the 2 studies use different types of NSAIDs, so we have one study that used an oral NSAID the other study used an IM etofenamate. All right, I will leave that for another day. But, I will leave that for another day, but, one's oral, one's IM. And if we take a look across the function scales we can see that there's no difference in either time frame for the oral versus the HA, oral NSAID versus the HA and so there was a small improvement. If you take a look at the WOMAC physical function, so no difference in success or meeting clinically important threshold. As far as the physical function scores, maybe a small improvement with HA again over the NSAID, but the strength of evidence was low. If we take a look at the success, the 20% decrease in score. There was no difference, at 6 months or at 12 months. Looking at pain scores, the WOMAC pain score moderate improvement with the HA versus the NSAID and strength of evidence was low for all of those. Looking at a forest plot that includes both of the studies with the different NSAID preparations, you can see that one the one using the oral NSAID does show a small improvement in the VAS pain whereas the IM NSAID there was no difference at either time frame. And so the strength of evidence was low that for the oral NSAID, and for the pooled analysis that there was no difference. And then, also, when you pool them together, there is no difference. But again, noting that one is saying something different than the other. Moving on then to other comparators. We have very few studies really looking at other comparators. And there's a mistake, I believe, here that one of the studies was industry funded for the, for the comparison of HA versus physical therapy. And you can see that the HA was probably considered a low, low molecular weight, 3 injections, a week apart, 20 min of superficial body superficial heat pack for the physical therapy with TENS and pulsed ultrasound in addition we also had one of the studies look at dextrose, a prolotherapy as a comparator and you can see that for the prolotherapy 20% dextrose plus some lidocaine, 3 injections total one month apart. Similar to what the hyaluronic acid frequency was. We also did have a one fair

quality study that, so it's again one fair quality study, that looked at different preparations one was an animal derived HA one was a non-animal derived HA and they included for the animal derived 4 doses of that, that preparation but for the non-animal they did one dose and then they did 3 sham injections which were basically an empty syringe, so not really an injection. So kind of interesting, but here's the here's the bottom line for some of these. So, for comparing, HA versus, I'm having trouble seeing I'm gonna, that the HA versus PR, HA versus the PT. There was no difference in, one study on the KOOS ADL, but when you look at the KOOS sport and recreation, it suggests a small improvement. So it depends a little bit on which effect measure is used, whether you see, an effect or not. Same thing with pain, a moderate improvement with VAS pain, looking at KOOS pain, the improvement was a little bit smaller in effect size. Only short term data were available for this comparator. Then looking at prolotherapy, we can see across the board the improvements favored the prolotherapy over the hyaluronic acid. Again, some difference in effect sizes depending on the measure. Strength of evidence was insufficient at short term but low for the for the KOOS ADL, but the others were low strength of evidence for a short term improvement again, favoring prolotherapy over HA. Looking at the pain, excuse me, physical function. This, so this is for that head-to-head trial of the 2 different preparations, animal derived versus non animal derived. And you can see that there's no difference at all. Intermediate term is all we had for data, for this one, but there were no differences in pain scores or function or responder categorization. So safety, I'm just going to go very quickly through this because there's a lot of detail and was previously mentioned by Dr. Farokhi things were very poorly reported there was a lot of heterogeneity in the classifications and how adverse events were described. And it's unclear in most studies that patients would have potentially more than one event. It appeared that serious and non-serious, serious and serious treatment related adverse events were rare. And many studies likely were underpowered to detect a difference. So the strength of evidence was insufficient for a variety of the adverse events for HA versus all comparators and for a serious treatment related adverse events. And we'll see some better, information in the tables here. So again, I realize this is a busy table. It's just to say that there is a fairly rare occurrence of serious adverse events, but the strength of evidence is insufficient because it's rare that studies were likely underpowered and again they were very poorly reported. You can see that the frequency of treatment related AEs, which may or may not be serious, was fairly high and that's what the orange salmon color sort of is intended to highlight is that there was a fairly common occurrence of adverse events in general related to the treatment. Again, these were not well described, didn't tell us what was included in this category. One reported a statistically significant difference that there were more, events in HA versus saline at any time period. If we go to the other, next slide, we can see that there is, again other adverse events, some of them describe them and again, various descriptions. But you can see there's a fairly large percentage of patients that experience some form of treatment related adverse event. Swelling, was a common one and, so again, just highlighting the frequency, the most common, the highest frequency events for these events. If we take a look at other comparators with HA again, insufficient evidence for withdrawal or serious adverse events. Treatment related adverse events again not necessarily specified as serious. There were 2 studies that showed a statistically significant difference of higher rates of events for hyaluronic acid versus

the comparator, one is with steroids, one was usual care which was not well-categorized, classified. And then HA versus steroid for all other adverse events. So you can see fairly common occurrence. Mild pain was common one study did indicate that there was a difference though in pain with HA compared with steroid. Looking at the HA versus PRP, really very poorly reported across studies and it was very it was insufficient to cross the studies to really get an idea of serious adverse events. Looking at the head to head trial of the animal derived versus not animal derived there were no statistical differences between groups. Any treatment related AE was fairly common and not statistically different between groups. And if they take a look at patients with at least one treatment emergent adverse event again, it's not specified. You can see that the frequency is fairly high. So looking then at effectiveness and safety related to the hip. Before I go on to the hip, any questions about the knee? Okay, okay. So hip is fairly straightforward. There are not a lot of studies.

Janna Friedly Andrea, sorry, I think we missed a, hand up from Conor.

Andrea Skelly Oh, sorry. I don't see hands very well. I'm sorry.

Conor Kleweno Oh, yes. That I put up. Sorry, just a quick question. You had mentioned on outcomes you know, invasive surgeries. I don't know if you mentioned it, I might have missed it. I was trying to pay attention. I didn't see it listed, in any of that data or maybe you're gonna get to that later.

Andrea Skelly I have, I have it in the summary slides. There really was very poorly reported and there were no differences. We can go back into the report and find, find what page you can, you can look at. But you're right. No, I have not and not gone over the data for that.

Conor Kleweno Okay, great. Maybe, maybe we can table it for now and discuss it later.

Andrea Skelly Okay. Okay. That sounds good and we can direct you then to you know where in the report we can find it like I say have a summary slide but, did not include here. Okay, looking at the hip, there were 3 RCTs, one had 2 different arms. And industry funding was available for one of them and then there was other funding for the other 2 studies. So there were 3 fair quality studies. Again, one was industry funded. There was a comparison of HA as a saline as a placebo and you can see what the protocol was. We had a comparison and one RCT of HA versus steroid and HA versus PRP again for another study. And all of them were single injections for those that were injected. So, looking at the HA versus the placebo for hip OA again, using WOMAC physical functions scores there were no differences between the 2 treatment groups at either 3 or 6 months nor was there a difference in the, other measure of function. Low strength of evidence. Pain on walking for a clinical and meaningfully full threshold of at least 2 point decrease and miracle a pain rating scale. No difference between groups and same thing with the WOMAC and VAS pain scales. No difference in function or pain basically. Low strength of evidence. Here we do have arthroplasty, as an intervention reported in none of the people with HA, 2.8% in other words, in a small study, one out of 36 patients, but the strength of evidence

was considered insufficient. Looking at saline, placebo adverse events versus HA again, no difference, but very limited information available. There was one event that was considered treatment related, arthralgia in the saline group, but again, things were very poorly reported with regards to adverse events. Looking again now at HA versus steroid. The Lequesne Index, no difference. We had to do a graph estimate, so that and the combination of them not providing any information on variability led to insufficient of, for a strength of evidence. No difference in the other measures that you see. The invasive procedures again, the arthroplasty, it's hard to provide any firm conclusions given that it's a rare event and it may not have been adequately powered to determine that. We have one study that states that there are no serious events, that pain flair occurred in 3 patients, but they don't tell us from which treatment that occurred. So again, in sufficient evidence for all of those outcomes. Looking again at hip OA versus PRP. Again, common theme, no difference between those 2 treatments, either at one month or 12 months. Same thing with a pain scores. The evidence on safety is insufficient. They only report that there were no adverse events. Low for the other outcomes. Let's see. Okay, differential effectiveness of hyaluronic acid. This was a study that was included in the prior report and we've, you know, included in the update report as well. And it had 3 arms, HA versus PRP, HA versus saline and so, we looked at them, they did not do a formal test for interaction. What we did is calculate the mean differences between the early OA and the advanced OA that they provided. And if you take a look at the overlap between the confidence intervals that suggest there may be a difference OA stage may modify treatment on the PRP patients with early OA may do have better function and quality of life than those would be advanced and this is all at 6 months. Because again, the, the point estimates, the mean differences differ for the early and the advanced OA and there isn't a lot of overlap in the confidence intervals. But again, there wasn't a test for interaction and given the sample size and no formal testing for interaction, we just, we concluded that the evidence was insufficient. And this is really a hypothesis-generating type of exercise versus a hypothesis testing exercise. There was another study that looked at saline, HA versus saline and steroid. And there was no modification by the Kellgren-Lawrence grade or presence of the Kellgren-Lawrence grade or presence of the Kellgren-Lawrence grade or presence of, intra-articular fusion. And that only outcome they looked at was change in pain while walking. And again, all tests for interaction were reported as not statistically significance, they don’t really give us sufficient data to really compare things effectively. So again, study was likely underpowered, and the evidence was insufficient. So on to cost effectiveness, we had 4 US based studies for non US based studies. Government was funding one and one did not report funding. The other 6 were industry funded. Most of them were poor to fair quality, moderate quality. There was also a systematic review that was done that included studies that had been reported in the prior reviews and then some additional studies that we included here. And 9 of them, they included 9 studies and they found a range of ICERs per quality life here again. And they state that the conclusions regarding the cost effectiveness were difficult to assert given that there was substantial heterogeneity not only in populations but study methods for the economic evaluation and what they included and what they didn’t include. And they note that industry-sponsored analyses found that HA was more favorable than the academic studies did. Focusing on the 4 US based studies. The bottom line is all of them felt

that, using the base case hyaluronic acid was cost effectiveness and a willingness to pay a 50,000 per QALY. There was one poor quality study that did compare HA versus PRP. And they concluded that the PRP was not more cost effective but patients did better at one year. It's unclear how they arrived at that really in a defensible way. And there was no detail of sensitivity analyses or funding source for that study. Again, the non US studies basically said compared with conventional care, HA was considered to be cost effective, but the applicability of these studies to the US system is unclear. So moving on to key question 2, which is Erika.

Erika Brodt Okay, great. Are there any questions on key question one before I move on? Okay, alright, so moving on to, the effectiveness of PRP. We get to. Next slide, Andrea.

Andrea Skelly Oh, I'm sorry. I'm sorry.

Erika Brodt No problem. Yep. Okay, there we go. Alright, so this slide gives an overview of the included trials for PRP and.

Andrea Skelly There we go. Now we're cooking the gas.

Erika Brodt Yep. Okay, there we go. Alright, so this slide gives an overview of the included trials for PRP and for knee OA. So I just want to note that other than, I believe the one trial reported in key question one that compared p, HA with PRP for hip OA, there were no other, studies identified comparing, PRP and hip OA say compared to saline. So everything you'll see that follows is simply a knee OA. So we had a total of 34 RCTs that we included that we identified and included. And I wanna briefly note, you'll see it says number NRSI and it's kind of grayed out, so we had 4, RCTs that actually randomized patients by knee. So each knee got a different treatment and, because of that fact, because patient factors may influence outcomes, those were considered non-randomized studies. Observational cohorts for the purposes of this report. And they are not presented here in this, presentation, but you can find them in the full report, they were described separately and there are some that analysis across those. So our focus is gonna be on the 30, pure RCTs. And as you can see, most of them compared PRP with saline or corticosteroid. And there were also a number that compared one versus greater than one injection towards the bottom there. None of these were industry funded and interestingly none were conducted in the United States so briefly the populations are pretty consistent across even both the HA and the PRP studies. So most of these populations are going to be patients who are about mean of 60 years old, primarily female with OA grade 2 or 3. Rarely did we see 4 but there are some. They have chronic symptoms of course about 5 years or so. And some studies did have bilateral knee OA and some unilateral. So I'm not gonna go into great detail about the populations because they really are consistent as you'll see on the following slides. Okay, so for the comparison of PRP with saline again we had 9 RCTs that encompassed on just about 1,600 patients a little more. The there were 4 RCTs in bilateral knee OA, 2 unilateral, and in 2 RCTs both. The PRP injections again varied greatly across the studies. Some gave one, two, most gave 3 injections. And the, the frequency varied as well from 2 weeks to one month, well weekly and up to one month. The platelet count varied widely and often wasn't well described. And most study self-described as either leukocyte-poor, leukocyte-rich.

The volume varied as well and the use of an activating agent, was generally not well described. Though some did use calcium chloride to, to activate.

Andrea Skelly Sorry, Erika, I got ahead of this.

Erika Brodt Oh, you're fine. No, you're fine. So looking at functions, these are WOMAC physical function scores. As you can see, it's short term. We have small improvements, intermediate term, a modern improvement and a lot at long term a large improvement all favoring the PRP compared to saline. The strength of evidence was moderate short term and low at intermediate and long term and at short and intermediate term those do exclude some outliers. All of these were fair quality. So continuing with function and you'll see this theme and as Dr. Farokhi mentioned. The effect really varied for PRP based on the outcome. So in general, when we're looking at the WOMAC we saw in effect with PRP. When looking at KOOS, we did not and I'm not entirely sure why that is. Cause they're fairly similar measures with some differences but anyway, so for the KOOS as you can see no differences at any time point. The strength of evidence was low for all of these and results were similar when we looked at the KOOS sports and recreation which you know, is good for more active patients. It really looks at more like squatting and more extreme kind of activities but the results were similar we don't present that data here but it's in the report. So looking at the international knee documentation committee score. At short and long term we have small and moderate improvement respectively with PRP, the strength of evidence was considered low at those time points and that was in one, really large fair quality RCT. But I do wanna note that those results should be interpreted with caution because this trial did exclude patients who underwent knee surgery like total knee arthroplasty or who needed additional injections during the study period and they do not report how many patients were lost for those reasons. and so the impact is unclear. And then at intermediate term, we have insufficient evidence just really in precise and a lot of heterogeneity. So moving on to pain, looking at the WOMAC. A short intermediate term there was a moderate improvement with PRP compared with saline at both time points. At long term, the evidence was considered insufficient due to risk of bias issues, inconsistency and in precision. And none of these trials reported pain success and, I should have mentioned the trials reported function success or responders either. So moving on to the KOOS. Again, similar pattern, no differences at any time point and the strength of evidence was low for PRP compared to saline. For the VAS at short term and long term there was no difference across studies you can see there's a lot of variability and heterogeneity in the estimates across all time points. And at intermediate term, we did see a moderate improvement. Strength of evidence was low for all of these. So one fair quality trial reported the proportion of patients who were considered responders based on the on the OMERACT and so this is a composite outcome that combines thresholds for improvement in both pain and function. And at short term at 3 months there was a greater likelihood of achieving response with PRP compared to saline. But not at 6 months at intermediate term, fairly similar there. So for secondary, invasive procedures as Andrea said, this really was not well reported by most studies. Here we have one good and one fair quality trial that reported this only up to 2 years with similar results so no difference between the 2 and the strength of evidence was low. So for PRP, compared with

corticosteroids again, you can see, it's gonna be pretty much similar. PRP injections varied, pretty widely what they did across the studies as well as the use of an activating agent. Most of these studies were leukocyte-poor. Self-described that way and the steroid injections were usually or most of them used triamcinolone and again, the volume, varied there. But, across these studies, the injection protocols were did run in tandem so similar with HA, if they got one injection of PRP, they got one injection of steroid and so on. So for function for PRP versus steroid according to the KOOS ADL, we considered the evidence here insufficient. Even though there was some, some differences, statistically when pooled the individual studies conflicted and this could be due to differences in injection regimens, OA grades, maybe steroid type, it's really unclear. So same thing for the KOOS sports and recreation. See very similar, almost identical pattern. All evidence was insufficient.

Sheila Rege Can we take a break and just make sure there's no public comments? I think we're coming to the end of our public comments. And I know we had opened up chat, for anybody wanting to do public comments.

Josh Morse (HCA) Yeah, thank you, Sheila. We did not see from what I can tell, Val, correct me if I'm wrong anyone who wished to sign up and make a public comment today, Val, can you confirm that?

Val Hamann (HCA) That's correct.

Josh Morse (HCA) So, and I'll just remind folks that we disable the chat during the meetings because we have discovered through these virtual meetings that the chat can be not helpful during the meeting. These are public meetings. It's best that everything happens, on the record recorded and outside of the chat. The chat is recorded, but it's not helpful to the process we found. So we will be disabling the chat again and we ask that you not use it during the meeting. Thank you.

Sheila Rege Sorry about that interruption. Thank you. Please go on.

