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Health Technology Clinical Committee Public Meeting
November 15, 2013

- Craig Blackmore: Good morning, everyone. I'm Craig Blackmore, chair of the Health Technology Clinical Committee, and I'm going to call the meeting to order. We have a quorum of the committee members. The first item on the agenda relates to previous business, and the first piece of that is for the committee to review and approve the minutes of the previous meeting. So, that has been distributed and made publicly available, so I will invite a motion to approve from the committee or any discussion of the minutes from the previous meeting.
- Michelle Simon: So moved.
- Seth Schwartz: Second.
- Craig Blackmore: So, if I could just get a show of hands, approval of the previous meeting minutes. The second item on the agenda is looking specifically at the previous draft findings and decisions documents. So we, at our previous meeting on September 20th, reviewed two technologies. We reviewed carotid artery stenting first and made a decision on that technology and then our staff, our team, has compiled that into a draft findings and decision document, and this has been distributed and made publicly available, and I would invite the committee to either provide comments or a motion to approve, and as we do that, I had a couple of things on the carotid artery stenting, which I thought maybe were typographical errors or were a little unclear. So, I don't know if I could get the committee members to turn to the draft findings and decisions from carotid artery stenting. Yeah, there's a couple little things. So, I'm looking at the draft findings and decisions document on page four, and under action the third sentence says the committee reviewed the NCD and determined that based on the availability of more recent evidence to: Cover extracranial CAS, I believe this should be 'cover symptomatic extracranial CAS' without a requirement of study participation for patients at high risk for CEA, and it says in here, 'with stenosis of 50 to 70%,' and I believe that should be 50% or greater. So, our intent, and that would be as outlined on the first page of the document, our intent was to cover patients who are at high risk for carotid endarterectomy and who have symptomatic carotid artery stenosis greater than 50%, and these two should be reflecting the same thing. Is that, am I reading this correctly? So,

I'm not, I don't have the NCD in front of me, and it could be that this is the way in which we extended the decision with regard to the NCD, but I think it's clearer if what's on here parallels what is our actual coverage on the first page. So, the amendment would be, after the colon in the fourth sentence, it would say 'cover extracranial CAS,' sorry, it would be, 'cover symptomatic extracranial CAS without a requirement of study participation for patients at high risk for CEA with a stenosis of 50% or greater.' Then, also under action in the second paragraph, there's just an incomplete sentence. The first sentence says, 'the committee determined noncoverage for intracranial stents based on evidence indicating serious safety concerns and recognizing that state agency programs may provide coverage in the context of, and then the sentence doesn't end, and it should read, 'of research,' so that we are enabling the agencies to provide expanded coverage in a research context, which is what they already have. We're just making explicit our interest in that process occurring. Again, I think that's just a typographical error. Any other comments on the previous findings and decision?

Chris Standaert: One question on the language. We say 'patients who are at high risk for carotid endarterectomy.' That would seem to imply they are at high risk for, it's, the language is odd. I don't know if that's what we said, at high risk for carotid, high risk for complications of, high risk for, I mean, for patients at high risk for carotid endarterectomy, does that mean they are at high risk for actually undergoing the procedure...

Craig Blackmore: Right.

Chris Standaert: ...not complications of the procedure?

Craig Blackmore: Right.

Chris Standaert: The language is funny.

Craig Blackmore: We do say what high risk means.

Michael Souter: Just emphasize surgical.

Craig Blackmore: High surgical risk.

Chris Standaert: High surgical risk.

Craig Blackmore: Okay. So, that would apply for both bullet points one and two under limitations of coverage, and it would apply under the action sentences that we just talked about. So, here it would be, 'for patients who are at high surgical risk for carotid endarterectomy,' so it doesn't sound like they're at high risk of undergoing the procedure. They're at high surgical risk if they undergo the procedure, and that would be true throughout the document.