Erika Brodt No, no worries. Excuse me. Okay, so. Looking at the Knee Society Score. So here, we still see a little bit of difference in the individual studies, but they're more consistent across them. So the strength of evidence here was considered low for no difference for short term and for a moderate improvement with PRP intermediate term. So looking at other outcomes that were not amenable to pooling, for WOMAC physical function scores there was no difference across one fair quality or in one fair quality study in the short and long term between the 2 interventions and that was considered low strength of evidence one poor quality or the rest was evidence here is based on poor quality studies the 6 month physical function scores and the IKDC scores so all that evidence was considered insufficient. After pain for KOOS pain there was no difference a short term strength of evidence was considered low also no difference in immediate term in the pooled estimate. But again, as you can see, there's extreme variability between the 2 individual trials. One was fair, one was poor. And so that evidence was considered insufficient. The poor quality trial is the one that's showing the super large effect. So for, again, you can see a lot of variability across the different estimates, small improvement with PRP short term

and strength of evidence was considered low and no difference long term and that was also considered low strength of evidence. But intermediate term, the evidence was considered insufficient because the data is just too heterogeneous and imprecise. So secondary invasive procedures, so total need arthroplasty one study reported this at 13 months. And we can, said there was insufficient evidence. For this. It's just, just not well reported. So moving on to PRP versus oral analgesics. We see similar, similar patterns with injections. Use of activating agents. All of these were leukocyte-poor PRP. And I'll talk a little bit more about the leukocyte concentrations later on and why I keep mentioning that. Analgesics primarily let's see and NSAIDs in 2 and then acetaminophen in 1 trial. So compared with analgesics, PRP resulted in a large increase in the likelihood of response. At 6 and 12 months in one fair quality trial and this is for physical function response. And that strength of evidence was considered low. For the WOMAC physical function scores again, we see consistent improvement with PRP. There was a moderate effect short an intermediate term in a small effect long term. And the strength of evidence was low for all. Moving on to pain. Let me look at responders based on both the WOMAC and the VAS across this one fair quality trial again. Large increases in the likelihood of achieving response with PRP compared with analgesics. And the strength of evidence is low. That's all intermediate term evidence. So looking at WOMAC pain, again we see modern improvement short term and a small improvement intermediate term with PRP compared with analgesics. Strength of evidence was low at long term however the evidence was considered insufficient even though individually both studies show an effect when pooled there was no effect given the extreme heterogeneity across the trials. So with VAS, we see similar pattern, moderate improvement short term, small improvement intermediate term, both low strength and evidence. Long term again we have insufficient evidence So for the comparison of PRP, with exercise versus exercise alone, across 3 RCTs. Exercise, consisted of home exercise in all instances usually range motion and strengthening. 2 RCTs that was all they got was the home exercise one RCT included TENS as well. And you can see the different PRP injections used there. So the evidence across 2 RCTs, two fair quality RCTs at 6 months, was low for no difference between PRP with exercise versus exercise alone in both WOMAC function and pain scores. And so we have a number of other outcomes that were reported for which the evidence was insufficient. And I've just listed them here for, for transparency but did not provide a lot of details. I will note the need for total knee arthroplasty is there at the bottom at 12 months, one RCT, again, no difference, but just poorly reported. So looking at PRP versus other comparators, all the trials. Yes? Okay, all the trials for these comparators were poor quality. So we had PRP versus physical therapy that was one, trial there. And PRP versus prolotherapy 2 trials. Again, all insufficient and that evidence is provided in the report for you. So we had 6 RCTs that did attempt to look at whether a single injection performed as well as multiple injections. And again, we give the overview of the populations here. Here we did have one RCT, interestingly that did have, about 30 patients with grade 4, which most did not include grade 4. In fact, they all often excluded such severe OA. So the number of injections across. If you could go back?

Andrea Skelly Sorry.

Erika Brodt Oh, that's okay.

Andrea Skelly I have to ask a stupid question. How do I go back? That's how I go back. Okay, there we go.

Erika Brodt There you go. Okay, now that's okay. No worries. I just wanted to point out that across 4 or 4 RCTs compared a single injection versus 3 injections. 3 compared one injection versus 2 and one RCT compared to injections versus 3. And we looked at all those separately. And the intervals in which they did, you know, did the injections varied, platelet count again, was just not well reported across these studies and 4 were leukocyte-rich and 4 use and to use leukocyte-poor PRP and you can see that debating agents used one, half did not report it. So, for the KOOS Sports and Recreation, there was no difference in pooled analyses at any time point. Strength of evidence was low at short term, and we considered it insufficient intermediate and long term. Given that the point estimates for the 2 different studies one was good one was fair were going in opposite directions. And then for the remainder of the evidence, unfortunately we just considered it insufficient. And I list it here again for just for transparency, these are the other functional outcomes that were reported and these can all, data for this can all be found in section 5.2.1.8 of the report. And there are a number of figures that do accompany these the next slide as well Andrea, if you wanna move on to pain, similar, similar pattern here just the data was insufficient it was to too heterogeneous to really be able to draw any conclusions. So, 2 RCTs did head-to-head comparisons of leukocyte-rich compared with leukocyte-poor PRP and I'm sure our clinical expert can expand on this if needed but you know there's some debate I think at least in our reading as to which is better to use this leukocyte-richer or leukocyte-poor PRP. And the issue is as you centrifuge and kind of separate things some of these leukocytes can stay in the, the leukocyte, are, you know, white blood cells and I think the issue is that they can cause pro-inflammatory effects the higher the more you have in there, which can cause more local reaction. And so a lot of people were in a lot of the reading, the leukocyte-poor tends to be, favored or they think that might, potentially be more beneficial, but there's just no consensus on what time the type is best for clinical use.

Andrea Skelly Looks like Dr. Liem has his hand up.

Brian Liem Yeah, just to clarify that that point I think I put something in the chat, but understand we're not using the chat here for the typically for joints we use leukocyte-poor because we, we don't want the neutrophils and the monocytes to basically cause any inflammatory reaction in the…

Erika Brodt Yep.

Brian Liem …joint tried to decrease inflammation. We actually think that potentially leukocyte-rich PRP is better for tendinopathy, so for tendons. So in a in a tendon population, again, we're not covering it here, but the tendon is not to be degenerative. So by putting in some of the leukocytes, we actually want a little bit of inflammatory reaction to sort of clean up this degenerative tendon before the tendon can rebuild with new tenocytes. So that's kind of the main difference, the thought.

Erika Brodt

Okay, great. So I wasn't far off. Yes, that's the leukocyte-poor here in this instance, yeah, the idea is that it causes less pro-inflammatory effects, which is better for this population. Okay. Perfect. Okay, so Andrea, we can move on to the next slide. Okay. Pretty clearly no difference at any time point between leukocyte-poor and leukocyte-rich. And the strength of evidence was low that was for function, sorry, WOMAC physical function scores. Here we have WOMAC pain scores again. And no difference in the pooled estimates at any time point. However, the individual trials reported conflicting results. The good quality trial Zhou reported no difference. The fair quality RCT favorite leukocyte-rich PRP actually. But the treatment regimens did, did differ. And as did the OA grade actually. So, who knows, what could be the reason for some of these differences we're seeing. So, the next slide for VAS pain. No differences again in pool analyses at any time point. Strength of evidence was low short term and we considered it insufficient at intermediate and long term, given that heterogeneity between the 2 different studies. Again, the good quality trial tended to show no difference. So moving on to key question 2B, which is the safety of PRP. So of the included studies, 14 RCTs and one non-randomized study, that we considered a non-randomized study because it randomized by OA, did report adverse events. The sample sizes were all pretty small and the similar caveats to what Andrea talked about with HA apply here. That harms were just poorly reported they were often, it was often unclear if a patient could have more than one event and there was just a lot of heterogeneity regarding how things were described. And often studies merely stated there were no serious adverse events but provided you know no, no definitions or may not have said that they look specifically for that in their methods. So we have 9 RCTs here that looked at serious adverse events. And we considered this evidence insufficient, primarily because of the poor reporting and small sample sizes and the fact that most simply stated as you can see that no serious adverse events reporting occurred. There are 2 trials only here, PRP versus placebo and the good quality trials Zhou that did platelet poor versus, or sorry, leukocyte-poor versus leukocyte-rich PRP. And that one did actually show some more adverse events with leukocyte-rich in this population which might make sense given our prior discussion. But that evidence was all insufficient. So moving onto other AEs. Next slide, Andrea. Yep, perfect. So these are, you know, your mild pain, your swelling, knee stiffness, and other common events not really defined. So it's not uncommon for patients to experience pain, swelling as you can see there weren't any differences across the groups. Although I'd like to point out that for the PRP poor and PRP rich although it wasn't statistically significant again the, or sorry the leukocyte-poor and the leukocyte-rich. There were more at adverse events with the leukocyte-rich in this population. And there were more adverse events with 2 PRP injections down towards the bottom Patel. There were more injections 44% or sorry adverse events 44% with 2 injections versus 23 with one. So not uncommon. So differential effectiveness for PRP. So this is actually the same study that was included in the section on hyaluronic acid again from the prior report. We didn't identify any new studies looking at differential effects and same story for PRP. It appears that patients with early osteoarthritis, may do better with PRP then those with advanced osteoarthritis compared to saline both in function and quality of life. But again, the evidence is insufficient for the same reasons that Andrea mentioned earlier. And for

cost effectiveness of PRP, we had no evidence, other than that described for HA versus PRP, which was summarized previously for key question 1D.

Andrea Skelly

Okay, well then we get to the grand finale. So, you've already seen this slide, Dr. Farokhi had shared it with you and as you see that across timeframes, short an intermediate term a well as looking at the different measures with the exception of WOMAC physical function at 3 months or less than 3 or what months or less. There was no difference between HA versus a saline placebo. We don't have any long term evidence really to speak of and with regard to invasive procedures Conor in response to your question there was no evidence for the HA versus placebo. If we move on to the HA versus PRP. We have again no difference short term in pain or function with the possible exception of VAS pain where PRP is favored and you can see that the other time frames and for all of the all of the different measures, PRP was favored over the HA. Now remember this is based sometimes on small numbers of RCTs but some of them and they're really this is a mistake here for long term there were not 42 RCTs. For the for the small if that effect size for PRP being favored. I believe there were 4, we'll, we'll clarify that either Shay or Dakota can help us clarify that. And then for WOMAC pain. Success and WOMAC, and VAS pain scores again, PRP appears to be favored. Looking at steroid we have not a lot of evidence for most time frames or across measures, but where we do have evidence there was no difference. Small, no difference, low strength of evidence at short term and moderate evidence at. Short term for pain VAS or WOMAC pain, and function no difference at intermediate turn or no evidence to meet intermediate term. And for WOMAC pain and VAS pain, there's no difference in moderate strength of evidence. Then we look at NSAIDs nothing, we didn't have information at less than 3 months But again, no difference short term or intermediate term for the success or for the long term and that's based on the oral NSAID you remember there was an oral and an IM NSAID. For WOMAC physical functions scores, there was a potential small improvement with HA versus the oral NSAID, but interesting at long term that small improvement favored the oral NSAID not the HA. It's unclear why that why that would be. Looking at the pain there was no difference at intermediate or long term in terms of those meeting up a potentially clinically important threshold again for the oral RCT, oral NSAID. For WOMAC pain scores, a moderate improvement with HA versus the NSAID intermediate term, but no difference long term. And if you look at the VAS pain scores again pointing out that the score somewhat impacts the result. There was a small improvement with HA over the oral NSAID but looking at long term again the oral NSAID was favored over the HA in that single RCT. For the intermuscular injection of an NSAID there was no difference at either intermediate term or long term in pain. Prolotherapy and physical therapy show very similar patterns that the PT seems to be favored over the HA when you look at KOOS Sports and Recreation and VAS or KOOS pain. And when we look at the head-to-head trial of the animal derived versus with the non-animal derived, there were no differences at intermediate term and the strength of evidence was low. Harms and safety, again, insufficient information really to draw conclusions about serious treatment related or serious AEs or withdrawal from treatment due to adverse events. There were a of things that, that things treat treatment, there were no differences between treatments related AEs in any of the studies, those were more common and generally there were no statistically significant differences between the HA and

comparators and we pointed out where there were some differences previously one was HA versus saline in one RCT and then there was a higher risk of treatment related adverse events in a single RCT. When we look at single RCTs, one roots is, steroid and one HA versus usual care. And for most of the reported outcomes that were not insufficient, the strength of evidence was low and most importance for the treatment related and other adverse events. In summary then for harm's for knee OA no serious treatment related at reverse events when we look at HA versus PRP, but the evidence was insufficient for that and for withdrawal and for HA the animal derived is the non-animal derived they gave a lot of detail but they don't really tell us which ones were serious and which ones weren't serious. There was a high frequency of any reported adverse event regardless of the preparation. If we look at HA versus placebo for hip again, no differences where there was evidence, you can see there's a lot of in sufficient evidence and no long term evidence. And again, the AEs are poorly reported. And low strength of evidence for treatment related AEs and then withdrawal due to adverse events. HA versus PRP for hip OA again we're on the hip no differences at short term in any of the measures you see. arthroplasty again, there was no difference, but there are very small numbers available for that. Long term no difference in any of the measures and serious AE reporting was really inadequate and in sufficient. Looking at HA versus steroids again mostly no evidence or insufficient evidence. And where we do have short term evidence for Lequesne index, no difference and in terms of differential effectiveness, again, the strength of evidence is insufficient. Cost effectiveness, again, most of the studies concluded that HA was cost effective. However, again, I think we need to caveat that with the, with the caveats that we've had in terms of heterogeneity and treatment heterogeneity in protocols, heterogeneity in the way the studies were conducted, and most of them were industry funded. Hip OA there was a one poor quality non-US based study but again felt that they felt that HA was cost effective. Again, poor quality study of PRP they concluded it was not more cost effective than but that patients did better after one year with the PRP. So, summary for key question 2, which is the PRP versus various comparators.

Erika Brodt

Yes. Thank you. And so in reminder all of these, are for knee OA, we have nothing in the hip. So for PRP versus saline, we had a total of 9 RCTs and the efficacy really varied depending on the outcome looked at. So when looking at WOMAC physical function, WOMAC pain and even VAS pain and intermediate term we did see I'm small, moderate, even large improvement with PRP compared to saline. By looking at the KOOS, both the ADL, sports and rec and KOOS pain there were no differences at any time point. So again, unclear why that is. There was a different small, increase with PRP compared with saline for responders using the OMERACT short term. And no difference long term regarding the risk of invasive procedures, need for additional invasive procedures. And strength of evidence was low, well, mostly low with some moderate evidence. So for PRP compared with steroid with the exception of the Knee Society Score again, we have 9 RCTs total represented here. There was moderate improvement intermediate term with PRP compared to steroid. There was also small improvement, both short term and long term on VAS pain favoring PRP. But at all other time points and for all other outcomes there was no difference and strength of evidence was low for, for everything and we had no, no evidence or insufficient evidence to make conclusions on invasive procedures.

Andrea Skelly Yep, there we go.

Erika Brodt Yep, thank you. So, on the next slide, we had a total of 3 RCTs. that compared PRP with oral analgesics. Pretty consistently PRP was associated with improvement in both function and pain. Based both on responders and the outcome scores but the magnitude of effect varied across the different outcome measures and time points. As you can see here and strength of evidence was low for all of these. And, we had no evidence, earlier time points and insufficient evidence long term regarding the need for additional invasive procedures. PRP compared to the exercise pretty clear the evidence here. We only had 2 RCTs that combined give us low strength of evidence for no difference in WOMAC pain scores intermediate term. Everything else was insufficient, or there was no data. So, for the comparisons of PRP with physical therapy and prolotherapy again all the evidence here was insufficient due to poor study quality. So we can move on to the next one. Thank you. So, looking at greater versus fewer number of PRP injections. Again, mostly insufficient evidence just due to the variation heterogeneity across the different studies. At short term we did find no difference across 2 RCTs and a KOOS sports and rec score. That was the only outcome for which we had low strength of evidence. And again, we had no evidence on invasive procedures for that. For leukocyte-poor versus leukocyte-rich PRP no difference in WOMAC physical function scores at any time point or as pain scores. At short term and strength of evidence was low for those. All other data was insufficient or there was no evidence. So regarding safety. Here I'm just summarizing our serious adverse events, which were of course the most concern. We had 9 RCTs and one non-randomized study that reported serious adverse events across various, different comparators comparing PRP. Only 2 studies actually reported an event, a serious adverse event is defined by the authors which included a severe swelling and mild fever in 3 leukocyte-rich patients versus no patient in the leukocyte-poor group. And of note one of those did require arthroscopic debridement to treat the symptoms in one study. Severe inflammation with swelling and stiffness immediately post injection was, required one patient randomized to leukocyte-poor PRP versus no events in the saline group but it did, improve on its own after about 2 weeks. Across the other 8 RCTs, no serious treatment and adverse events were reported to have occurred. And the next slide, you know, just basically summarizes that we considered the evidence on safety and harms for PRP insufficient due to generally poor reporting of serious adverse events and small sample sizes as well as substantial heterogeneity regarding how they were categorized and again the fact that many just simply stated there were no serious adverse events. Key questions 2c and d, which look at differential effectiveness and cost effectiveness. We have insufficient evidence for differential effectiveness for PRP and then cost effectiveness again was covered in the prior section. And we had no unique studies in this, in this section looking at PRP.

Andrea Skelly So to and I've summarized a few things for consideration. As we've noted throughout, there's heterogeneity in the products that are available. The study protocols that were used to study those products, how those products, protocols for injection were delivered, and methods of studying them. Excuse me. And as again noted, there's lack of standardization with regard to high versus low molecular

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| | weight, the protocols for injection, dosing, frequency and timing. Across the included studies and in the literature we have very few RCTs looking at hyaluronic acid versus conservative measures specifically and very few in hip OA. Most of the RCTs for HA were industry funded. For the PRP, for treatment of knee and hip, we don't have anything for the hip, there is again substantial heterogeneity across the studies related to the products used how they were for how they were derived and for leukocyte-rich versus leukocyte-poor. There's not a lot of standardization and the treatment protocols again varied. Of interest, again, no US based trials for these, for PRP. And for both HA and PRP there's insufficient evidence to really draw conclusions about differential effectiveness or harms. And as we've said, the reporting of harms was very poor and there was a lot of heterogeneity across the studies with regard to how they classified, when they provided information about classification and for rare harms they really didn't have the power to evaluate those. So we do have basically the appendix summary slides that you've seen before from Dr. Farokhi that we can chat about or if they are any other questions about our presentation, we're happy to entertain them. |
| Sheila Rege | Thank you. Dr. Andrea Skelly and Erika Brodt, that was excellent. I mean, you got through it remarkably well in a short time despite the amount of evidence you're presenting. Question for the committee members. And we'll do it by raise of hands. Is everybody good going on without a break or would people like a break right now? We are a little overdue on a break. We could take a 5, 10 min bathroom break and I know there are some people. So. Okay, Conor asked for a break. Is a 5 min break enough or do you need more? Please unmute and speak. |
| Laurie Mischley | That is great. 5 is great. |
| Sheila Rege | Let's go on. What? Okay, let's go on a 5 min break come back at 10:25 which is 6 min |
| Andrea Skelly | Okay, and. Should I stop sharing? Josh? |
| Josh Morse (HCA) | That's good. You can leave it up there. |
| Sheila Rege | For now, you can stop, but we may ask you on the questions that's gonna come later to go back to sharing. |
| Andrea Skelly | Okay. Fair enough. |
| Sheila Rege | Thank you. |
| Andrea Skelly | Thank you. |
| Sheila Rege | Sorry I'm late coming back. Is, are people back? We can get started with questions. And I think Janna is able to see the raise hands. So go ahead and raise your hand if you have questions. |
| Janna Friedly | I see Clint first. |

Clint Daniels Thanks yeah it's Clint Daniels. I was curious about one of the comparators namely corticosteroids and I was curious, I think this may be for Dr. Farokhi. Is that currently a covered treatment for OA for the knee and hip?

Azadeh Farokhi (L&I) Steroids?

Clint Daniels Correct, yes.

Azadeh Farokhi (L&I) Yes, I believe it should be covered.

Clint Daniels Okay, and then per the 2013 determination HA is currently covered as well for knee OA?

Azadeh Farokhi (L&I) Correct with conditions.

Clint Daniels With conditions. Sure. So then with your recommendations to not cover today, that would supersede the 2013 if we followed that route?

Azadeh Farokhi (L&I) Correct.

Clint Daniels And that treatment would be no longer an option that's covered?

Azadeh Farokhi (L&I) Correct.

Clint Daniels Okay, thank you. So I guess then for Andrea and Erika, I was curious, you know, as we looked at HA versus steroid, it seemed like there was no difference. Is that correct? So that basically HAs as good steroid?

Andrea Skelly Yes. And let me pull up the summary slide. Do you want me to share it or its slide 143 if you're towards at the end of the deck. Well actually that's for saline, I'm sorry. HA versus steroid is slide 131. So, there was no difference at short term, in function whether you looked at WOMAC physical function or the KSS the society score. No difference in KOOS pain, no difference in WOMAC pain. If you look at VAS pain, there was maybe a small improvement favoring, I'm sorry, that's the PRP I am so sorry

Sheila Rege Yes, PRP versus steroids looking at it.

Andrea Skelly Oh, you're looking at, but you had asked about HA versus steroids, right?

Sheila Rege I'm looking at one.

Clint Daniels Yeah, I asked about HA.

Erika Brodt So that's like 119, Andrea.

Andrea Skelly Yeah, I'm so sorry. 119, okay. Right. Yes. So still not so similar. So WOMAC physical function and KOOS ADL both show no difference across 4 trials at short term. There was no evidence at either intermediate or long term. Looking at WOMAC pain and VAS pain neither showed a difference between HA and steroid. There were 2 RCTs

for the WOMAC pain. One RCT for the VAS, excuse me, 3 RCTs for the VAS pain and we considered the strength of evidence to be moderate.

Clint Daniels So, no big difference there. And then when you can, compared HA to the placebo, I think there was also minimal difference there, maybe, maybe short term improvement with the HA. With those 2 when it was compared to placebo. So, we're kind of seeing the difference between the 2, but is there, do they benefit?

Andrea Skelly Yes.

Clint Daniels Did both groups benefit? Or was there kind of no effect when you looked at those studies?

Andrea Skelly You know, I would have to go back and look at the, the raw data to whether both show to benefit, both groups show to benefit or not. We usually focus on the comparison between the 2, but I would have to go back and look at whether or not both groups, did improve to a similar degree if that's what you would like.

Clint Daniels And the, and then, so I guess for Brian. Why would somebody pick steroid injection, verse HA, versus PRP in your role?

Brian Liem Yeah, so at least clinically, steroids are readily available. We have them available here in the pixel system, so in our clinic, we, it, if we want to perform a corticosteroid injection for knee OA, we can do it the same day we don't need any pre-approval process so it's easy to do. It gives short term relief. So we always counsel patients it can take 2 days of 2 weeks for the steroid to take effect. So, for immediate relief and individuals are having difficulty with significant functional walking, sleeping, steroids we go right away. Hyaluronic acid because traditionally because of the recommendations of 2013 and other recommendations from payers, you've got to wait a while to basically have failed steroid injections, other conservative measures before you can go to HA. So, it's never our first line to go to, it's always a second line after they've done everything else. PRP for the similar fashion is PRP, it's not covered by any insurances, right? So, there's a cost to it here at the University we charge $930 for a PRP injection. So, for a lot of individuals who can't afford, you know, PRP, it's, it's definitely not something we bring up at the first visit, but steroids are. So that's how we choose it.

Clint Daniels A follow up on that. Is there a big other than cost ,access difference between HA and PRP? I know PRP is a bigger ordeal to administer. It takes more time and is that something that's only available at like major medical centers or whereas HA may be available more readily?

Brian Liem Yeah, I think, so HA's probably more readily available. Just, because if it's, it's history of being around with PRP, it takes a bit more effort to do the PRP. One, you've got to have someone qualified to do a blood draw, right? Whether that be a trained medical assistant or a nurse available. Then the time it takes to spin it down typically for the centrifuge of blood it takes at least 15 to 20 min to do it. So that's the process that's there and even within the University system we've got multiple different

clinics that do sports medicine, but within all the clinics there's maybe only 2 clinics that we have that actually can't administer PRP or have the centrifuges and that you know that's beyond sort of my sort of pay grade in terms of why some of the clinics don't have PRP available but just even within a big academic institution like ours, it's only available in 2 clinics, right? You know, obviously if you're in private practice, it's kind of a different setup here, where you can just get a machine from a supplier, or a vendor will just bring a machine to you and then you know it depends on the cost for getting it but yeah there's an access issue.

Janna Friedly Right, I see I'm Conor next and then Christoph.

Conor Kleweno Yeah, just a question for the evidence group. You know, we saw differences of effect with the WOMAC versus the KOOS, you know those are almost essentially the same and so I was wondering if you could comment on whether the, the influence was those being within the same trials or different trials is it is it more so the takeaway that some trials showed effect and some trials didn't or the same trials had mixed effects. So when you collate all that data, what, wat would be our takeaway there? Because it's obviously confusing to have very similar outcome scores with despair at that conclusions.

Andrea Skelly I think it. Go ahead, Erika.

Erika Brodt Yeah. Oh no, no, go ahead. I'm just going back and looking. So if you have some.

Andrea Skelly Yeah, I'll have to go back and look too, but in some instances, the KOOS, the other, outcomes were only reported in isolated studies compared with the majority of studies reporting on WOMAC. It's hard to tell why they should be different and, we can go back to some of the figures to figure out which of the studies may have used WOMAC versus KOOS versus, different.

Conor Kleweno But were they was it more so that they were conflicting studies or a single study had multiple outcome measures and they conflicted?

Andrea Skelly Most of them had multiple outcome measures. Yeah, Erika, go ahead.

Erika Brodt Yeah. Yeah, no, I think I know. Yeah, who is acting asking and looking, you know, looking at the plots actually, you know, there's really only one study, Dorio, that reports both. And WOMAC was, was reported more often just across all the studies but there is not a large overlap in the studies reporting. So I think you're asking are they unique studies reporting these measures or are they the exact same studies reporting the different measures? And they appear to be different studies. With the exception of Dorio.

Conor Kleweno Okay, okay, cause you know one strategy to show a difference is just keep asking the same question with different measures.

Andrea Skelly Yeah.

Conor Kleweno I just didn't know if that's what we're seeing or we were seeing some studies said great.

Erika Brodt Yeah.

Conor Kleweno Some study said that. And so.

Erika Brodt Yeah, no, yeah, you're right. And I think, you know, in general we try, we try to avoid reporting everything like that. So we looked at what most reported and started with that and then if they did not report it or not in a way that could be pooled and moved on.

Conor Kleweno Our takeaway is some studies showed a difference. But it but it seemed to have some odd effect that we can't explain that was instrument dependent.

Erika Brodt So. Yeah. Correct.

Janna Friedly Well, yeah and Conor, in my understanding, although they're very similar and I think the KOOS was derived from the WOMAC, if I understand, and I think the KOOS was derived from the WOMAC, if I understand, if I if I'm understanding it correctly, that it is a little bit more geared towards traumatic knee injuries, and, has a little more, has some directed questions about sport and recreation. So it may be that the outcome measure is a little bit different, in subtle ways that is less, less appropriate for maybe older adults with knee OA. I think we're seeing also similarly differences in the VAS, versus the, the WOMAC pain scales and when you look at those, I think those are more functionally based or pain with movement pain with specific activities versus just a standard pain measure, as well. So, I think some of it may be the outcome measures that are being used.

Conor Kleweno Yeah, I mean the subtle differences, but it would have to say, okay, is that the reason why there's, you know, are those several different tweaks on questions, is that the effect? You know, you'd have to get pretty granular, but.

Erika Brodt Yeah, and we did report so it's reported such both measures you know that you report physical functions separate like in the KOOS from.

Janna Friedly Yeah, yeah.

Erika Brodt From the sports and rec because that is geared more towards generally your younger or more active people. So, they report each kind of area separately. Then you know I actually have them both up right now the 2 measures and they are incredibly similar regarding the function daily of living, daily living questions with some differences. You know, the biggest difference with the KOOS is they ask in the last week. Whereas the WOMAC seems to be more geared toward currently. You know, so I don't know if that could be a piece of it like the recall is an issue if they're trying to think over that. Yeah, I'm not as familiar with these measures, but that's the one difference I can see. If that's helpful?

Janna Friedly Christoph is next.

Christoph Lee Thanks. Yep. So this question is for Dr. Liem most likely. Trying to get a handle on. I know that they in terms of the number of injections. So I'm trying to understand, how many loading injections are needed for PRP up front? Because some of the trials had say 3 to 6 injections over a very short period and that counted as the therapy, right? And then they looked at 3 months and 6 months intervals for outcomes. I'm curious, from your expert opinion, what is the loading dose? Is it just one injection or is it several injections over a short period of time? And then how long would you say a PRP last? You know, based on the evidence, it looks like around 6 months you stop, stop seeing any benefits. So trying to get a sense of what the injections are up front and then how long it might last?

Brian Liem Yeah, so I haven't seen any sort of great baseline studies that say what the loading doses. This goes back to like even look at 2010 sort of evidence. So, you know, we typically just do one injection and obviously something that's also limited by cost, right? So if it's $930 per injection and you're trying to advocate for 3 different injections or 3 injections once weekly for 3 weeks as quote of a loading dose. I don't think that anything in the evidence that justifies that 3 is better than one even harking back to the baseline, so we just do one and the thought is typically that you've got you have to have a concentration theoretically of about a million platelets per micro at any microliter, if I'm giving it the units correctly in order to have some sort of minimal benefit from it and the concentration has to be about at least 2 and a half times what you have in baseline whole blood, right? So, in most cases when we have the devices, the commercial devices that we use, we use several of them here, they have bit that minimum criteria. And so the other thing that we think about too is the reason for at least historically the series of 3 when you see 3 or versus one is because the next sort of best comparator is hyaluronic acid or at least in the past it has been right and so a lot of the formulations for hyaluronic acid being like uflexa, ortho disk, mono-vis, or cinvis series of 3 have been series of 3. So, in order to conduct obviously really, you know, robust clinical trials, randomized control, blinded, you've got to have 3. So I think a lot of the studies go by 3 just because of historically it's been comparing hyaluronic acid.

Christoph Lee Thank you. And then Dr. Liem, how for patients that do get PRP, how often do you allow them to get an injection?

Brian Liem Yeah, so typically what we've gone through, there's a study, by Smith, a small little study like 2016 which kind of showed the trajectory of PRP and obviously it's been a while here but typically we would see and compared PRP to steroid and believe placebo group as well and basically, we saw that the benefits for PRP started to actually take effect with, at least back then, about 3 months. So, we would wait at least 3 months to see how they did and typically in about 6 months to 9 months is when we would consider repeating an injection again because it took that long just to take effect.

Christoph Lee Thank you.

Sheila Rege I think Jonathan was next.

Jonathan Sham Thanks, Jonathan Sham here. Question for Dr. Liem and then I guess the follow up for the data folks. So, you start to touch on this a little bit, but can you talk a bit in more detail about the standardization of the actual procedure? I mean as you know, baseline platelet count can be between 150 to 450,000. So is there a standard concentration? Do you take a standard volume? Is there standard injectate? And if you don't have that standard threshold, do you just draw the blood and not inject? And then the follow up is for the for the data folks, can you speak to any of the standardization protocols and studies included for PRP if there was a minimum concentration or injective volume used? Just try.

Brian Liem Yeah, so, there is no source standardization that we have here. Typically it's, a lot of, that we have here, typically it's, a lot of, it's dependent on the practitioner how much volume you want to use in particular but for most of our kits when we're doing knee OA we use a kit called Regin kit. Typically, we're drawing about 5 CC's total of PRP. So, we take about 9 to 10 CC's of whole blood and spin it down to about 5 CC's and that's thought to be enough to reach that sort of minimum threshold but we don't we don't routinely check platelet counts. I mean I look at labs in the most recent CBC for an individual to make sure that at least within the 150 to 450 range baseline, but we don't actually take a look at the composition of the individual platelets and then figure out if it's enough to inject, we sort of assume that it adequate

Jonathan Sham Yeah, it just seems they were looking at these. I guess objectively small differences in outcomes, you know, it seems like there's a 3 full difference in platelet count, you know, amongst patients. You know, there's gonna be variability in effect.

Brian Liem Right, that's been, that's been the struggle with the studies and then heterogenicity is how do we how to quantify that and to do the best study we you know we probably should have those numbers and there are some studies I can't remember which ones exactly but they do have they've done some analysis and looking at the baseline platelet count, but they're not verily reported in any in any robust studies that we have.

Erika Brodt Yeah, and so to follow up from the data perspective, I mean, we have detailed data on the interventions in the appendices, I believe it's appendix G. But yeah, I mean we reported what they gave us but sometimes they didn't even tell us how many platelets there were, some did some I mean gave us a ton of detail to wade through, some gave us absolutely none same with leukocyte count. I mean it was just so variable we tried to look at this from a ton of different angles to decrease the heterogeneity, but we just could not do it.

Jonathan Sham And sorry, is appendix G available in the online data report? I just was having trouble finding it.

Erika Brodt It should be. It's the, there should be a main appendix. I believe that should have been posted alongside the report. I'll have to check the web.

Andrea Skelly Yes. And this is the Excel file? Sorry, Erika. There was this the Excel file. Okay.

Erika Brodt No, this is the word document. Yeah, this is not the Excel file.

Janna Friedly No, I don't know that we have access to that. I at least it.

Sheila Rege No, I don't either.

Janna Friedly And it's appendix G seems to be an important piece of information throughout the.

Erika Brodt Yeah, so this is the Word document that has appendix A through N. And then we do have Appendix F is the, was the Excel that kind of had our meta-analysis data but appendix G has our detailed patient characteristics and demographics that also kind of tries to highlight the pieces of the intervention specifically PRP.

Andrea Skelly I could email it to Melanie and Val and they.

Josh Morse (HCA) I'll post a link to it. It is on our website.

Andrea Skelly Okay, that's better. Thank you.

Janna Friedly Josh, it is currently on the website?

Josh Morse (HCA) It is on the website. Yeah. I'm inside the organization though, so hopefully it's I see.

Sheila Rege I, I was not able to see a link.

Josh Morse (HCA) Definitely from the report.

Sheila Rege Does was anybody able to see who's a committee member? Let's go back to that from outside and see if he can.

Josh Morse (HCA) Oh, that's the wrong link. Big apologies there. Let me delete that. That's not gonna work. Okay, I posted the link. If you have access to the chat, which hopefully you do.

Erika Brodt And also when reported it was variable, you know, kinda large ranges.

Janna Friedly So I just had to follow up a question because I, because I wasn't able to access appendix G. But, could, could you clarify? The studies, that, had the bilateral knees that were, excluded from, your analyses. What were the outcomes of those? I couldn't, I couldn't see that or maybe I missed that Were they very similar outcomes to?

Erika Brodt Sure. Yeah, that's actually in the main, main report. Let me pull not in the appendix. And the reason those it wasn't just that they had bilateral knees, there were some studies included with bilateral OA that we still included in the primary analyses.

Janna Friedly Okay.

Erika Brodt This was that they randomized each. So one, he got one treatment one he got another and that's problematic. For a variety of reasons, but yeah, absolutely.

Janna Friedly Yeah, I just wanted to, I just wanted to, like, go ahead and say, I couldn't see Appendix G so I couldn't get more.

Sheila Rege You don't actually.

Erika Brodt Yeah, and it's in, let's see, I think what to say in my slide. So it's gonna be they were PRP versus placebo and then I believe one versus steroid and they start, well they're kind of woven in. So we give the

Sheila Rege Can you tell us a page number, Erika?

Erika Brodt Yeah, let me see. So.

Sheila Rege Janna, I actually saw this, when I opened it a week or 2 ago, but not today. I don't know why. So.

Erika Brodt Yeah, so starting on page 116 with figure 17. So, this is for PRP versus placebo, so they run in parallel kind of one after another. So for instance, figure 16 reports PRP versus saline as randomized by patient that's in the title and then figure 17, same outcome randomized by knee. And it does show, similar results a little bit more of an effect in the randomized by knee. But similar pattern, yes. And so that goes throughout the section. They're reported that way when the data is provided.

Janna Friedly Okay.

Erika Brodt One right after another. If that's helpful. And so there were. Again, let me go back to my, 3, I know for saline versus saline and then, I think it was one versus. Oh, that's my. Is this it? Oh, one versus exercise actually. Which I don't even know how you do that. One knee gets exercise and one knee gets PRP. So, which is interesting. So, obvious problems with blinding there but yeah so the main ones you'll probably want to look at are versus the saline.

Janna Friedly Yeah, yeah, right. Okay, thank you.

Erika Brodt Yeah, absolutely.

Sheila Rege Any other questions?

Laurie Mischley I just have a question for Dr. Liem. You know, in using some of these comparators that are, you know, anti-inflammatory, I philosophically think of these interventions as a little more regenerative. One of the studies even looked like benefits got better over time and so I'm wondering about your goal in clinic. Can you just address is it a fair comparator to compare NSAIDs to these regenerative therapies in terms of your in clinical goal long term?

Brian Liem Yeah, certainly. So clinical goal, I, you know, whenever I'm considering things like NSAIDs versus another injection, there's obviously a multiple of patient factors you're considering right one do they have any underlying you know gastric or renal contradiction so those are things that we kind of consider as well are they on anticoagulants that make it difficult for them to take NSAIDs or even different analgesics, right? So my goal for a PRP is not typically regenerative to be very honest with you, it's, it's mainly to help with inflammation and pain. There's a study that I think probably within the studies looked at is in JAMA, 2021. It's called the restore trial out of Australia and one of the things that they took a look at besides the outcome measures, I believe if I have it here, was the pain scale. They also looked at the volume of MRI so they took an MRI baseline for these patients and then took an MRI 12 months later or year later to see if the cartilage loss had been restored and there really wasn't any difference. So, I, really never sell this injection necessarily as for knee OA or hip OA if we do it, it's really for pain and function. But is it a fair comparison? Yeah, the thing is we're always looking at PRP or these injections as sort of the third line after we've tried analgesics because analgesics obviously are readily available, right? They're easy for people to access, easy for us to prescribe or as a process is much more involved for PRP. It's an invasive procedure and then obviously as mentioned earlier there's a cost.

Laurie Mischley Very helpful. Thanks.

Sheila Rege If there are no other Andrea, did you raise your hand?