- Richard Phillips: But is, high risk is defined well here.
- Craig Blackmore: It is. It probably doesn't matter, but I think it is a little clearer.
- Richard Phillips: Right.
- Craig Blackmore: Okay, so I would ask then, are there, if there aren't other comments, I would ask for a motion to approve the draft findings and decision, as amended, under carotid artery stenting.
- Michael Souter: So moved.
- Michelle Simon: Second.
- Craig Blackmore: So, a show of hands, please, in favor.
- Josh Morse: 11 in favor.
- Craig Blackmore: Okay. Alright, and then the other decision that we undertook at the last meeting was around cardiac nuclear imaging, and we have, again, a draft findings and decision document, and again, I will ask the committee members if they have any comments or corrections to that document. Otherwise, I would solicit a motion to approve.
- Carson Odegard: Move to approve.
- Craig Blackmore: Alright, could I have a show of hands, please, in favor.
- Josh Morse: 11 approve.
- Craig Blackmore: Okay. Alright, so that concludes previous business, and I apologize. I skipped the order a little bit. We should have done the HTA Program update before, so we will do that now if that's okay, Josh?
- Josh Morse: Okay, I'll give a quick presentation of the HTA program and today's topics. Today's topics are hyaluronic acid or viscosupplementation and hip resurfacing. These are both re-reviews of these topics. They were previously reviewed in 2009 and 2010.
- So, the HTA program is located in the Health Care Authority, a state agency in Olympia. The program was created in 2006, and it's designed to use evidence reports and this panel of clinicians to make coverage decisions for topics that are selected based on the evidence of safety, efficacy, and cost effectiveness. Multiple state agencies participate in the program to identify these topics, and they implement these policy decisions. The programs include the Health Care Authority, which manages the Uniform Medical Plan for state employees and retirees and the state Medicaid plan, the Department of Labor and Industries,

and the Department of Corrections. The implementation is done by these agencies as a mandate through the statutory framework of the program.

The purpose of the program is to ensure that the treatments and devices and services paid for with state healthcare dollars are safe and proven to work. We provide a resource to the state agencies that are purchasing healthcare. We develop these scientific evidence-based reports on the topics that are selected, and we facilitate or provide staff support to this clinical committee.

Our objectives, overall, are better health for the citizens and those receiving healthcare through the State of Washington. We strive for transparency and to minimize bias, as well as to be cyclic and keep our policies current.

This is an overview of the process. The technologies are ultimately selected by the director of the Health Care Authority. Nominations can come from any source but are primarily coming from the State of Washington agencies. Once topics are selected, we contract with groups to review and provide an evidence report. We develop key questions. We publish key questions. We publish draft report and the topics. We then bring that information to the clinical committee here in a public meeting for a decision. The agencies then implement these decisions.

The primary questions are: Is it safe, is it effective, and does it provide value? We use these questions to guide the development of the evidence report. We strive for transparency in the publication, again, of the topics, the criteria for reviews, the reports, and the conduct of these meetings here in public. We seek the best evidence that is available, and we are striving for independent decisions from this group of individuals on this committee.

The clinical committee decisions must give greatest weight to the most valid and reliable evidence, objective factors for evidence consideration include the nature and the source of the evidence, the characteristics of the studies or trials upon which the evidence is based, and the consistency of the outcomes. Additional factors include how recent that evidence was developed, how relevant it is to our state populations, and conflict of interest or bias in the research.

So, as I mentioned, today's topics were previously reviewed. These will be the first re-reviews of the HTA program. The program law includes re-review of topics when new evidence could change a decision from the committee. The first topic, hyaluronic acid, was identified for this update based on a new meta-analysis published in 2012. Hip resurfacing, which is the afternoon's topic, was identified for this update based on new evidence from large registries published since the original determination.

These are the topics that have been reviewed, thus far, in 2013 and will be reviewed in the first half of next year. You can see bolded there are today's

topics. Coming in the spring, our next scheduled topics are facet neurotomy and non-pharmacological treatment for treatment-resistant depression, and then in May, we have scheduled proton beam therapy.