Andrea Skelly Yeah, just to point out that page 142 of the appendices, hopefully now you all can find the appendices. Has side by side comparisons for the different treatments and there's a table that lists the patient characteristics but also procedural characteristics in terms of volumes of platelets, different types of things we tried to make it fairly easy to look at those across studies so just wanted to point that out.

Brian Liem And then I just one other comment here. Andrea, when you look at the studies, some of the studies were report in terms of mythological where the injections done with ultrasound guidance or not ultrasound guidance as well. And that has a small little effect I think overall in the outcomes, but it does sort of matter in terms of when we get into for patients with like say BMIs greater than 30 or 35 when we're trying to do these injections non-image guided, they can clinically be very challenging to get into the joints. And if you're not using that in the direct way, I've had people say that they've had hip joint injections without any sort of image guidance and so that really skews a lot of the results because you have no idea if it's actually in the joint or not. And I know in a lot of places from an access standpoint, they do not do ultrasound guided. So, and, here we used to separate out PRP injections, for example, with ultrasound guided versus non ultrasound guided from a cost and there was a $300 difference between the 2.

Andrea Skelly Well, yeah, I'm not surprised. Yeah, so we do have in the table which studies did look at ultrasound guidance and if they reported it we looked at it. We really didn't have

any data to separate out those or we didn't look at those that were and those that were not ultrasound guided as any sort of sensitivity analysis but we at least noted it.

Sheila Rege Is the group, I know there was some confusion about the appendices. Is the group okay with continuing on? Or would people like a little break to look at the documents that were circulated in more detail? And we could always take a break later. If you will project Josh or Melanie, or Val, page 198. Kind of the.

Josh Morse (HCA) Of the appendix or the report itself?

Sheila Rege For the report itself.

Josh Morse (HCA) Yes, just give me one moment here.

Sheila Rege And this is, just for our discussion initially, not, during the actual voting and going around the room. I just wanted to make sure that whether the key factors in terms of safety that has been circulated is that comprehensive do we need to add anything more to it and that's on page 198 for anybody who's got multiple screens up. So they've got any stiffness, swelling and pain.

Josh Morse (HCA) So are you seeing that what you want to see here, Sheila?

Sheila Rege No, it's on the, it's on the on the item with 213 pages. It's the, what's on the website.

Erika Brodt There might be a difference between the PDF and the Word document.

Sheila Rege Its where the discussion document is where I'm at.

Josh Morse (HCA) In the evidence report? Am I in the right report?

Sheila Rege And. Yeah, and the evidence report. Maybe, I am.

Josh Morse (HCA) Or is it the, the appendix is?

Sheila Rege You know, kind of the, no it's not the appendix. It's Josh where we kind of go to a kind of discussing the, the what we have to fill out on the safety outcomes.

Josh Morse (HCA) Oh, I'm sorry, the decision aid.

Sheila Rege On the special, you know, kind of starting our discussion. On kind of the straw poll and stuff.

Josh Morse (HCA) Apologies. Yes, I'll get that document up.

Sheila Rege My apologies for not communicating that. So, my thoughts when we go to actually making a determination is to consider it for knee osteoarthritis and hip osteoarthritis separately. And then do HA separate from PRP. Any of the committee members have any opinions about that? But while we're talking about safety and efficacy and what

we're going to be using as criteria, I, that will lump it all together in terms of, you know, pain, swelling, stiffness at the knee. Was there anything else that the evidence showed us? Yes, that's the document. Did anybody see anything else in the studies? I didn't see anything leading or anything like that. I just didn't see that.

Conor Kleweno Oh. There was, there was a think a couple of examples where they had to go and do an orthoscopic procedure after that. I thought that came up during their presentation.

Sheila Rege You are right. I don't remember that. Sure.

Conor Kleweno A secondary invasive procedure but not conversion to arthroplasty was due to I think a stiffness complication or something.

Sheila Rege How would you phrase that, Conor?

Conor Kleweno Just say, I guess I wouldn't put secondary. Sorry. I thought I was just reading that thing below on the efficacy.

Sheila Rege Follow up, invasive procedure.

Conor Kleweno Yeah, and then I didn't see too much, but you know clearly under serious adverse events would be infection, you know, joint infection. Under serious adverse events.

Sheila Rege Any other treatment related adverse effects that any of the studies show that we don't have on this form? Okay, how about, and before we go on a straw poll, how about efficacy? We have a lot of you know kind of pain scores and everything else but and physical function scores. I don't know, I mean for my patients they always complain of pain and function. This seems like, I mean, which ones are we gonna use? Which ones are more important than I'd be interested in a clinical expert or opining on what you use in clinical practice.

Brian Liem Yeah, in clinical practice primarily I use it WOMAC which is the general WOMAC score. So I mean, you have it, you have it right here physical function scores WOMAC, that's the subset of that activities of daily living. Pain scores we just use the VAS, we also just use the VAS not the numerical rating scale. So those would be the team most important. I really don't look at QL or anything secondary invasive procedures.

Sheila Rege Okay, so we'll just remember that when we're drafting criteria and stuff that's the WOMAC scores and maybe the VA. Is everybody, anybody else want? So anything else?

Conor Kleweno Yeah. Can I comment? Can I comment, Sheila?

Sheila Rege Yeah, Conor. Yeah.

Conor Kleweno We are gonna have a second period for our own comments, is that right? I just don't wanna derail the conversation yet, but I have a comment on outcomes.

Sheila Rege Well, we are going to go to value. Is that what you're talking about? Efficacy outcome?

Conor Kleweno No, I have a number of comments on this topic, but I also have a specific comment on outcomes. So if we're gonna have a period, we're all gonna comment in general, I'll wait.

Sheila Rege No, it's a good time. Yeah, we are. We're gonna go around the room.

Conor Kleweno But I'll specifically comment on outcomes. So In terms of secondary invasive procedures, for example, or should be specifically conversion to arthroplasty, I think the committee should sort of understand this in the framework of how we wanna view this treatment because it was presented at the beginning as arthritis. Okay, so we are dealing with the diagnosis of arthritis and looking at the costs associated with arthritis. And so, if in that care cycle of cost you're including total joint arthroplasty, I just think we should be mindful of then considering how that actually occurs. So in one of the studies, they had an outcome of conversion to arthroplasty with the follow up rate of 3 to 6 months. If you walked into an arthroplasty practice it would take you 3 months just to get on the books for surgery, much less get an appointment within 3 months, so that's not valid. Secondarily, if you looked at one of the other studies that had conversion to arthroplasty of 6 out of almost 300 patients. So the overwhelming majority of these patients are not getting arthroplasty because they're including people with very, very mild or no changes on x-rays so that Kelgren-Lawerance scale the KL scale, these studies included KL one and KL twos. Right, that would be all of our knees if we got x-rays would be ones and twos. And so the diagnosis and what we're dealing with, it's people that are getting an arthroplasty, you're gonna be KL fours for the most part. And so I just want us to understand kind of overall what we're talking about and what we're treating and why because I have knee pain, I go in my knee for sure x-ray will show one or a 2, but I actually have a meniscus something or patellar tenonitis or something and so when we talk about a secondary invasive procedure, I think it's very important to consider that are we going to change the natural history? Is this going to stop an eventual arthroplasty or is it going to delay arthroplasty? Because if we're looking at the cycle of care of the diagnosis of arthritis you take all the people over 10 years, do they all get arthroplasty or they do they all get arthroplasty plus 3 PRP injections now? So. Or do they delay their arthroplasty? So I just think that when we're considering the outcomes, conversion to arthroplasty, you should be, sort of placed in the context of how that actually occurs and what patients were discussing. Sorry, that was a long winded, Sheila.

Janna Friedly Sheila, can I, can I follow up on that? Just, I, thank you, Conor. I think that's, really helpful. I don't know that we have that data to be able to really answer that question, from, from the data that's available. But my thoughts about the outcome measures as well, were that you know really we're talking about a chronic condition and so when I think about treatments I struggle with treatments that have short

term effects for pain but don't impact long term outcomes or function so for me and the functional outcomes certainly are more important in my mind. And really considering the trajectory of the disease and how this, how this plays out so if you have a treatment that has a substantial cost or risk and it's, only providing very short term really for a condition that is expected to be progressive or chronic and you just have to consider, consider that in the in the thought process as well. Again, I don't know that we have enough data on the long term outcomes to be able to really know the long term outcomes to be able to really know, but, but that's, some of the things that I'm struggling with.

Sheila Rege Good point. Andrea, you had your hand up?

Andrea Skelly Yes, thanks. To Conor's point, most of the studies did not have as a goal looking at conversion to some sort of joint replacement. And the things that they reported were sporadic across the studies. And so, I think Janna's points well taken that you know that the studies were not geared towards looking at that endpoint and for the economic studies I know that that's not as high a consideration. Their modeling really didn't include conversion to arthroplasty or any of that kind of stuff. So I think the data are very limited based on our scope.

Conor Kleweno I agree. You know, it would be very difficult to do that study. I acknowledge it.

Andrea Skelly Yes.

Conor Kleweno But if you're looking at it from if you want to measure the cost of this disease diagnosis, then you absolutely would want it, right? Because you would say, I inject something that patient's disease goes away and they don't get an arthroplasty, that I'm saying in the most extreme situation. Or something to that matter but given we're talking as Janna said that this is a chronic potentially progressive not always but chronic and progressive disease where the only definitive end is either the patient expires or they get an arthroplasty, then that would be something that would be of relevance. I acknowledge we don't have the data with what has been out there, but I would sort of submit to you that this it'd be very difficult to do that for the people who design these studies and they would not want to focus on that anyway.

Sheila Rege Dr. Bramhall, how you have your hand up?

John Bramhall Question for either Conor or Brian, just, incidentally is, are these interventions like HA and PRP are they on any of the insurance companies sort of prerequisites for approval for arthroplasty? Is this something that you may in some circumstances have to go through in order to get an arthroplasty approval.

Brian Liem No, it's certainly not anyone's criteria.

Conor Kleweno I, I would say that steroid injection sometimes is, but not HA or PRP.

John Bramhall Thanks.

Sheila Rege Following up on that. What comparator would this group like to use? Erika, I see your hand up. Let's have you comment. Sorry. Oh, no hand.

Erika Brodt Oh, I, yeah, I just wanted, yeah, this is Erika. Sorry, I just wanted to point out and I don't know if it'll affect what's here, but just that quality of life, was not, it was considered a secondary outcome. So, we did not do strength of evidence on it. There is data on it in the report. When it was reported, but I don't know if these are supposed to reflect evidence that was kind of primary or not, but I just wanted to point that out. All the rest we did do strength of evidence on.

Sheila Rege For, for comparators when we're looking at safety or efficacy or providing value, what do you what do we want to use as a comparative based on the evidence? Would it be steroid injections? Would it be a placebo? What do people feel? Please feel free to give me insights.

Brian Liem I'd chime in and say that I think steroid injections would be a fair comparator. We have a lot of individuals who are concerned about steroid injections given what's been sort of reported as potential adverse effects on the bone health and cartilage health long term with repeated steroid injections. So even if, even if they're just having one steroid injection for the first time, we have a lot of individuals who just expressed concern about steroid just in general and then for the population that has diabetes, you know, there was a concern is elevation of blood sugars with steroid. So, you know, of comparison for a safety standpoint, steroid might be the next best comparator.

Sheila Rege But on the evidence, and this is a question for Erika and Andrea, did most of the evidence use that as a comparator on the RCT or? I'm okay with it as steroids. Is everybody okay with that?

Erika Brodt Oh, sorry, I was muted. This is Erika. Let's see. I think, you know, let me go back to my summary slide here. I think the biggest comparisons were at least for PRP saline of course, which isn't probably what you want to compare to and then yes, corticosteroid would be the next biggest with 9.

Conor Kleweno Didn't you also describe studies comparing exercise?

Erika Brodt Correct. Yeah, there were 3. Yeah, basically PRP with exercise compared to exercise alone.

Christoph Lee And I'd probably put oral analgesics in there too, right? So, a lot of NSAID use seems to be pretty standard and that has that, adverse effects as well. So, we're gonna look at steroids as a comparator, I'd probably put oral analgesics as well.

Sheila Rege Let's go as a straw poll, safety using steroids as a comparison and injection of steroids not oral. Are you ready for a straw poll or does people want a little more discussion? We can discuss again after this straw poll for safety. If we would.

Janna Friedly Sheila, I'm sorry, can I, can I interrupt and just go back to the comparator, the steroid? I'm generally okay with that although I don't, I don't really want to ignore all the other evidence for different comparators. But what I struggle with is when we compare, when we look at studies and compare to a treatment when we haven't looked at the evidence for that that comparator treatment. So, we don't really know, I don't know based on this report and this data, whether steroid injections are a placebo or are they are they effective for knee OA and so when I'm looking at the comparison between PRP and steroid, if, if the data shows that steroids are no better than placebo, then making that comparison between PRP and steroids to me is not the right, then making that comparison between PRP and steroids to me is not the right, you know, is, it may lead us to say that they're both equally effective or that PRP is more effective based, but when you look at it against placebo, it's no different. So, and I don think that is necessarily changes what we do here or based on the data on, just as a, just to note about the comparator.

Sheila Rege Right.

Janna Friedly And maybe this is for also for future, we've, run into this in the past too with the comparators and not, not having the data on that comparator and the efficacy of that.

Laurie Mischley And the safety profile of the comparator.

Janna Friedly Yeah. And the safety, yeah, thank you, Laurie.

Sheila Rege Correct. Correct, Laurie. Well, let's put that on as actually Josh and staff for, we're doing a retreat in September so we can just talk about comparators and what this group may want in terms of information. So, Janna, would you prefer no treatment as a comparator or a placebo injection as a comparator?

Janna Friedly I mean, I think for this discussion for PRP, it may not make a difference. And so, I don't feel I don't feel strongly, but in general, that's what I prefer is compared to, it is, compared to a placebo, but I recognize that clinically, if the choice, you know, if you're really thinking about one versus the other treatment, then that's clinically relevant comparison. So, you know, it's hard for me to just isolate one, I look at them sort of globally and think of them have to think of multiple different comparisons when I'm thinking about a treatment and whether it's useful. But in general, I prefer placebo.

Sheila Rege Laurie, any thoughts on this topic? Not in general, but this is on this topic.

Laurie Mischley Yeah, only in that the point of reference as I understand it is going to change if we're comparing to placebo, it needs to be better than if it's if we're comparing to the other covered therapies. we're looking for no difference. Am I thinking about that correctly?

Sheila Rege That's how that's how I think of it. I mean, if there's something that everybody accepts works then, you know, is it more effective then? That's just my logical thinking.

Josh Morse (HCA) Hi, Sheila, could I make a comment here?

Sheila Rege Yes, please. Help us out.

Josh Morse (HCA) Yeah, so, you know. This aspect, and are you hearing me okay?

Sheila Rege Yes.

Josh Morse (HCA) Okay, this aspect of the. I gotta switch microphone sorry, I'm getting a feedback here. Made a mistake with the setup. Can you hear me now?

Sheila Rege Yes.

Josh Morse (HCA) Okay, so the purpose of this part of the document, you know, was to have the conversation you've just been having about the relevant outcomes from your perspective that you have evidence on or maybe that you wish you had evidence on. And then to move to your take overall on whether you think and this is not, you know, this is on the pathway to a final determination here, but your take on whether you think the technology itself in terms of safety, for example, is, is in one of these categories, whether you had evidence, no, and sufficient evidence to know that it's yes, it's more effective all the time than the things that it's been compared to, which again may not be perfect, may not be everything that you want so you may not know, for example some of the comparisons but to what you had evidence for, you know, this is generally what's your temperature here on how safe is hyaluronic acid compared to the variety of things it was compared to? And you've traditionally, you know, faced this complication where you have multiple comparators and sometimes you lump them all together and sometimes you are very selective and you want to vote on them separately. But this is just, you know, meant to help provide some structure to the thought process as far as evaluating the groups take on the evidence. I hope that's, my comment is helpful.

Sheila Rege Yes, yes it was. And I think just each of us. So, if we used to do this going around the room with our little paddles but in the virtual world we'll do a poll kind of a safety is it unproven we don't have the information, less safe than the other therapeutics that are available and covered, equivalent, more in some ,more and all. Can we create a poll on safety? And I'm just gonna lump just HA and, then we'll do another poll for PRP.

Val Hamann (HCA) And you just want it for safety because right now we have it with the question having safety, efficacy, and cost effectiveness where you can vote on all 3 at one time.

Sheila Rege Oh, we could. We could do it all in one time.

Val Hamann (HCA) And then we also have it HA knee, HA hip broken out. So that's.

Sheila Rege Sure, better than, yeah, that's what that's eventually what we're gonna have to do. So that's good. If you've already done that, then let's vote on. Let's just. This is just a straw poll.

Val Hamann (HCA) Okay, yeah, and just a reminder before I launch this that this is for just for voting members of the HTCC so anybody in attendees please do not vote even if you see it pop up so I am launching.

Sheila Rege Just where are we? Where do we fall? And we do have quorum, correct?

Val Hamann (HCA) Yes.

Conor Kleweno And this is all towards comparing to steroids, is that correct?

Sheila Rege You, whatever you decide, I mean you may decide steroids, you may decide in your mind, exercise the alternative.

Conor Kleweno No, but that's, that's totally different, right? So if you don't get a knee injection at all and you just ride a bike, you'd have no risk of safety for knee infection.

Sheila Rege I think in my mind I'm going to be comparing this to some sort of injection being placebo or steroids and I'm probably in my mind for efficacy thinking of steroids which is a routinely covered and you know our expert has also said that's what most patients get.

Conor Kleweno Yeah, I'm okay with that I just think if we're all in the same page for what we're comparing it to, it may be easier to discuss.

Sheila Rege Yeah, that's why I'm personally and I think everybody, Laurie and Janna, are okay with us assuming steroid injections.

Conor Kleweno Okay.

Sheila Rege As for Brian's recommendation. Okay, polls coming up, I hope.

Val Hamann (HCA) Yes, it is up. I have 5 answers so far.

Sheila Rege Oh, I'm gonna have to give you verbal, but I'm not I'm doing this on my phone while I'm using my computer to, to see the. I'm sorry, I'm doing it verbal, so I, I may have to log in by my computer. I'm sorry.

Val Hamann (HCA) So then with that, we should have one more vote cause we have 7. Okay, just kidding, we have 8 so if you wanna give your Sheila by voice, I think we can do that.

Sheila Rege Okay, I think safety, I think it's equivalent, I think for efficacy and I'm, oh, how am I gonna do that a voice? I will. I'll put it via the chat. Is that okay?