There are multiple ways for people to participate in the HTA program. We have a new website address indicated on the top of this slide. You can join our stakeholder distribution list, which is how we communicate changes to the information we put out. Anyone may comment on proposed topics, on key questions, on draft and final reports, and on draft decisions or here at the public meeting before the committee, and anyone may nominate technologies for review by the HTA program, and this is our contact information. Thank you, very much, for being here today.

Craig Blackmore: So, next item on the agenda is the scheduled and open public comments period. So, we have a number of people who have identified to the committee ahead of time that they wish to speak on this topic. I'm just going to... it looks like we have six.

Josh Morse: We have five [inaudible]. You have a letter in your packet, which is the sixth one.

Craig Blackmore: Okay.

Josh Morse: [inaudible]

Craig Blackmore: Okay, so that's number six.

Josh Morse: We have people signed up to speak today [inaudible].

Craig Blackmore: Right, and it looks like a few people have brought slides? Is that? Okay, and we have given them a time? Have we discussed time with the?

Josh Morse: We're leaning towards [inaudible] today.

Craig Blackmore: Okay, and we've got... we're five minutes early. So, okay, so we have, it looks like we have five people who have prescheduled comments, and we can allow five minutes for each of those presenters, and then we also had a couple other people who signed up outside when they came in and we can allow three minutes for the unscheduled presentations, and if there's anybody that wishes to address the committee that hasn't already signed up, please do so, and we will have time for you, as well, and we will start with Dr. Ghislaine Robert, and please forgive me if my pronunciation of your name is incorrect. So, for all the presenters, I am going to ask when you come up that you introduce yourself and you tell us if you're speaking as an individual or if you're representing another organization or company or group of people, and also if you could please tell us if you have any conflicts of interest and let us know if you have slides and we will get those queued up. Thank you.

Ghislaine Robert: So, my name is Ghislaine Robert. I am a sports medicine physician. I have no conflict of interest. I was asked by the Hyalgan Company to come and talk to you about my clinical experience with viscosupplementation.

So, I started to use viscosupplementation injections in 1990 in Montreal, Quebec. So I have 23 years of experience with visco. My practice is 100% sports medicine, so I see patients who want to be pain free and stay active. I see an average of 20 to 25, I perform, sorry, 20 to 25 visco injections per week, all under ultrasound guidance.

I just want to go very quickly over the conservative options for osteoarthritis. For me, the patient is not only a knee that I need to treat. We need also to consider that they might need to do some weight loss; exercise is very important, physical therapy, orthotics and leg limb discrepancy correction, braces, supplements. I also recommend an anti-inflammatory diet for people with a lot of osteoarthritis, and there's a place for medication, but I think when we talk about visco, it's way far superior, as far as safety and efficacy. So, injections, we can do steroid injections. We can do visco. We can do PRP.

What's the clinical effectiveness of the viscosupplementation injections? First of all, it improves the quality of the synovial fluid. It increases the hyaluronic acid level to normal values for up to six months. It decreases the level of pain. It improves the function level, and, very importantly, it protects the remaining cartilage from further damage.

About the question of product effectiveness, all products will increase the intrinsic production of hyaluronic acid, remember that whatever we inject, it's gone after three weeks. The long-lasting effect of the visco, up to six months, is the own patient's chondrocytes response to the exposure of hyaluronic acid. So, in other words, all of those products are effective in improving the capacity of the patient to produce more hyaluronic acid for up to six months in their synovial fluid.

Side effects are very minimal; local soreness, possible infection, as with any kind of injection, bruising, the case of hyaline is a little different, because that's the only one we can give the reactive synovitis. The prevalence of it is 7%. It can increase to up to 20% with repetition of the injection. It's totally unpredictable, and it's not an allergy reaction. There is no antibodies in the synovial fluid when we analyze it. So, compared to the use of NSAIDs, narcotics, steroid injections, and surgery, it is certainly the safest option, and my colleagues will give you more data in a little while.