Val Hamann (HCA) Yeah, that's fine. Then I will end this poll so everybody will be able to see. And the results are up now.

Sheila Rege Any discussion?

Conor Kleweno I didn't see a lot of discussion on HA cost, but I think Brian did mention that steroids are quite cheap and I would just predict that steroids are much cheaper than HA, but maybe Brian can comment on that as well.

Brian Liem Yeah, I don't I don't have exact cost for the steroid injections, but it's sort of a pretty cheap here. And then for HA, just from a just general speaking, if someone has to pay for a series of 3 out of pocket, the out of pocket cost typically charged here is about a $1,500 with ultrasound guidance for all series of 3.

Sheila Rege Any discussion on? But I'm trying to log into my computer so I can start voting. But any discussion on the way we're gonna be taking this in terms of by hip and knee and then HA and PRP. Janna, I'm gonna have you take over temporarily while I switch to a computer.

Janna Friedly Okay.

Val Hamann (HCA) Just let me know when you're comfortable moving on to HA for hip.

Janna Friedly Yeah. Was there any anyone else had any discussion about the last poll before we move them? Otherwise, we can just move on to the to the next poll.

Josh Morse (HCA) I had a clarification question. Dr. Rege, your vote on the efficacy question was, was, for HA. What was that? Or, how did you capture that?

Val Hamann (HCA) I only receive, safety as equivalent, so.

Sheila Rege Less. I had less. Recording.

Josh Morse (HCA) Okay, thank you.

Val Hamann (HCA) And then what about for cost effectiveness, Dr. Rege?

Janna Friedly We can't hear you.

Sheila Rege I said it was more costly, sorry.

Val Hamann (HCA) Okay. And I can launch HA for hip if that sounds good?

John Bramhall Again, our comparator with this for the safety is? Is it placebo?

Sheila Rege No, we're gonna do steroid injections for all.

John Bramhall All right, okay, so okay. Yeah.

Val Hamann (HCA) And I currently have, okay. And there's 9. You should be seeing the results of that.

Sheila Rege Any discussion on that? Then let's move on to the next poll for PRP.

Val Hamann (HCA) You should be seeing the results.

Sheila Rege Okay. Discussion, and we're gonna, kind of start discussing, let's do HA for, let's start with the easy one, HA for hips.

Josh Morse (HCA) One more to go.

Val Hamann (HCA) We still do have one more vote for PRP for hip.

Janna Friedly You know, we.

Sheila Rege Oh, I haven't done that. Okay, sorry.

Val Hamann (HCA) Yep, here it is. So, you should see the results now

Sheila Rege Thank you. Let's look at. Any discussion? Going around the room just taking maybe HA for hip and then PRP for hip. HA for hip. What are the thoughts on cover versus not cover versus cover with conditions?

John Bramhall This just conversationally, yeah?

Sheila Rege Yeah, just conversationally.

John Bramhall Well, the evidence is really poor that it's effective. I mean it isn't it is there isn't evidence that it's effective in most cases the HA, either for knee or hip to be honest from the data that we've been given. So, just conversationally, I don't think it's something that would be covered, it should be covered.

Sheila Rege Does anybody?

John Bramhall Not to mention, especially, you know, especially, this the thing going through my mind for these previous votes. I think a crisper, I'm not asking for anything to go backwards, but it's the crisp thing in my mind is, you stick a needle in. Let's say you stick a needle in what you hope is the knee joint and inject saline or aspirate a little bit of synovial fluid or whatever you do as you control and that sets you up and you've got a certain risk of contamination, certain risk of damage and atomic, a certain set of complications that you could have and then your comparator is let's say it's HA, which is pharmaceutical, presumably clean, presumably sterile is easy to keep it sterile I think, just like any other injection and you inject that in and then the question in my mind is well is there a bigger risk here is the more dangerous to have done the, the stick with HA or the stick with saline. Pretty clean in my mind and we go to the hip. That's the same thing, but the whole idea of sticking a needle in the

hip blind is worrisome. So, in my mind I'm thinking both these things are more dangerous than, than they need to be if there's no effect, no beneficial effect. With the PRP, I know people who do this and, you know, I know something about the sort of equipment that's used, but you know when we do blood patches which is something analogous to in the neuraxial world, there's always this risk of contamination because you're doing 2 or 3 extra steps you know you're aspirating blood from a vein, you've got all that phlebotomy risk and then you're transferring it one way or the other, in a sterile way to the injection site and it just in subjectively without access to data, but subjectively it seems that there's more risk with PRP than there would be with HA. So that's, that's just conversational as what's feeding in my mind, are these things and then, and then of course we come face to face with the data and the data that we have are not very articulate about risk. They're not very articulate about complications because they're not tracked very well.

Sheila Rege — So continuing kind of and this is kind of going around the room, but, just the easy one of HA in hips. Is that something that, people think should be covered, either with conditions unconditionally or not covered? And can we take a poll on that? Or, you know, kind of, or do you need more discussion? And I'm kind of trying to get the easy ones done so we can spend time on the hard ones.

Christoph Lee — Sheila, I'd say just do a straw poll on the 4 different scenarios now and that'll give us a clear picture of where to focus our time.

Sheila Rege — That would be great. So why don't we do like the second vote us drop. How have you created this polls? Kind of

Val Hamann (HCA) — Essentially the same. I have HA knee, HA hip, PRP knee, and PRP hip for coverage. So.

Sheila Rege — Why don't you put that up and we'll do a straw poll and then we can based on that we can spend time discussing.

Val Hamann (HCA) — Yep, and here it is.

Sheila Rege — And let's do all the polls. And then talk about it.

Val Hamann (HCA) — I currently have 7 votes so waiting on 2 more. Just waiting on one more vote.

Sheila Rege — People are thinking.

Josh Morse (HCA) — Is there one person who's still?

Val Hamann (HCA) — I have 8 votes in.

Clint Daniels — Chris said he had to step away for a moment. I don't know if that's who you're missing.

Val Hamann (HCA) — I can't actually see until after all of the votes are in. So I can end it at 8 if that sounds okay?

Sheila Rege Yeah, let's do that. And let's just go to the next one.

Val Hamann (HCA) Did you wanna look at the results quickly or do that later?

Sheila Rege We'll do it later, all of them.

Val Hamann (HCA) And here is hip. We have 8. So going to PRP for knee. And going to hip. Okay, and we have 8 votes for that as well. Did you wanna start by looking at the results for HA?

Sheila Rege Yeah. Sure. We'll discuss this, all of them afterwards. Let's just scroll through the results first. Okay. Thank you. So, I think the HA for hip with I think we all feel that it should not be covered. So, if everybody's okay, we won't talk about that. Let's go ahead with HA for knee, where majority thought not covered, minority had covered with conditions and I'd like to just a discussion so we make sure we haven't missed anything there. Anybody want to speak on the conditions that we may be thinking about?

Clint Daniels I think I'm probably the holdout on this one. This for me, this is the hardest one of all of them. I really struggle with it's already covered and it's equivalent to the other most common treatment. And I'm, I wish it was more clear against the placebo. I think there was there was one that showed small benefit in the short term. But I struggle with it being equivalent and then no longer covering it. When it's already covered. So that's where I'm wrestling with that one. I'd love to hear if Dr. Lem has any., any thoughts? And where I'm also struggling too is for individuals who either have already failed steroid or can't tolerate but aren't good candidates for arthroplasty.

Brian Liem Yeah, I mean, personally looking at how it's currently covered now and then based on this newer evidence that says essentially it's really no not much more benefit than say placebo. It's a struggle for the patients that we have that, ave not done well with the corticosteroid injection where Kellgren grade 2 3 right, we're not talking about patients who are like really at the point where they're definitely arthroplasty, but I think about the young individuals who are, you know, they've got post traumatic OA and they're really not a great candidate for arthroplasty and we just, we have nothing else to offer them, really other analgesics, but clearly that's not a big population that you can, you know, have had on a major decision. So, yeah, I would struggle with that too, but based on the evidence I would say yes, don't cover it for knee OA but since it's currently being covered I know it's gonna you know what if the decision comes through it's gonna be a big shift for a lot of patients that we see.

Sheila Rege Go ahead.

Clint Daniels I also, I was gonna say, I also wonder if there's a little bit of an equity issue. If it becomes not covered and say we do cover PRP, but that not actually being very accessible to most patients or a lot of patients.

Conor Kleweno Can I come in on that too or Brian first and if I can come in on that?

Brian Liem Go got it. Go ahead, Conor.

Conor Kleweno Oh, I would just say I, I, I would not predict that to be an issue because as Brian sort of articulated the ability to get somebody to draw blood as very easy and the purchase of a centrifuge machine, when you build it into the margins expected by a business model of doing this many times over. So, my expectation is you would see expansion of access with a coverage decision, particularly of PRP. The reason why not with HA is because if you're in a private practice you have to purchase the HA and it cost money and so that cuts your margin. When you do PRP, you don't have to purchase the PRP. You purchase the machine. It's it's a fixed cost and then the patient brings their own injectable material. So, you know, small costs of, syringes, needles, things like that, but compared to what the pharmaceutical company will charge for HA, PRP is much more cheaper from a business model. And so I think my prediction would be access will profoundly increase at many different areas of the healthcare system and not seeing an expert like Dr. Liem.

Clint Daniels Dr. Liem, do you do you agree with that? Cause I know there's extra staffing and time that has to be factored in too.

Brian Liem Right, so I mean, I personally feel you could probably trade and so we have currently half of our MAs and half of our nurses and half of our nurses in draw blood so I think you can train that really easily for an MA staff, so the cost would be lower for that. You don't necessarily need a level of a nursing staff to do it. There is a fixed cost with the with the centrifuge itself, but then you also do have a variable cost with each kit you use. And so there is there is a little bit more of an ongoing cost but with coverage I do expect that it would expand access. I think a lot more offices would start offering it. And, and we're, you know, just as a side, I'm seeing currently a lot of Kaiser patients, they're not currently offering PRP, but we're on the street as they're gonna start bringing it in because they're losing money and business to it. So I think that when the expansion comes a lot of other insurances and payers are gonna get a jump on board and, it's gonna be more accessible. So I don't I don't have so much concern for the equity.

Clint Daniels Thank you.

Josh Morse (HCA) If I, could add, related to the original policy, I don't know that it's been brought up or that Dr. Farokhi got into the specifics. I think it was in her slide presentation, but it was meant to be extremely narrow coverage of HA originally and, frankly, it wasn't supported by the evidence base at that time. I think it can be interpreted that way. It was meant to be kind of a, a last chance but it became very problematic in the implementation and that's part of the reason why it's back here today.

Sheila Rege What are your thoughts?

Conor Kleweno I'm actually surprised it's, I was actually surprised to hear it was still covered.

Sheila Rege I was too. I mean, given the evidence and what our orthodox searches now are recommending. Clint, any more questions?

Clint Daniels No, I think Josh's comment there was helpful to give more context. So, I appreciate it.

Sheila Rege If we were to go to a final vote, Clint, are you comfortable with not, no coverage or would you like us to spend more time on that?

Clint Daniels I think.

Sheila Rege Okay, I lost you, but I think you said you were comfortable. So, then we are not gonna speak about HA on, you know anymore at this time. For PRP in the knee, majority of us thought it should be covered with conditions. So that's something we'll have to work on. But let's go back to PRP for hips and majority on PRP for hips thought it should not be covered. So, I'd like to hear from then you don't have to identify yourself but did we miss something because they were some people who thought it should be covered with conditions. Just kind of helping the group understand what conditions and what we may be missing, especially if we if we come to a conclusion I'm not covering. Does that mean everybody's okay with not covering PRP for hip? Okay, so then we are left with PRP for knee and covering it with conditions. In the past I have started with a template of the agency medical director, if that's something we would like to do? And then go from there or would we like to create our own conditions? Looking for insights.

Clint Daniels It’s helpful initially.

Sheila Rege Okay, so let's. Can we bring up the, Dr. Farokhi’s cover with conditions and look at that document and this is still in discussion phase, we're not at final votes, this is just discussion though I would like to do the final vote if possible before Conor has to leave.

Azadeh Farokhi (L&I) Sure. Would you like me to my PowerPoint or do you have it Josh?

Josh Morse (HCA) So bring in that. Oh no, I have. I think I haven't.

Sheila Rege So yeah.

Azadeh Farokhi (L&I) Perfect.

Josh Morse (HCA) This is typically where we transition to a draft document and I have cut from Dr. Farokhi’s slides as a starter because this is often where we land as a starting place. Is this what you were wanting to see or?

Sheila Rege That is what I was wanting to see.

Josh Morse (HCA) Okay.

Sheila Rege And I think what I've heard from the agency medical directors is a little more, they, do better with little more clarity in terms of, you know, and helping out here, kind of. Failure of conservative treatments clarity of timeline or things. So age greater than 18, any comments, somebody more smarter than me. Oh good, Janna and Conor have their hands up.

Janna Friedly Well, a couple of things. One I'm still really struggling with, with the coverage decision for PRP and the evidence. And so, I'm, still in my mind still working through that and, and found this to be a really difficult question because the evidence is so mixed. And there's, and there's differences when you look at, against placebo versus, versus steroid and, and so I I'm still struggling with that, but in terms of the, if we go with, coverage with conditions, it should be adults, 18 years and older, not greater than 18. Then people who are 18 to 19 can't get the injections.

Sheila Rege So you're thinking 21 years old?

Janna Friedly No, no. This excludes people who are 18. If you wrote it, right, written.

Sheila Rege Oh, so you want 18 and over.

Janna Friedly That's a very minor. Right.

Sheila Rege Actually, I did it incorrectly. I mean, I know majority said, here to cover, but the minority has said do not cover. We should hear from them. What, why, I mean, if you want to speak now, if you feel.

Janna Friedly Yeah, I mean, I, you know, some of the things, sure. I mean, some of the things that I'm weighing in in my head. One, you know, the, we're seeing mixed, mixed evidence and as Conor you know pointed out with different outcome measures, different results, it doesn't the evidence of whether it's better than steroid is very mixed and I and the evidence about steroids is not, you know, great either. So, it, to me, and, thinking about this as a, sort of long term chronic condition where we're not thinking of this as a regenerative treatment, we're thinking of this as, you know, a pain relief. We don't have long term outcomes, so I don't really know what effect this has. So, you're thinking about this as a short term treatment for pain. Is it really better than anything else that we have out there? I'm still not convinced. And, it's costly, and, there's so much variability on how it's done and there's no regulation of how it done and people, what I worry is that your open this up to people who start injecting and using all different sort of techniques and we really don't know what people are injecting and there there's no regulation of it so that concerns me of the implementation of is and the widespread use because I do think that once if you do make a coverage decision it will be used very broadly and, and I don't know how often you should use, it how many times, is it safe in the long term? I feel like there's still some unanswered questions. So that I'm struggling.

Sheila Rege Yeah, I struggled with this one too about whether to cover it or not. And I know. I was leaning towards not covering versus covering with conditions similarly. Because

I'm not convinced and maybe our expert Brian, you could tell us. It just doesn't seem like it's regulated as well and it just seems like it's.

Brian Liem Yeah, and I would agree with all the points that Janna, Dr. Friedly, just made. It is really, I mean from for a practitioner that is facing patients with knee OA and going off of the most available evidence, we try to keep this as not necessarily like the first line resort, but I can see certainly the Wild West could happen in you know I used to be in private practice so I'll say this yeah private practice practitioners are saying hey look it's covered let's go ahead and offer this and really just bypassing any available evidence about exercise, analgesics, or trying any conservative therapy. So, you have you have conditions here a failure of conservative treatments, but I guess what does that really mean and for how long? So, I think that that really has been delineated and then yes, there's no FDA regulation, there's no standardization about, hey, you have to have a certain amount of platelet levels. What kind of centrifuge are you gonna use? Is it just gonna be an off the shelf centrifuge that you purchase, you know, at a laboratory, a wholesale store and then say it's PRP, right? So that's going on right now. So, you know personally as much as I think that the access would improve for patients with coverage, it also opens up a lot of Pandora box. Part of it is, you know, we have status quo right now and it's not being covered. I don't know. I'm conflicted on both, both ends, right? Because I know that access would be higher but at the same time this is gonna open up the Pandora's box where you know being coverage you're gonna have a lot of unscrupulous practitioners practice this and just offer it and really don't care about the science behind it. It's just dollar driven issue. That's my 2 cents.

Jonathan Sham So I think if I could just follow up.

Janna Friedly Conor and Jonathan have their hands up.

Sheila Rege Oh, go ahead, sorry.

Jonathan Sham Sorry, Conor, I, I know you were before me but maybe I could just follow, cause it has to do with what Brian just said. So, it sounds like, you know, Brian, you know, I definitely agree with what you just said and It sounds like in your gut. I mean, you offer this to patients, right? It sounds like in your gut you think there's some type of signal there. Are there any guardrails that we can place, you know, obviously we can define what conservative, failure of conservative means but on the on the procedure itself are there any guardrails that we could realistically place? Obviously, we can't regulate the centrifuge, we can't do some of those technical things. Because as I mentioned before, like yeah, I agree, I don't really know what PRP is. Like, what does it really mean? Like, what does it really mean? What are we, what are we actually injecting? And maybe some of the heterogeneity and the outcomes data is just due to the heterogeneity in the procedure itself. So is there anything that you can recommend to this committee on guidelines we can give, suggestions, anything to kind of give the most effective type of PRP understand the limitations that we have.

Brian Liem Yeah, I mean, you could maybe see a commercially derived product that has at least 2 to 3 times the concentration, documented concentration right and so any of the any of the manufacturers you know, they've got to be sort of vetted or at least like

Arthrex or Genkit. So, they've got a document that their product can deliver that. So, I don't know if you're able to specify that specifically, but that would be one guardrail.

Sheila Rege No, because what if, another one comes up that's even better than that? We don't wanna.

Brian Liem Well, I, yeah, at least.

Sheila Rege Yeah. So. No, we need some generic language. I know Jonathan Conor have the hands up too. So I don't know who was first.

Jonathan Sham Well, I guess just a follow up on that. So, I mean those are FDA cleared like 501 kind of clearance? Or like I guess we could have some sort of I think it's a good idea, Brian. I guess I don't know if there's this precedent for that Josh and our recommendations but just something to say hey like the someone other than the practitioner has looked at this technique or kit or whatever to validate it in some way.

Josh Morse (HCA) Yeah, so to answer your question, the committee has required FDA approval in the past. Mostly for PMA approved devices, I'm thinking of artificial discs, for example where it referred to the FDA labeling. It may have occurred for a couple of others. This would be could, you could reference the FDA, marketing approval under 510K. I'm not sure what as you, basically, said what, what level of meeting that would have as far as efficacy goes because it's just approving that the, that the thing does what it's supposed to do which is to centrifuge for example. So.

Sheila Rege You know, I started when I when I first saw this topic, I started looking at some of the studies and in our journals, the NIH kind of journals and stuff. And I saw in the inclusion criteria for, for patients, I mean, they had things about the hemoglobin, and you know that kind of stuff and I'll put it. Josh, I will send it to you and you can somehow sent it to the group. But they really, I mean, I know we are going to 18 with they actually had, you know, ager 40. I mean, I don't know most kids who have osteoarthritis. But just so.

Brian Liem Yeah.

Sheila Rege I'm struggling with even that age. Because I was on the brink cover with conditions on not cover. I put it to you, Josh. I can put it to the group, but I know we're not supposed to use the chat so if you can project that in some way and Conor go for it but I was looking at some of the studies and somebody smarter than me can help.

Conor Kleweno Yeah, just a specific response to your first or the comment you just made. So you can and, Dr. Liem commented on this. You could have post traumatic arthritis. So even at a young age, if you fracture, break your knee joint, you, you can get arthritis. So I don't have a problem with the 18 years old issue because that can include people with arthritis. To take a step back, I guess I have 2 ways of looking at this. One is the sort of the practical and the real world analysis and that gets back to Dr. Friedly and

Dr. Liem's points. So, 2 biases have to acknowledge, right? I'm a surgeon, so I like surgery and I do know Dr. Liem, so I, you know, try to make sure my comments are objective without offending him as well. So, this is really a holy grail topic, right? Pain in the joint, right? Everybody is gonna have pain in their joint and the ability to like inject something and it goes away or gets better. That's been something we've been discussing for decades and decades and decades. So, I do have concerns that were raised but that the level of ability to provide this will be dramatically decreased and so the utilization of this will be profoundly increased. I just think when we think about cost that should be understood that every single practitioner, practitioner office will be able to provide this and that may be great for access if it's effective. If it has very modest benefit or effectiveness, then you're definitely gonna see a value change because I think the utilization will dramatically increase. Because, you know, almost anyone I think as opposed to now or you know, Dr. Liem was saying. It's, you gotta get kind of a setup and even at University of Washington, there's not that much of it, but I think with coverage the access and the ability to provide this will, skyrocket. So, I do think that when you look at cost, it's gonna be hard to compare what we've done before and if you're looking at the cost of a diagnosis of osteoarthritis expect that cost of care cycle for that diagnosis to go way up with this. From a, my second part was from a research and evidence base. I think I would call the committee back to kind of thinking about our session that we had with the, the presenters discussing research bias and you know bias and evidence that are a kind of mini retreat that we had Sheila with the 2 presenters. And so what we have here are lots and lots of studies, right? 60 plus randomized control trials.

Brian Liem Good. Yeah.

Conor Kleweno That's a lot. And so we, why is that one? Lots of patients are available because everybody has knee pain. And why do they need a lot of studies? Is it because the first one was dramatically awesome and so we don't need more? Or was the first 10 sort of I don't know and so they kept going kept going, kept going, kept going so lots and lots of studies should try to show something of benefit. And so, when we think about that, does that mean that we're just not designing the study right? Is it the heterogeneity of the of the PRP? Is it not capturing the right patient population? Or are we just fishing and fishing and fishing until there's some sort of, you know, statistical signal that's just showing up. And I do think it's upon our charge to try to interpret that best we can. And so I guess those are my 2 concerns. There's the practical aspect of it and then are we really understanding this data?

Sheila Rege Conor on guardrails, I just looked at it and I study and I sent that to Josh, we, you can look at it. But their inclusion criteria, I'm okay with 18, but I like our experts opinion about, you know, kind of they wanted at least 4 months of knee joint pain. This is just to get our thinking and they didn't want it to be severe osteoarthritis. I mean, I don't know if this is something used clinically. And you know, no fractures and stuff. I, or this is just for a study. But I'm sorry I jumped out of turn, but if you guys would look at that while we're talking, I don't remember Janna or Christoph first.

Janna Friedly Christoph.

Sheila Rege Christoph.

Christoph Lee Thanks. So I thought there were some FDA standards for blood products. It's not. Obviously, you know, PRP itself is not a product that's approved by FDA but the machines that are used to extract the PRP from blood. I believe there are standards in terms of how the FDA approves those equipment and that has to be a single unearth, then you have to at least like 250,000 platelets per microliter to call it PRP. So, there are FDA standards around this and I wonder for guardrails, can we point to those? I don't know if Dr. Liem or others have, have any information on that or background but.

Brian Liem Yeah, I don't necessarily that background there. I'm looking at this criteria here and then also to Conor's point about the age. Yeah, I would agree. We have a lot of individuals who have post-traumatic osteoarthritis in their twenties. And then individuals who have had a history of ACL tears, they're more prone to develop arthritis so we have a lot of those who have torn their ACL as teenagers and then present to us in their late twenties or early thirties with osteoarthritis and, you know, they're just not responding to any of the quote unquote conservative measures. In regards to the 4 months that it's listed here, that's generally speaking for us 3 to 4 months where you know that's enough time where they've done at least 2 months of physical therapy, tried maybe some NSAIDs, acetaminophen. So I think 4 to 5 months is a reasonable time and it takes this long to get into physical therapy these days anyway. So, I can take a while. From a Kellgren Lawrence scale, we, I pretty much tell everyone clinically if they have grade 4 that PRP is at least the evidence doesn't show that it's gonna work at all. I've had one exception in the past sort of like 10 years of doing this and that it's worked, but vast majority of people who have requested a Kellgren Lawrence grade 4, I've not seen anyone really get better. It's more likely 2 to 3 and more likely the 2. And let's see here, anything else? Hemoglobin levels. You know, I'm not quite sure the, I think they're looking for anemia, but we're looking at platelets and I mean, I'm not hematologist, but I typically if the platelets levels look fine and hemoglobin are maybe low, I don't really care too much about the hemoglobin.

Sheila Rege So, Janna, you had your hand up, I think.

Janna Friedly Well, I think it's related, you know, and I and this is and I struggle with this again more broadly, but when we start to come up with very specific, coverage criteria, I try to go back to the evidence and see, you know, it does this reflect what's done in the studies and is this are these evidence-based conditions right so and that that's where it's really challenging with the with the heterogeneity of the studies done to really say that yes if you have these product standards or you have this amount of, platelets or you have XY or Z that that is what will make this a more effective treatment for patients or that patients are better candidates for this. So that's a little bit where I'm struggling and particularly when you think about the comment earlier about the correlation between the imaging findings of osteoarthritis and the severity of symptoms and how they don't necessarily correlate either. So, you know, just thinking about even knowing that they knee osteoarthritis is the source of the pain, is also, you know, maybe a little bit challenging. So I think if we go with coverage

with conditions, I personally think we need to do a little bit more deep dive into what those specific criteria are particularly around the, the procedure technique to put some, some of those guardrails in place. And then I just as a general comment wanna just echo what Conor has said about the evidence and I really appreciate his, his perspective and I think that's important.

Sheila Rege I would agree and I put my hand up so to go next but I, what I'm struggling with is that the evidence really was studies from I think one was from Iran and you know kind of not whether liability and stuff or there was possibly less, less concern of liability and stuff. So, if there were all American studies and that's why I went to an American study and just pulled what they criteria was. In my mind looking at the evidence it seemed to work for earliest stage osteoarthritis, and it didn't work for late stage. So, I personally would like something there that, you know, you can't do it for everybody just because they've come to see you. I would like a timeline of, you know, kind of how long you've got any joint pain, not just that you got pain for a week and you're coming in. So those would to me the more important to put guardrails on. So, is everybody okay with symptomatic? Let's go back to the criteria to get us moving forward. Symptomatic knee osteoarthritis. Is everybody okay with putting a time frame there? And I don't know if the studies had a timeframe. Andrea or Erika, was there some consensus in the study? I mean 4 months, 6 months?

Erika Brodt I would need to review. I wanna say. I wanna say at least 3 months up to even 6 months. Maybe in a study or 2, but I would have to review. The inclusion criteria, which I could do. If that would be helpful to you, I can kind of run through the table and see.

Sheila Rege That would be helpful. So we'll just table that too. And then treatment at a failure of conservative treatments, is that something that is done in the clinical realm? I mean this shouldn't be the first thing you try. I mean, people are steroids or exercise should be the first thing that's tried. Do we wanna put something in there? And I would, I would like for something about, early stage osteoarthritis. Maybe I'm I just don't want you know my mother who probably has bone on bone doesn't want surgery going in and getting this.

Conor Kleweno Sheila, I raised my hand but I if there's silence I guess I can speak if that's okay? One thing I'm assuming that we are no longer discussing coverage versus non-coverage, first question and to your point, I think that the Kellgren-Lawrence scale is pretty reasonable in terms of its extremes. So, although there's probably some quite a bit of variation in grade 2 and 2 and 3. If you said excluding end stage arthritis of you know radiographically documented grade 4 KL. That would be pretty specific, I would think to use the example of your mother. I agree with you. They shouldn't be selling her this if you do have end stage arthritis and I think Brian nicely articulated that at least in his experience no, no, benefit in that age group, but I think we do have something relatively specific about, excluding severe osteoarthritis.

Sheila Rege Let’s actually do a poll after this discussion. That's a good point before we start working on this. Maybe people have changed their minds. Do people think they should be let's go back to PRP, the poll of cover, cover with conditions, or do not

cover. Let's just make sure we're all still thinking cover with conditions and let's, let's make this the final decision so we can start working on this and then we'll do the final polls for the rest too. But can we, can we put that poll up just in case people have changed their minds?

Val Hamann (HCA) Yep, I can relaunch it right now. Okay, ending that and you should be seeing their results.

Sheila Rege Oh, it gets worse. Now we're close to 50-50. This is not good. But it probably signals that we need to clarify who should not get it would people agree? I mean do people feel strongly that it should not be covered. Jonathan?

Jonathan Sham Yeah. I think there's a good conversation, important conversation to have amongst committee and I think going back to Conor's previous point about kind of why there's so many trials in this space. I completely hear that. I think that at least how I interpret that when I when I look kind of at the totality of the report is just this is a hard problem just to study like you know as a clinical trial as I know how difficult setting up this criminal trials are. You have a heterogeneous disease population heterogeneous path of physiology likely. You have a heterogeneous treatment. An intervention and just like all of these things just layer upon each other to where again, just looking at it on mass, I don't get the sense that they're just kind of retesting, retesting, retesting to try and get a different answer. It's more just, it's such a hard study to get a grasp on and particularly if it's able to see mild benefit we'll say at most. And particularly in different practice settings, it's just I think difficult to get a firm answer. So, you're not gonna get a hazard ratio of 3, you know, and something like this. So, I did, you know, just to throw it out there, I did vote for cover with conditions because of that. It seems like the preponderance of the evidence you know in the legal sense 51% at least in my mind is leaning towards coverage But that's why I was really focusing on, on kind of finding some language to put some borders on how we cover. But I completely understand those in the group, you know, that aren't swayed by the you know, measly improvement and some of the qualitative outcomes. Just my 2 cents.

Janna Friedly Conor?

Conor Kleweno Yeah, really not trying to take too much of the conversation. I do think this is a tough one. I agree with, Jonathan. It, you know, sort of like if somebody said to you, okay, you have knee pain and we could do this thing that we inject your knee and in terms of our responsibilities of the committee, 3 categories, safety, effectiveness, cost, right? Those are our charge categories. I think this is a appropriately safe treatment. And so somebody said we could do a safe treatment for you and some patients that offer some mild to moderate benefit. And I think most people would say, okay, that sounds reasonable. And if I said to you, by the way, it costs you 5 cents. I think most people would say, yeah, I'll give you a nickel and let's go. If I said, yeah, it's gonna cost you a million dollars, most people would say, sorry, I don't kind of got a million dollars. So, we're in the middle, right? Because it is gonna cost something. And I do think that coverage at, my prediction is coverage will increase costs. And so then we get back to effectiveness and I do think there's some mixed signaling in the data. And

I agree with John, it's definitely a difficult, problem because there is so much variance and the same looking x-rays and even, Brian had mentioned, patients have highly variable symptoms with the same looking x-rays. So, we have blunt instruments and highly variable patient group with it, with a treatment that we're not quite sure about yet. So, I do struggle with this as well just to echo that and hopefully I'm articulating myself fairly.

Sheila Rege And I know we look at this afterwards, but at least when I'm talking to my local. Oh, sorry, I shouldn't go out of turn. Brian and Christoph.

Brian Liem I'll let Christoph go first.

Sheila Rege Go ahead.

Christoph Lee Yeah, you know, it's. Just looking at sort of the safety effectiveness and costs. It really does look equivocal and the data is insufficient at some times in terms of whether it is effective. The safety is probably there, but in terms of the cost, honestly, if it's something so on the on the border on the fringe of improvements and their soft improvements in terms of measurements. Why not let patients pay out of pocket if they're willing to take on what is, you know, considered experimental by most parties right now. So, I'm leaning towards not covering because it's something that doesn't show obvious effectiveness. And we're asking the state to cover the cost for something that's not obviously effective even if it is safe. So. Yeah, we have a lot of technologies like this in radiology where they're not covered. Maybe they work. Maybe they don't. They're FDA approved and right now all of them are considered experimental even though they're in use broadly and commercially, but patients pay out of pocket for that if they want that. And that's sort of where I'm placing this right now.

Brian Liem Yeah.

Sheila Rege We had the agency medical director had us slide up on what other ensure I know there's no NC, they know there's no NCD. I think, she had a slide on, all the other insurance companies are we, are we, do most insurance companies cover this or is this investigational?

Janna Friedly None do.

Brian Liem Yeah, none. The one exception is I try, Tricare. There are Tricare the for the Army or military, they are starting to cover PRP in certain cases. But yeah, I mean, as your, as you're sort of the clinical expert, someone who does PRP, I'll be honest with you, I would sort of lean towards, I mean, it's safe and it's modestly efficacious, right? So those are 2, 2 aspects as Conor mentioned, but from a cost standpoint, if you guys are looking from a state standpoint and the cost of the state, I think yes, I do agree your cost is gonna go up if you approve this and so then from that aspect, I would say I lean towards not covering this.

Sheila Rege I don't think we're looking at cost as long as it's effective. I think we're charged with making sure it's effective. Laurie, sorry.

Laurie Mischley One thing that hasn't come up and we didn't really get into it in this review, but in NSAIDs and steroids aren't without side effects. And so I'm wondering how often does one turn to this because they aren't eligible for, or they've tried steroids and it doesn't work. I mean, can you just talk about why the subgroup of people who might not have those other options available? That's to our expert Dr. Liem.

Brian Liem Yes, so yes, I mean, the NSAIDs this comes up all the time. We have a lot of individuals who are systemic anticoagulants right? Eliquis, or they're on Plavix and they, they aren't gonna give you good candidates for using NSAIDs, but at the same time, you know, things that inhibit platelets. They're not giving a great candidate for PRP as well, but it comes up a lot where, you know, they're not, they're not able to take oral analgesics and PRP is an option but honestly, we're recommending steroid and exercise and just pushing that the most, rather than PRP.

Sheila Rege Jonathan?

Jonathan Sham I wonder just to kind of round out the conversation if one of the AMD representatives might speak to kind of why they came up with their proposed recommendation. You know, given I know this spent a lot of time looking at this as well.

Azadeh Farokhi (L&I) Yeah, that's a great question. You know, I think just the evidence. You know, when I reviewed it was very clear, you know, we felt, or at least I felt that given the progressive nature of this disease and the fact that we don't have a whole lot of options, you know, I felt if we're gonna cover something, PRP is what should be covered versus HA, which we have been covering for a long time even though the evidence really showed that it wasn't beneficial. Does, does that sort of help?

Jonathan Sham Yeah, I guess maybe more specifically, I understand the PRP versus HA but just, yeah, I guess in your mind why did PRP reach that threshold of coverage, which is I guess what we're kind of the group is on that, kinda on that level at this point.

Azadeh Farokhi (L&I) Yeah, I mean, I think the evidence did show that PRP was effective when compared to placebo, and to some of the other treatments. So I mean, I guess I feel like I, I don't know that you can sort of ignore that. You know it wasn't consistent you know across the board with you know every outcome measure and you know perhaps that's some of the heterogeneity that exists but overall, I still felt like it really was showing that it would be beneficial. Dr. Franklin?

Sheila Rege So. Yeah, Dr. Franklin?

Gary Franklin (L&I) Yeah, so yeah, we kind of went strictly with the evidence on is it effective? But some of the stuff you will have brought up in this discussion are really, I, fantastic points that you were making and It's, yeah, there's a context here that you're bringing up these issues that maybe we didn't talk about so much when we reviewed the evidence and came up with our recommendation. So, I think that the

recommendation we came up with was pretty strictly related to the 3 categories. But you're raising some other issues here that, we probably didn't talk about so much. So, I think that's really important.

Sheila Rege I think in the interest of time, Conor, I may call you back if you could make sure when we go to voting, I think you have experience in this, but we will go in 9 min or 8 min, we're supposed to go to the SBRT topic. And then, I think we should just do final votes and final language and Conor will call you back, for you know, for the coverage, with conditions if that's where we go on any of them to kind of learn from your expertise. Is that okay? And we won't keep you for long.

Conor Kleweno Yeah, yeah, so to specify the timeline and what you were talking about for calling me back.

Sheila Rege So, 12:30 we're supposed to go to SBRT for 15 to 20 min and then we'll come back and we'll do votes and you're welcome to send Josh your votes on cover or with conditions or not cover on any of them. Well, I think those are the only 2 we've been talking about for all of them because you know and then we'll call you back when we have final language. Which will probably be in hopefully an hour or hour and a half. Is that okay?

Conor Kleweno So yeah.

Sheila Rege And if you can't, it's fine. I think we've got quorum. I just wanted to give you the opportunity.

Conor Kleweno No, I appreciate that because I do you know think I provide some, some context here. I wanna be as helpful as possible. So Let me know when you want me to be here. Just.

Sheila Rege Okay, and if you will email the best number to reach you at. That would be good. And then let's take a break and Janna, you're gonna be running the meeting. I know it's lunchtime. Is everybody okay with just a 7 min break because we promised Dr. Yen it would be 12:30. Put lunch in the microwave and come back. Is that okay?

Josh Morse (HCA) Yeah, just for so we need unfortunately Dr. Yen couldn't be here, but we really were hoping to have Dr. Yen here for the final vote on SBRT. So we're deviating from this topic for just a few minutes because of his schedule. So really awkward calendaring today, but please bear with us. We expect him at 1230.