So, varying effectiveness by sub-population. So, I just want to emphasize that to get effectiveness, for best results, we need to also take care of their weight, their alignment, kneecaps, so that's why it's so important to use visco in combination with other treatment options. We know that with that severe

osteoarthritis, it does not work as well as it is with mild-to-moderate osteoarthritis, and the reason is most likely because there is decrease or even absence of chondrocytes with severe osteoarthritis. So, therefore, it is very important to start viscosupplementation early in the disease.

Cost implications: Considering the cost of daily use of NSAIDs, multiple steroid injections, if we repeat every six to eight weeks and surgery, the viscosupplementation is certainly the less costly option considering also that we can allocate and even postpone all of these options. In other words, the patient is using viscosupplementation won't need to use any other of those modalities like use of narcotics or NSAIDs and won't need to go to surgery for most of them or can postpone the surgery, which means that in the long-term they might have to avoid at least one replacement.

My final comments, the viscosupplementation injections are safe and effective. They protect the knees. They allow the patient to stay active physically, which is also decreasing the long-term cost of their health by decreasing the risk of obesity, high blood pressure, diabetes, heart disease, and hyperlipidemia. They have minimal side effects compared to oral medication and steroid injections. They help to postpone or avoid future surgery, decreasing the healthcare costs here, as well, and they are the best one-year outcome for mild-to-moderate knee osteoarthritis when associated to physical therapy. Thank you.

Craig Blackmore: Thank you. Next on the list I have Dr. Vinod Dasa.

Vinod Dasa: Thank you. I do have slides. If we could pull them up, I'd appreciate it. So, my name is Vinod Dasa. I'm from LSU. I'm an associate professor, and my area of specialty focus is arthroplasty. Area of research is around inflammation, infections, things like that. I am sponsored by Bioventus to be here. So, if we could... there we go.

So, as most of you probably understand the challenging traditional paradigm around OA of the knee is pretty limited. So, what we usually use are ibuprofen, Tylenol, as you can all imagine, and we come into issues when people are on Coumadin or Plavix or renal disease, narcotics are in there too. When that fails, then we move on to steroid injections and then ultimately arthroplasty. So, that's the traditional paradigm that really hasn't changed in quite some time. So, when we talk about managing knee OA, there's a huge amount of options that we've got, but traditionally, the previous slide is what most clinicians hang their hat on.

You can see hyaluronic acid fits in a pretty wide spectrum, and I'm going to point over here. It fits in a pretty wide spectrum of disease progression. So, traditionally, what are our options? NSAIDs, aspirin, ibuprofen, Naprosyn, and most of you know the GI and cardiovascular side effects, and unfortunately, narcotics. Most of you probably already know the issues with NSAIDs and the costs associated with them, and it's in the lay press, and we have to answer to

that with a lot of our patients, and they're not very happy about it, and I struggle with that almost on a daily basis. As you probably realize, this is another huge issue that just came to our attention this year, and that's the CDC report on deaths from narcotics, especially in middle-aged women. We also know narcotic usage pre-total knee and then following post-total knee, our results are not as good. So, patients do not have improved results and actually compromised our results with when they're placed on narcotics preoperatively.

So, you can see our armamentarium, in terms of managing knee OA, is pretty limited with a lot of downstream effects that are basically unwanted. So, when we talk about steroid injections, moderate-to-severe OA, crystalline forms the best, because you have lower systemic reabsorption, generally about three to four injections per year, and occasionally this rare synovitis. So, we did a study in Louisiana looking at steroid injections. So, we all use 'steroid injections,' but what does that mean? Most orthopedic surgeons, and I would submit to you a lot of clinicians, do more than steroid injections, and we all have our own personal cocktail, and you can see at least in Louisiana that a lot of our surgeons use lidocaine and lidocaine plus Marcaine, that's mine, and then when we look at the combination, you can see that triamcinolone lidocaine really outnumber most everything. Why is that important? Because when we look at the literature around steroid injections, it is more important to look at the cocktail, as opposed to just cortisone, as well, which will, I think, open your eyes in a couple seconds. So, steroid injections usually get pain relief within about 24 to 48 hours. It can last up to six weeks. Again, in diabetics, we had to be careful about systemic hyperglycemia. I've seen sugars up to 300 two to three weeks out from a cortisone injection. So, it's not something to take lightly.

And this is the important thing. So, as we look at the options that we've got, aside from hyaluronic acid, we have to pay attention to what the literature and science shows. At a basic science level, steroids are very chondrotoxic. They kill cartilage cells. There are very elaborate studies, especially done out of the University of Pittsburgh where they took fissures, which are very common in OA, and they looked at what happens to the cartilage cells at the base of that fissure when you inject steroids. It kills all the cartilage cells at the base, at the columnar section of the typical cartilage cell distribution, which is where growth happens. So, when you're knocking off, the cells actually recreate cartilage, we're in big trouble.

The other point of this is looking at the chondrotoxicity of all the analgesics, the lidocaines, ropivacaines, bupivacaines. They all kill cartilage cells to a pretty significant degree, as well. Again, with stem cells, there is some new data, so as we go into the era of regenerative medicine and stem cells, when we expose stem cells to steroid injections, it basically kills all our stem cells, as well. So, again, as we start getting into this area of trying to maintain the lifespan of our joints, our options, again, are very limited and may, in fact, be shooting ourselves in the foot.

So, we had the bright idea of orthopedic surgeons of infusing bupivacaine into the shoulder after shoulder surgery. What happened? The cartilage began to die. So, young guys coming in for rotator cuff tear were going home with a shoulder replacement. Why? Because we gave bupivacaine into the shoulder. So, when you go to Google and you type in the word chondrolysis, which is cartilage death, you get a bunch of lawyers, right? So, the point being is, our options aside from hyaluronic acid are very detrimental, and so when you remove hyaluronic acid out of the armamentarium, we are actually probably hastening the disease process.

A couple of other issues I wanted to bring up, I took exception with some of the comments about the Hayes reports. They said that non-U.S. FDA products included in the meta-analysis was appropriate. FDA has a very rigorous control over U.S. approved products, and if you know how hyaluronic acid is produced, you have no control if it was made in Rwanda and the RCT was included in the Rutjes meta-analysis, which triggered this re-review today, you can see that we have significant issues in non-U.S. products being included in that Rutjes meta-analysis. So, that's a big problem. Number two, the Hayes folks feel that KL-3 and KL-4 is not severe OA. KL-3 and KL-4 is severe OA. If you look at the arthroscopic data, when you look at cartilage and you correlate that with KL-3, it's almost down to bone. You can't expect hyaluronic acid to work in patients that are bone-on-bone. I mean, they need a total joint replacement. They don't need hyaluronic acid. They don't need steroids. So, the Hayes folks feel that that's not important, and I'll have other issues, if we have time, if you'd like to discuss. Thank you.

Craig Blackmore: Thank you. Next is Michael Schucker.

Michael Schucker: So, first off, I want to thank the committee for letting me speak. I also want to thank Christine Masters for attaching an addendum to my conflict of interest that I signed. I do speaker programs for Ferring, and I do some consulting and injection clinics, and I think the addendum kind of explains that a little more than just signing the COI. I come here from a different perspective. I come from the perspective of a patient and a provider. I have been in the Spokane area for over 12 years. I am a practicing physician assistant. My specialty is sports medicine and orthopedics. So, I see a great deal of these patients, and I use a great deal of hyaluronic acid.