Sheila Rege Alright, break till 12:30.

Tony Yen Can you hear me? Can you hear me?

Josh Morse (HCA) I heard you. Was it Dr. Yen?

Tony Yen Yes, sorry, like I'm sure gerry rigging stuff together right now to try to get online. Like I'm Yeah, so pain in the butt, sorry.

Josh Morse (HCA) No problem. Thanks for joining us. We're taking a brief break right now.

Janna Friedly And Josh, are we, are we also a reviewing minutes as well or are we?

Josh Morse (HCA) Yeah, that's a good point. Why don't we start with the decision itself. I think that's if that's okay with you?

Janna Friedly Yep.

Josh Morse (HCA) So whenever you're ready, Janna.

Janna Friedly Okay. And do we have quorum? Do we have everyone back? Okay, is that a yes? I can't tell. Looks like most people. Okay, well, so, at this point, we are to review our coverage decision for SBRT and the and comments that have come in to determine if there are any changes that we need to make, any updates or whether we can finalize the, the decisions that we've made. Josh, so it looks like there are several comments. Do you wanna scroll through those would that be?

Josh Morse (HCA) Yes, I can do that. Here's the first comment from Dr. Kim. Dr. Kim asked that the, for clarity regarding the, the items for stereotyping radio surgery that were not included in their current update that they were still to be covered. And yes, that is the case. These were not part of the scope of your review in June in May of this and the document that we have with your draft decision does not contain this information but once this is finalized we will be combining into one document for clarity for the use of the policy. Does that make sense?

Janna Friedly Yes, that does. And as a point of clarification, when you get a comment like this back to do you provide an individual response back to the person who, who made the comment about how it's being addressed.

Josh Morse (HCA) Good question. Typically no. But we, we address it here in the meeting.

Janna Friedly Okay, thank you.

Josh Morse (HCA) So, the second comment. I'm going to have a hard time recalling. The second comment.

Val Hamann (HCA) Is from Dr. Kim as well. He's, he's sent two kind of back to back.

Josh Morse (HCA) Oh, okay. Thank you. And this ask for clarification of primary bone as far as not being covered to Limit the confusion related to metastatic coverage. In the draft I have put an example of what this change looks like based on the very specific helpful language that was provided here.

Janna Friedly Okay, so we so just to clarify we did not include the word primary.

Josh Morse (HCA) Correct.

Janna Friedly Okay. That sounds like a helpful change to make.

Josh Morse (HCA) This third comment addresses the question I think of renal cancer coverage. Yeah, there it is. At the top of this, we looked at this study, I believe this I asked Beth to look at this. This study was included in the report. You I think discuss this in some detail at the last meeting.

Janna Friedly And I don't recall off the top of my, this particular study and how we looked at that in relation, I have to I'd have to pull up the transcript but does anybody, does anybody want to comment on this to provide us a refresher? To make sure that we have addressed this. That this doesn't raise new, questions or concerns. It doesn't sound like it does, but, but I wanna make sure.

Jonathan Sham Yeah, yeah, I just, I don't recall this study specifically, talking about it specifically in the context of the rest of the evidence report.

Laurie Mischley Nor do I, I was just wondering if the vendor had anything other else to say other than it was included.

Janna Friedly Josh, do you?

Josh Morse (HCA) Yeah, I'm looking at the message from our vendor on this particular. So, here's the message from Beth from a week ago. We did include the study in the report. Technically it was published after our search dates, but Dr. Lo highlighted the study through peer review and his other comments so we added it as it did meet our criteria. However, for our purposes, this was not a comparative study. All participants received SBRT or SABR. As reported in the paper, and then outcomes for people who received single or multiple fractions of SBRT were compared. So, we reported only harms from this analysis.

Janna Friedly Okay, so this was not a, this was not a comparative trial or this was a this was a prospective cohort, it sounds like?

Josh Morse (HCA) Yes, is missed.

Sophie Miller (HCA) Hi, this is this is Sophie Miller. Sorry, I wasn't I wasn't a panelist before. This was this study is non-competitive. There was no control group. Everyone was received SBRT and thus it was we felt it to be low quality evidence because it was a non-competitive study.

Janna Friedly Got it. Okay. Thank you. That's helpful. Okay.

Josh Morse (HCA) So that's the third comment. The, I think that's the third comment anyway. We then have a very detailed comment here. I think from a meeting attendee. This comment again addresses the question about previously covered conditions which we will address. It also raises a very important question about the scope and whether it included both non-small cell lung cancer, which you did modify a decision for. As well as small cell lung cancer, which you did create a decision for. We investigated this,

and yes, they were both within the scope. The, the previous determination included stage one. It was covered for non-small cell. The new determination that you have, you have modified that to include stage one and stage 2. So, the forward looking search looked for things that were not already covered so this they were both within scope, which is one of the key questions that came out of this.

Janna Friedly So.

Josh Morse (HCA) So, we don't amend a modification based on the comment here.

Janna Friedly Okay. Thank you. My I have to admit my, my vision is not good enough to read what's on the screen there. So I can't see.

Josh Morse (HCA) Yeah. And these comments are in your materials as well. But they are published, all of this is published.

Janna Friedly Yeah. Okay, any, any comments about that? Thank you for making that a little bigger. Any comments from the group? Any concerns? Okay, so Josh it sounds like from and that was the last of the comments, yes?

Josh Morse (HCA) No, there is one more comment that is this also addresses, I believe, the renal cancer coverage.

Janna Friedly So, I think it would be. It would be, so this, again, addresses, renal cell carcinoma, which we have address. But the question of, could I get clarification about the oligoprogressive versus oligometastatic in this in this comment and, and how that pertains to our, our decision.

Josh Morse (HCA) Dr. Sham?

Jonathan Sham I was reading that other paper. We don't typically use the term oligoprogressive, you know, oligometastatic we've are already defined, oligoprogressive. I imagine they're saying they just some of the multiple tumors have are progressing. I'm just reading through this here.

Janna Friedly So, patient with 10 total metastases less than 5 sites of progression would have Oligo progressive but not metastatic disease.

Jonathan Sham Yeah. Correct. Correct. I'll be honest, this is not a standard term that we use day to day. In the oncology world, it may be kind of a, a niche scientific, you know description for the purposes of clinical research.

Sheila Rege I would agree and I mean it's not like there's new evidence there, is there?

Janna Friedly No, no, it's just a sounds like a terminology issue. So I just wanted, I'm not familiar with that term either. So I just wanted to get clarification if there was anything. With that that we needed to consider differently.

Jonathan Sham Yeah, I mean, I guess it speaks to the biology of the disease. You have 10 lesions and they're all stable, one is growing, should be able to treat that one lesion. One could make a broad biologic argument for that but again, we certainly don't have data specifically saying that.

Janna Friedly Okay. And then the second concern again raises that same point about the same, the same paper that we just talked about in terms of the renal cell. I think this is a, an overlapping concern.

Jonathan Sham Yeah, I don't, I certainly don't wanna get too bogged down on that, but I just pulled it up and the only reason why I think it just deserves a second look is because it is in Lancet oncology, you know, one of the premier oncology journals out there. And, you know, I hear that it wasn't comparative, but it is a high end over a long period of time showing pretty impressive outcomes. I'm just looking to see it in the paper there, they describe like I don't know what the historical control you know would be to compare it to. Off the top of my head, this isn't my field, but just the fact that it was published in this journal at least just raises my interest just a little bit.

Tony Yen Hey Jonathan, this is Tony Yen. In that paper, is this we referring to an observational study? Is this really kind of what we're talking about this Lancet paper.

Jonathan Sham Yeah, I mean this would be a retrospective cohort trial or study.

Tony Yen Oh, okay. That sounds really interesting and probably doesn't like, yeah. I don't know that meets that though it's in a in a very prestigious journal. Not too sure if it reaches a threshold for us to say that this is effective. Yeah, I think it, it gives us directions like, oh this, this is, the type of therapy that probably deserves further exploration and, probably a randomized study for a comparative study of some sort.

Jonathan Sham Yeah, I mean, so as you know, often times the reviewers and editors will make you put that in your conclusion, right? Like that's your conclusion. This this warrants further evaluation. That's a common last line.

Tony Yen Yeah.

Jonathan Sham They go even further and again, I'm just trying to pull up the actual full text here. They go, they do say that. These mature data lent further support for renal FR as treatment for option for patients unwilling or unfit undergo surgery. And to be clear, this is actually now that I'm now that I'm really looking at it more closely. This is looking at single fraction SAVR versus multi-fraction. And so I think it, it wasn't even like looking at that versus surgery. It was looking at the actual dosing of, of the SABR. Which to me even raises the interest because then it's kind of using multi-fraction as the, the control you know as, as the quote unquote standard. So yeah, I don't know what the groups general threshold is for we have to have comparative studies to quote unquote believe it versus you know, the versus not. But certainly this. I'll say this is impressive data just on the face of it.

Janna Friedly I think, you know, the standard, you know, typically that we've used as if we have, randomized, control trial data that is, certainly what we primarily look at, but in the

absence of randomized controlled trials there is a, there is a role for looking at up there, at other data other study designs. So I think the question is then how does this fit in with the in the context of the other evidence.

Jonathan Sham And I would have to just pull up the evidence report and again and look up so I don't have all of that, that memorized. You know, what were the other comparative studies? This Josh, do we have that easily available?

Josh Morse (HCA) We can access the report for sure.

Tony Yen Speaking for myself, I feel that comparative studies are really probably the basis of making decisions about efficacy.

Jonathan Sham Yeah, I mean, I again, from a methodological standpoint that's true for some diseases. If you have a disease process with an overall survival timeline of 10 years, you're not going to have a comparative study prospectively. I just that's that is not feasible. A lot of the that I look at have 10 year timelines. So, you have to look for these surrogate either surrogate endpoints or in this case retrospective cohort trial that that's just the only way to study it. So, I guess I would just, just comment on the type of disease really affects the study design.

Josh Morse (HCA) So, it appears, I believe you're talking about this study right here. Right, this is in the report. This is on page 56. And I'll just point out a procedural issue that, you know, the what we hope to happen here is based on comment was evidence overlooked in the process that should be considered. This could be a an important stopping point if we miss something significant. And then the next question is does the proposed finding decision document clearly convey the attendant coverage? Because we're not equipped today to really go through the evidence again. We don't have the right team here for that conversation. So. I'm glad that this paper was in the report because that's something we didn't miss an opportunity but I appreciate the, the questions now the way it's being presented in these comments I think it's important so I would ask though for your help in determining the path forward here based on that.

Tony Yen Yeah, and Josh, I apologize for intruding, but I really only have 10 min left.

Josh Morse (HCA) I understand. Thank you, Dr Yen. And yeah, we, time should not be the concern here of the committee. If we can come back to this if we need to rather than rush through it.

Janna Friedly Yeah, and I apologize. I've just been trying to review our transcripts just to refresh if we had specifically discussed this, this paper and, in, in the context of, of the evidence but I'm not seeing a specific discussion about this one paper. In at least in the transcript that I can see. Okay. So, I think the question then is, you know, for the committee is, you know, does this, this, study was included in the report that we had, and in terms of the decision, does this, does this, you know, did we overlook something in our, decision and should we, spend more time re considering this

decision for renal cell cancer or do we feel comfortable with the decision that we made which was a non-coverage decision?

Clint Daniels This is, oh, sorry.

Janna Friedly Go ahead.

Clint Daniels This is Clint Daniels. So we might not talk about this study, but we did spend a lot of time talking about feasibility problems for studying renal cancers and I think ultimately decided to go with just what the evidence we had at the time but we and recall we definitely spent a lot of time on this topic.

Janna Friedly Should we, Josh at this, does anybody feel that we should revisit our decision or are people comfortable with our decision as it stands given this, these comments?

Laurie Mischley This is Laurie. The only thing I'll say. Given that a couple oncologists who know a lot more about this than I do have presented some fairly compelling data that this intervention might be quite effective in this cohort. I'm uncomfortable being dismissive this quickly. If there were some way to either include this or table this portion of it, that would be okay. I just, I given what has been presented just in this brief period of time, I'm not comfortable saying yeah, don't cover it. For renal cancer.

Janna Friedly So, Josh, Josh, what is the, what's the protocol for going forward? You know, if the committee does not have consensus about.

Josh Morse (HCA) Yeah, good question. So, there's not so much a protocol other than what we've experienced, you know, in the past, you know, from this topic here just in May. I feel like what you're we're basically landing on this question one there is a concern that evidence wasn't considered to the degree that, you would like at this point. I do think we'll need to reconvene about this. The challenge there real, in you know that we'll we will have to deal with here on this is let me get back to the right document We can't parse this out from the rest of the decision. So. Yeah, I was on the right document. So this is your draft decision from our last meeting. The, the covered conditions, the non-covered conditions up here include renal. Right. So, I think this.

Janna Friedly Should we go ahead and at this point since we have limited time just do a vote to see where the committee is landing and if we if we don't have consent if we are not, in agreement that we should move forward with this decision that we, that we'll, have to table it for another.

Josh Morse (HCA) Yeah, and I'm thinking rapidly here. I think what may be good is to vote. Do that vote on the whole thing as written. And if it's in, if it's not, supported, then to remove the renal and we'll just deal with that one separately. It's not saying it's not part of the scope, just needs to be voted on at a future date then we don't have to deal with the whole thing.

Janna Friedly Yeah. And this includes that one word change.

Josh Morse (HCA) No, I have a different version of that. Apologies here. Let me just switch to that version. That is not it. Here we go. Here's the word change.

Janna Friedly Okay. Okay. Do we wanna take a a quick poll or just do hand, hand votes?

Josh Morse (HCA) Val, you ready for a vote?

Val Hamann (HCA) Yeah, I, I can do a vote. So I just launched that and again it's on this current findings and decision.

Jonathan Sham And Josh, so I just clarify but this is for everything except for renal or if we don't agree with the renal, we should say no.

Josh Morse (HCA) That's Janna.

Janna Friedly Yeah, I was reading this as, as exactly as is. So if you don't agree with renal and you wanna pull that out then say no.

Laurie Mischley Well, can I unsubmit mine then? Okay.

Janna Friedly What should we do?

Val Hamann (HCA) I, I can end it and relaunch.

Tony Yen And Val I'm not able to vote at all.

Val Hamann (HCA) Okay.

Josh Morse (HCA) Yeah, you will use the voice vote for you, Dr. Yen.

Val Hamann (HCA) Did you want me to relaunch at all? Okay.

Janna Friedly Yes, please. So yes, if you approve as is no if you don't approve as is that and want to change something.

Josh Morse (HCA) And, Tony, what's your vote?

Tony Yen Yes.

Josh Morse (HCA) Okay. So that is a 3 to 3 tie for yes.

Janna Friedly Okay.

Josh Morse (HCA) And then, yeah, Janna. Take out the renal.

Janna Friedly Yeah. So we'll have to take out the renal and deal with that separately.

Josh Morse (HCA) So we'll strike this from the decision for now. And revote is that your.

Janna Friedly Yep.

Josh Morse (HCA) Can you relaunch it, Val?

Janna Friedly So now we're voting removing renal. We'll deal with renal later. Do you approve of this wording? No.

Josh Morse (HCA) And Tony, what is your vote?

Tony Yen I approve.

Josh Morse (HCA) So that is a 6. Approve, 0 disapprove. Okay, so, thank you. for that. Oh, the complexities here.

Janna Friedly So we. So we will, we will reconvene on how to deal with that with renal cell separately. Do before Tony leaves, do should we approve the minutes from the last as the last piece of business that we need vote does that require a vote?

Josh Morse (HCA) Here are the minutes. Val, do you have a vote for that?

Val Hamann (HCA) I do and I just launched it.

Josh Morse (HCA) And I can move through here or.

Janna Friedly And Tony, do you, I think you need a verbal?

Tony Yen Yes, I approve. Sorry, I'm getting paged constantly right now.

Janna Friedly Okay. That's okay. If I think.

Josh Morse (HCA) That is 7 approved for the minutes.

Janna Friedly Okay, so I think we all approved. So I think Tony is off the hook then, right?

Tony Yen Okay, I gotta go you guys. Thank you.

Janna Friedly Okay, thank you so much. Bye.

Jonathan Sham I think perhaps Janna may just set us up for that next discussion to have the vendor just weigh in on why.

Janna Friedly Yeah.

Jonathan Sham They evaluated that specific study as high risk of bias just because that's a little bit incongruent with the least the place that it's published, if it's the only, if the only reason is, Is the site design and I think we should just know that versus if there's

something else about it that you just scroll up. Yeah, right there, the high risk of bias in the second column. I think that's just the question at least for me would be most helpful.

Josh Morse (HCA) Okay, thank you.

Janna Friedly Right. So, Josh, should we pivot back to, for the topic for today?

Josh Morse (HCA) I think we already see that.

Janna Friedly That's more, more to come on renal. Okay, so I'm gonna turn it, can I turn it over to Sheila? Is she here? Okay or should we. I think she may not be. She may not be here.

Sheila Rege I'm sorry, I kept talking, but I'm, I'm not. I was on mute and I couldn't understand why you guys could hear me. So. Going back to this. I think we're ready. I mean, we've had a lot of discussion. I think we're ready for our final votes on, HA for knee, HA for hip, PRP for knee, PRP for hip. Is that reasonable to take the final votes? I mean, and then start discussing issues. Because everything we've done so far has been a straw poll. Is everybody okay with that?

Val Hamann (HCA) And how we've had the final written is for languages written or did you wanna go back to, you know, cover not cover, cover conditionally.

Sheila Rege Help me out as a process, do we have to go back? I mean, I didn't announce it as a final vote, when we did it last time with the cover, not cover, cover with conditions. Josh as a process because I didn't announce it. Are we okay? Should we do that just to for the minutes?

Josh Morse (HCA) Yeah, we haven't taken a final vote. So are you seeking to do a final vote on?

Sheila Rege Everything. So final vote on knee HA, final vote on hip HA, final vote on knee PRP, final vote on hip PRP and this will be the final votes.

Josh Morse (HCA) Those are 4 separate votes. Now I just wanna clarify. I just wanna reorganize this here a bit and what you're seeing, hopefully you're seeing this on the screen. I'm confident.

Sheila Rege So.

Josh Morse (HCA) What I understood that you, this is where you were landing. Or

Sheila Rege That's where we were on the straw poll, correct.

Josh Morse (HCA) Okay, and then you were still contemplating conditions. Is that right?

Sheila Rege Correct, but I think we have to vote formally and then you know everything before this in my mind we were negotiating, discussing, bringing up new evidence.