A background of myself, the reason I went into medicine, I used to be in the military. I'm actually a disabled vet. I worked with special warfare and explosive [inaudible] disposal for ten years. I got hurt parachuting. So, since then, I've received 15 knee surgeries, 2 ankle surgeries, and basically live in pain on a daily basis. This product, personally, has helped me out. It allows me to enjoy my family, my kids, which I have three, 11, 14, 25-year-old daughter, and my 25-year-old daughter is actually in PA school. So, this, this is a very important product to me. I think it would be a tragedy if it's taken off the ability to give to our patients. So, this week alone I probably injected over 20 patients.

I have varying patients in ages, as young as 25 and as old as 90, and I had some of those this week. I had a 90-year-old that thanks me every time she comes in. She comes back every six months for injections. You know, one thing to come back and have your knee stuck three times with a big bore needle, you know, is not something people look forward to, and for them to come back and get these injections, I mean, that says that it works, and I get that response back from my patients. This week, I was kind of telling them that I was coming here to talk to this committee, and I had a lot of patients that were worried. I mean, I have a great deal of patients that are on state insurances, Molina, Group Health HO, and this allows them to be a viable part of their community. For some people, it's as simple as getting up from a chair. They couldn't before, and they can now. So, it makes a world of difference to these people. It changes their lives. I have younger people that I inject that, you know, try to be active. Sometimes, they can't, and it has allowed them to go back to maybe not high-impact activities, which they would like, like running, but they can participate, and again, and you look at the cost of healthcare. If we can have people that can remain active, healthy, you're going to decrease their overall cost of healthcare during their lifetime, because you, I second the comments of the other presenters. You decrease obesity, decrease comorbidities, and multiple things. So I think this is really an option we need to keep for our patients.

If you look at many patients I inject, too, they are morbidly obese. If you look at the total joint surgeons. Most of them, at this point, don't want to do total joints in patients over a BMI of 40, which is quite a bit overweight, and on some of these patients, it is the only option for them, because they have failed corticosteroids. There's significant side effects to NSAIDs, anti-inflammatories, as mentioned earlier. So, this is one of their only options. When you look at post-bariatric patients, those patients cannot be on anti-inflammatories, and we really want to keep them off narcotics, because you have significant secondary issues from narcotics to include addiction side effects. So, this is a great option for them, and the response rates I get, I think, are wonderful. I mean, if I had to put a number to my patients, I would say 75% to 80% get very, very good relief. So, again, I would think it would be a tragedy to take this off the formulary or to allow us to use it on our patients, and I appreciate you letting me make a comment. Thank you, very much.

Craig Blackmore: Thank you. Next is Jon Block.

Jon Block: Oh, good. You got the slides up, excellent. Good morning, distinguished members of the panel and the audience, and while I had great respect for Dr. Blackmore in the past, I have even greater respect now that we share the same haberdasher. Glad to know that we're both the only ones that can tie a bowtie in this room, especially early in the morning. It's tough for me. I got it on the second try this morning.

In response to the Rutjes article that was the impetus for this evaluation...

Craig Blackmore: Sorry to interrupt. Thank you for the compliment, but could you please tell us if you represent anyone or have any conflicts of interest?

Jon Block: Oh, I'm sorry. Yes, I do, I am the founder of the Jon Block Group in San Francisco. We're an independent clinical affairs consulting firm, and I represent the coalition of hyaluronic acid viscosupplementation manufacturers.

In response to the Rutjes article that was the impetus for this evaluation, we re-reviewed the data focusing primarily and exclusively, quite frankly, on the U.S. approved products in a recently published meta-analysis that was published in early September of this year. We used the Prisma guidelines, which are the preferred reporting items for systematic reviews and meta-analyses as our guidance for doing the meta-analysis. The inclusion criteria for the articles that we included in our study were U.S. approved products. They were randomized, sham-controlled, all saline controlled study designs. The primary diagnosis was knee OA. Identical treatment and follow-up conditions between injectable hyaluronic acid and sham-controlled groups and at least one extractable efficacy or safety outcome that we can extract from the article.

The exclusion criteria were concomitant interventional therapies, the study was in a non-English language journal, and we did not include any abstracts, conference proceedings, websites, or personal communications, only peer-reviewed articles.

Here was our, sort of, Prisma flow diagram in terms of sort of where we started and where we ended, starting out with over 1,500 records and ending up with 29 studies that qualified for our meta-analysis.

Baseline characteristics were fairly similar between groups for those that had hyaluronic acid injections and those that had saline injections across the board. No real differences there.

Now, the findings from our study compared to the Rutjes study in some sense is here we have both pain and function. These are the effect sizes, and as we see, this is a pre-post effect size, which was not calculated in the Rutjes article. So, we have an effect size, and the effect size, by the way, normally ranges from 0 to 1. These are all over 1, as you can see, in the first column under SMD 1.37, 1.4, 1.14 for pain, 1.16, 1.07 for function. These are extremely large effect sizes for the pre to post injection efficacy, and then when you look at versus the saline corrected efficacy values, we have effect sizes, which range around 0.4, 0.43, etc. for pain and then in the mid 0.3 for function. These are considered moderate effect sizes. Rutjes reported an effect size for pain of 0.37. Our effect size is 0.43, so it's a little bit higher when we look only at U.S. approved products.

Then, we looked also at safety issues, because there was a safety concern raised in the Rutjes article, and we found that there is very little difference in terms of risk for any safety concerns whether they are significant adverse events, withdrawals from the study, treatment related or nontreatment related, these are all very, very close to 0 in terms of the actual safety issues that may arise from injectable hyaluronic acid.

One of the problems, quite frankly, with the safety analysis at Rutjes is, they excluded all the studies that had zero events, and this was an inappropriate calculation. We included all the studies that had zero events. So, if a study was done and there were no safety issues, that study was included.

And what is the driver of why our difference is greater than theirs? The driver is that the U.S. approved products are not particularly good. Here we see differences between U.S. and non U.S. approved products for all the outcomes we looked at, pain, function, and safety. In particular, pain, you look at effect sizes, again, of 0.42 and 0.38 compared to 0.11 and 0.26. That's fairly significant, or substantial I should say, borderline significant at 0.07, and again at 0.05 for function at 4 to 13 weeks, 0.32 versus -0.02 for non-approved products. So, the real driver behind whether the effect size is larger or smaller compared to our study and the Rutjes study was the non-U.S. approved products being included.

We did a subgroup analysis looking at different types of predictors, etc. We found that the sample size and the actual methodological quality of the study were somewhat predictive of outcome for pain and again for knee function, gender, sample size, and again, methodological quality were predictors of function.

Then, we look at the... here is a very important slide. This was the standardized mean difference in the Rutjes article, which was 0.37. That's that red line there. If you look at the pre to post changes, you see that we are way greater than that 0.37 that they did, and then here are the articles we included in our study mostly all favor viscosupplementation.

Then lastly, one of the most important issues that we want to talk about here is, when you translate that effect size into a real-world situation where you have, for example, a visual analog scale of 0 to 10 in pain, Rutjes calculated that the effects would be approximately 0.9 cm out of a 10-cm scale. That's about one point out of ten. When we calculated it based on the pre-post changes, which is the appropriate calculation, we get 3 points out of 10, 3 cm out of 10 cm, which is approximately a 46% improvement. Rutjes showed about a 14% improvement. That's a dramatic difference in our two calculations, and our calculation of 3 cm is far beyond the minimal clinically-important difference of 2 cm, or approximately 30%. Thank you, very much.

Craig Blackmore: Thank you. Next, we have Samir Bhattacharyya.

Samir Bhattacharyya: Dr. Blackmore, Josh, Christine, and distinguished Health Care Authority directors, thank you for giving me the opportunity to share a truly new evidence, and I am emphasizing the fact, the new evidence and hopefully, you will find this evidence quite applicable for today's discussion.