Josh Morse (HCA) Gotcha. Okay, so if you happen, if you vote for one of these to be covered with conditions, you will then develop your conditions. Is that correct? Okay, thank you.

Sheila Rege So don't please save that.

Josh Morse (HCA) Yes, of course. It's here. So I think, Val, do you, are you gonna run the poll?

Val Hamann (HCA) Yep. Here's HA for knee. And Dr. Kleweno is no longer on, correct?

Josh Morse (HCA) He is not.

Val Hamann (HCA) Okay. Then we have 8.

Sheila Rege We have we have quorum, correct?

Josh Morse (HCA) We do. Yeah.

Val Hamann (HCA) Yeah, we have 8. We were at 9 before so. Here are those results.

Christoph Lee And Conor left his number. Do we wanna text him to come back?

Sheila Rege Maybe we should for the voting. And then we'll let it go. We'll bring him in 5 min forward and then we'll bring him back in.

Christoph Lee And.

Sheila Rege Or 5.

Christoph Lee And I just wanted to point out the way these polls are written is for non-coverage. So if you're saying yes, you're running for non-, no for coverage. So people were confused and redo the poll, just so everyone's clear.

Sheila Rege Okay, so we should redo the poll then.

Josh Morse (HCA) I think it's important. Yeah, to point out. I notice that too.

Val Hamann (HCA) I can relaunch. Okay, that poll is relaunched.

Josh Morse (HCA) So yeah, if you're putting yes, you're voting to not cover.

Christoph Lee I would say that the original straw poll, the way that was written is probably more applicable. So give people an option to say cover, not cover, cover with conditions.

Sheila Rege Yeah, I do like that better too.

Val Hamann (HCA) We, I can go back and relaunch those.

Sheila Rege That would be great. Thank you.

Val Hamann (HCA) And that is relaunched.

Sheila Rege Dr., Conor wants to rejoin. He is going to try and rejoin.

Val Hamann (HCA) We're waiting on one more. Moving on to HA for hip. Moving on to PRP for knee. There are those results.

Sheila Rege I'm sorry I didn't answer that. Can we go back? I was answering Dr. Kleweno. He's looking for contact information. Can we relaunch that one? I'm sorry, my fault. And I think he is joining. Is he on? Conor? He was texting me saying he's

Val Hamann (HCA) I am moving him to a panelist right now.

Conor Kleweno Sorry everyone. Can you hear me? I had to drive across town to our graduation thing so I'm here. And are we doing verbal votes or?

Janna Friedly Does Conor not have access to the poll.

Conor Kleweno Oh, I see it now.

Val Hamann (HCA) Okay. There are those results.

Sheila Rege Oh, it's still. Has that flipped from the first time?

Val Hamann (HCA) I'm moving on to PRP for hip. And there are those results.

Sheila Rege Can you summarize that for us?

Val Hamann (HCA) Yeah, so 9 votes for not covered for. Actually so, we voted on HA without Conor. So, 8 votes for non-covered for HA for knee. And then for hip, HA for hip, we add 8 votes for not covered. And then PRP for knee, we had 5 votes for not covered and 4 votes for covered with conditions.

Val Hamann (HCA) And then again, PRP for hip is 9 votes not covered.

Janna Friedly Sure we add Conor's votes for the just for because he's here for the HA, for knee and hip.

Josh Morse (HCA) So.

Janna Friedly Should we add his?

Val Hamann (HCA) Yeah, I can re.

Sheila Rege Right.

Josh Morse (HCA) We can do that by, can we do that verbally? Or do you wanna?

Conor Kleweno You want me to do it verbally?

Janna Friedly That should work, right?

Josh Morse (HCA) Yes.

Conor Kleweno Either way I can do poll or verbally, whatever you want.

Janna Friedly This is suspense is killing us, Conor.

Conor Kleweno Oh, so, present the question and I'll give the answer.

Josh Morse (HCA) Yeah, Val, can you just revote?

Val Hamann (HCA) Yeah, so HA knee coverage. So HA for any osteoarthritis should be covered, covered with conditions, covered unconditionally or not covered sorry.

Conor Kleweno Not covered.

Val Hamann (HCA) Okay, and then same question for HA for hip osteoarthritis should be not covered, covered with conditions, or covered unconditionally.

Conor Kleweno Not covered.

Sheila Rege That's 9 and 9. Our problem is the PRP is just a little close for my liking.

Josh Morse (HCA) This is how the vote came out for the original hyaluronic acid review.

Sheila Rege Any discussion on that? Is not a covered benefit.

Jonathan Sham I guess, I can weigh in. It seems like based on the previous discussion and Dr. Liem's comments that, there's kind of a slight lean towards there maybe benefit, but really what is pushing, I think and please correct me if I'm wrong, pushing some to vote for not covered is the cost and the kind of projected increase in cost to the system given the status of the evidence. I guess the way I look at it, you know, given what our expert has said, give and review the data, given how difficult it is to difficult a problem in this study and how difficult is to create a real trial to study this issue. Again, I do think there is a mild of benefit. And I do have some concern of saying well if people want it they'll just pay for it when we're talking about a Medicaid population, you know, so, so I do have a bit of a concern saying, okay, well, working on help people to pay for it because of the questionable evidence when Essentially, we're talking about a population who generally can't pay for something like this. So again, I'm completely recognize the status of the evidence as imperfect. However, just as the AMD is reviewed before, I do believe that the proponents have evidence to show a benefit. And I don't feel that the cost burden is enough to push me to the no covered, which is why again I would, I voted for covered with conditions.

Sheila Rege Conor.

Conor Kleweno Yeah, I appreciate that. I guess I would say from my perspective, you know, sort of from the trenches, I think that we will not change the natural history of this. We will have mild to moderate arthritis people with pain and eventually they will either get any replacement or expire or whatnot. So we will be driving up costs with injections of a costly thing. I'm not convinced by the evidence. It's taken multiple, multiple, multiple RCTs and we've been doing this for tendinosis, tendonitis in the ankle, the knee, the shoulder, the hip everywhere and osteoarthritis of the hip and the knee and so we're and the reason that they're doing that is because there's a lot of money to be made. And I know I'm not saying everything is nefarious here, but if there wasn't money to be made, I don't think there would be such a push to do so many trials. I do think there's a push to find an answer because it's a really tough question and really tough clinical scenario. But if we have multiple, multiple, multiple trials and we have some moderate to mile benefits for some people. I just, my expectation is the cost that we've been paying thus far is really minimal compared to what is gonna happen if with coverage. Gets back to my analogy of the sort of how much you're gonna willing to pay for something but I really think that the costs are gonna be very, very high here with mild to moderate effect. Temporary for a chronic condition. I do definitely appreciate the equity lens with this topic for sure and I don't think it's easy for just to say well then people should just pay. I also don't want people to pay for something that doesn't work and I've had a number of patients pay cash that's far above their means because they are desperate. And they had moderate to mild benefit that was temporary. So I guess I see it from that access as well.

Sheila Rege Christoph.

Christoph Lee Yeah, and it's just not cost. It's cost effectiveness, right? So we know that costs are gonna skyrocket. Where is the effectiveness is not gonna be much improvement. So when you take the ratio of cost effectiveness, this is not gonna be cost effective. I think we know that. So given that and that third, I guess, metric that we're looking at, I just can't approve this at this point. If it were truly effective and we knew that. I think the other thing to realize is that the application, the actual procedure is not FDA approved, right? That PRP is not an FDA approved product. It's the machines that extract the PRP are FDA approved. But there's no standardization in the approach and giving the procedure. And that really opens up this entire procedure to practices that we cannot monitor or have any quality control of. So I'm concerned about that factor as well.

Jonathan Sham Yeah, I guess maybe I could just perhaps just get some clarity. We don't think that cost effectiveness is going to go down, right? I should say costs are not going to skyrocket on a per patient basis, correct? We think that it's gonna be utilized more so therefore the state would have to.

Christoph Lee Right, I'm taking a society perspective, right? So for cost effectiveness.

Jonathan Sham To yeah, we're not we're not saying per patient because to say the cost effectiveness would go down, we'd have to say on a per patient basis. So I just wanna clarify that. We're talking about utilization what it would increase.

Christoph Lee Yeah, it's only just the life years per dollar.

Jonathan Sham But, well, it wouldn't, but it wouldn't be QALY dollar for QALY because that's per patient. So just be clear, like we don't think the actual cost of the treatment per patients going to go up if we approve, correct?

Conor Kleweno It will because the alternative is so much cheaper. So for the same diagnosis of arthritis of the comparator of steroid, the cost will go up because it's more it's more expensive than steroid and we don't think the effectiveness is superior to steroid.

Jonathan Sham Using the cost per treatment, total treatment of knee OA. Not, I'm talking about the cost per PRP session. That's what I'm getting at. The actual cost of the PRP treatments not going to go up. You're again, you're talking about the cost of the overall treatment of.

Conor Kleweno We don't have a comparison because we're not covering it right now. But if you're comparing it to steroid or you know.

Jonathan Sham Yeah, I understand that. I guess what I'm saying is I just wanna make sure we're not we're not claiming that the cost of PRP is going to increase if we if we approve this. Okay, so the only other thing I would point out is just, and again, please write my wrong, but in just in my recollection of the funding of the available trials were any of them sponsored by industry. Because and what percentage would work as I.

Conor Kleweno So can I comment on that as well?

Sheila Rege Let's have the expert comment first. He'd ask the question. No, they have heard our evidence report. So sorry.

Josh Morse (HCA) Yeah.

Erika Brodt Yeah, for PRP, none of them we're sponsored by industry.

Sheila Rege Because industry is not involved.

Erika Brodt Really involved. Exactly. Yeah, there's really nothing for them to make money on at this point.

Sheila Rege And then somebody else was gonna say something and I stopped them. Sorry, who was that?

Conor Kleweno That was me. I was just gonna say, I agree. There's no industry funding because there's no industry implants or something to sell. I mean, I guess the syringe is the and the centrifuges are not where the money is gonna be made necessarily. And so, one interesting thing is most of these studies were done internationally. And I can

tell you from traveling and actually it's a cash business. So, it's not the industry that had the influential conflict, it was the actual providers in some settings. So, it was. providers that had the motivation to do the studies, not a secondary company that was gonna sell a you know, an implant that was gonna be placed into the patient.

Sheila Rege Jonathan, did you have anything more to say or?

Jonathan Sham Sorry, just from my hand down.

Sheila Rege We'll go to Janna.

Janna Friedly Yeah, I think the only other thing that I, you know, I'm looking at the evidence. You know, I, to me, it's, it's, very mixed and the one sort of comparison that does stand out a little bit to me is that the one study and it's again one study and it's a small study, it's 65 patients, but, that compared a HA to PRP and it looked at it function and they looked at the percentage of people that had a successful response in a short term, intermediate and long term. And when you looked at the short term, it looked like, you know, 62% of people had a 30% decrease, in the WOMAC physical function, with PRP. Only 10% had a 50% decrease in the short term. In the long term, only 24% had a 20% decrease in WOMAC and in the intermediate 45% 20% so that to me those are not those are definitely favoring looking like they favor in this one study PRP but the percentage of people who benefit is in my mind relatively small and the percent decrease, is modest at best. So that, also has sort of weighed into, into this for me that it's a modest benefit for a subset of people who get, who get the procedure, If there's a benefit.

Sheila Rege I just raised my hand. What influenced me was that or you know, while you guys were actually doing the SBRT, I was looking back on some of the evidence and like somebody here has mentioned it was mostly international. And then I looked at, United Healthcare and at Aetna and even looking at Tricare and Tricare says we may cover it but then you've got to call somebody and they're not willing to put in their criteria. And that's the only company that so I went back and United had and Aetna had and the blues had the rationale and they looked at the same studies we did and their, their thoughts were kind of interesting to read on why they were not covering it. It was, I, I initially really thought it should be covered with conditions and after a lot of the discussion, especially with the expert, kinda leaned away from that. And you know, if you think of equity, if most commercial insurance are not allowing it for safety issues and and efficacy issues. Then think of a poor Medicaid patient that comes in and somebody says, oh, let's do it. I just, that's what I was having trouble reconciling. John.

John Bramhall Yeah, just for complete this, I, you know, what are my, what are my thoughts? Originally on the straw vote, I thought cover with conditions. But then, no, I mean, what conditions, right? It's just a nightmare to try and hone this down to a group of patients that you would predict would have good benefit from it. I so that's very clumsy. My prejudice and this is prejudice, it's nothing to do with our discussion today formally. You know, a couple of our residents have gone off and done this business. One of them in, in, in Vegas, right. And one of them somewhere else and they do it mobile, they have a mobile deal and little centrifuge in the back of the car

or something. The point is it's always struck me as pretty sketchy. To be honest. So when I when I came to this to topic, I did have a prejudice that this was pretty sketchy. It's a money making, the interest is in money making and that the effectiveness is not clear. So, reading the literature more objectively, I'm not convinced that the evidence really shows that there's a dramatic effect here. We saw, yes, it really shows that there's a dramatic effect here. We saw, yes, it was, who was it that I think it was Laurie, I think that mentioned the HA versus PRP study so a study setting up for HA with PRP showed a modest benefit at 3 months with PRP fine and then the same sort of reverse PRP against saline which was remember that's my little touchstone is it better than saline? Yeah, sort of, in, one study, but only at 3 months not longer out and Conor consistently makes the point that this is a, you know, the natural history of this disease is fairly long lived until you get a joint replacement. In many cases, it's, it's not a that none of this is a fix. You don't fix the disease. You don't fix anything. It's very short term, very palliative. And the data that we've been presented with suggests that the even that palliative response is really quite modest, and you really have to stretch to see it. So, I changed my, my vote from cover to non-cover for that. I'm not certain whether we're entitled, entitled to sort of look at the budgetary issues for the authority because this is a really big point but I'm just not certain that that should weigh in on a formal decision. The big point is what everyone said. If you open it up and you say, this is a, this is a recognized therapy, we are putting a seal of approval on it and we'll pay for it. Yes, an awful lot of people have got osteoarthritis and tendonitis and what have you, pain, they want therapy, they're gonna go for this. And so, there is a budgetary, effect, I think, on the authority, and on LNI. Gary, you probably would, comment on that. But I'm not certain that that is something that should pollute our decision about the actual execution of this, of this decision on the modality.

Sheila Rege Any other comments? Conor?

Conor Kleweno One last comment. I hope it's very objective is that. Joints hurt a lot and a lot of people have this pain and I very confident that when we do invent something that is very effective, it will be quite dramatic in the trials. And I think that the effect size will be large. So, I think that it's not difficult, if you have something that is effective to see a large effect size reproducibly.

Sheila Rege Jonathan.

Jonathan Sham It's only the other thing I would throw into that again also trying to be as objective as possible as. There's been a lot of talk about altering the natural history of these diseases and I think particularly in cancer therapies, we're kind of even moving away from that and really focusing on quality of life and palliation and patient reported outcomes and I think that's really where you know, I see this playing into the treatment of OA, even if it doesn't, change the fact that you may need a join replacement in X number of years, that doesn't mean that it doesn't have value as a treatment. Because the PROs are important.

Sheila Rege Like I said before, I don't like it when it's this close a vote. So really I encourage any discussion from people that you know in case we miss something about cover with

conditions. So speak now or the vote is gonna stand as that closer vote. And this just shows we're struggling with this. Okay, I'm gonna turn it over to Josh process.

Josh Morse (HCA) Okay, thank you all. Yeah, I will say, I've been here for a few of these meetings. A couple of you, others of you have as well. These are the, the closest votes come on these technologies where there's less than definitive evidence base in some cases and, and that's why we bring it to you. I don't know how better to say it. So. This is not, it's not unique to have a 5 to 4. Especially in a case like this so I don't think you're gonna get any closer than that or further apart. So, here's what you voted on. You said, essentially, a not covered for HA for knee and hip and PRP for knee and hip so going to the decision aid, you've completed your vote, so we just need to ask the question, you know, is this termination consistent with any national coverage determinations issued by Medicare and with expert guidelines and if it's not consistent with those what evidence was relied on. There is not a national coverage decision for hyaluronic acid. There is a national cover decision for PRP. But it's for certain non-healing wounds so it's not not within the scope of what you are addressing today. So there's not an NCD for what you addressed today. And then provide it to you in the decision guide in the report are the guidelines that our evidence vendor has found so I can scroll through these if you have any concerns about inconsistency here. You know, I think there, I think you're largely consistent with what with these some of these guidelines anyway. So just scrolling through, I see 2 bodies for, 2 bodies against and I haven't got to the bottom here yet. So. Any comments? Sheila, on the professional society guidelines? Sheila or Janna or others.

Sheila Rege I muted. I just muted. Sorry. Any. Any questions?

Janna Friedly No, it seems like we're consistent. The HA is a little bit more, mixed than PRP, but we are or in line I think with other insurers and other policies and guidelines.

Josh Morse (HCA) Okay, there are you have completed your decision then for today. You've actually made 3 decisions. So, thank you very much. We will work on addressing the renal cancer question with the vendor the question that has been asked thank you Jonathan for that and we'll find a way to incorporate this into one of the next meetings we are working on a retreat meeting for the I think right now the third Friday of September. We don't intend to have any topic conversations there that's more for process questions we're hoping so we may need to push the renal cancer question to the November meeting, but, that's where we stand now. So, Sheila, I think that's. That concludes the business we brought to you for today.

Sheila Rege Right. And if anybody has any thoughts that they want discussed on process if you could email Josh and myself, you know, so we could allocate time to discuss it at the as an agenda item that would be helpful and that is an in person meeting. So make plans to actually be aware of a meeting, Josh? At SeaTac Airport?

Josh Morse (HCA) Yeah, Val, can you come in on? Where are

Val Hamann (HCA) Yeah, that's correct. That's currently underway. It should be the same room and everything as of right now for, that we did in January, but more to come on that we

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| | did in January, but more to come on that as it's going through our process for, getting that all confirmed. |
| Sheila Rege | Look at your calendar. It's September 15th and I expect to see everybody there. In person, I once a year time to be in person. And I haven't told Josh this, but I may have a tabletop, a fun, kind of activity. We'll see. Just to get to know each other very short. 10 min. Bye now. |
| Josh Morse (HCA) | Awesome. Thank you. Thanks everyone. Thank you, Dr. Liem, for your time today. Really appreciate your participation. |
| Sheila Rege | Thank you. Yeah, thank you very much. |
| Laurie Mischley | It was very helpful. |
| Brian Liem | Thank you. |
| Christoph Lee | Thanks everyone. |