Craig Blackmore: Sorry to interrupt.

Samir Bhattacharyya: I am, I am going to introduce myself now.

Craig Blackmore: Yes, thank you.

Samir Bhattacharyya: First, thank you, and then introduction. My name is Samir Bhattacharyya. I lead evidence-based medicine and market access activities for Mitek Sports Medicine, which is a Johnson-Johnson Company.

So, just a couple of quick contexts. This research was done under the guidance of five prominent physicians in the U.S. and was presented at the American College of Rheumatology a couple of weeks back and CNN Sanjay Gupta's blog recently reported this research. So, I just want to make sure that I talk to you about that.

Let's go over the research, then. So, the objective was to really study the effectiveness, real-life effectiveness of hyaluronic acid injections using a payer database, which is most relevant for this discussion today. How we define effectiveness was basically, is hyaluronic acid delaying or postponing the time to total knee replacement? Is there any association using a payer database, recorded in the payer database? What database we use, you probably know, MarketScan database is one of the most well known and highly researched database, both in biotech, pharmacological, and medical device. Why is it so researched? Because it's cleaner than other payer databases. It has several millions of patients and their records longitudinally, and it contains multiple payer... multiple insurance company's data. There is not one insurance company. Multiple insurance companies put their data into this database, so it's highly representative of the U.S. population.

Alright, so what is the method that we used? Basically, in very layman terms, the two cohorts of patients we looked at, everybody had a diagnosis of knee osteoarthritis and everybody had total knee replacement. One cohort used injections, hyaluronic acid injections. The other cohort did not. So, those are basically the two cohorts, and we followed them from a specialist visit to the end and end is total knee replacement, and we followed them for four years.

So, analytic design, this is probably one of the most important slides. You may say are these two patient cohorts, patient populations similar? So, what we did, we used a gold standard methodological propensity scoring matching, and what that means is, every patient in one cohort is matched, age, gender, comorbidity,

resource utilization, Emergency Room visit, hospitalization, anything that's recorded in a payer database and matched one by one so that the two cohorts are as similar as possible, except the implementation of the hyaluronic acid injections.

So, now the results. So, the left line, which is the blue line, basically shows the time to total knee replacement when they're not taking hyaluronic acid, and the red line is the cohort, which are taking hyaluronic acid. So, the median time to delay is 233 days. So, you may say, is this really interesting? Let me show you the next slide, and you will know why this is a very exciting result.

This slide is the most intriguing results that I can share with you at this moment, the new evidence. Each additional course of injections the patients are taking will postpone total knee replacement about seven months. So, if you look at that most left graph, the first injection, the course, it may be three injections every week or one injection or five injections, it's postponing delaying total knee replacement 181 days, and then if you take another course, 241 days, accumulatively 2.6 years delay in total knee replacement in a four-year database, 2.6 years postponement of total knee replacement for the patients who are taking hyaluronic acid, and I, again, emphasize the fact that these are as controlled as possible. Using a payer database, this is as controlled as it gets.

So, I would ask the distinguished HTA directors, number one, what is the impact of 2.6 years in a patient's quality of life and mobility? We need to address that question. Number two, what is the economic impact of 2.6 years in your budget? Number three, wouldn't a physician be really happy seeing his or her patient mobile, happy for 2.6 years? Thank you.

Craig Blackmore: Thank you. So, those are all the originally scheduled public commentators, but we do have a couple people who signed up, Lynn McRoy.

Lynn McRoy: Good morning. I represent Sanofi Biosurgery and they are the manufacturers of Synvisc and Synvisc-1, which are cross-linked hyaluronic acid preparations.

I want to direct my comments to two of the studies that are included in the Hayes report. The first is the Rutjes meta-analysis, which you've already heard a fair amount about this morning, the second of the AOS guidelines that were published this year in 2013. Speaking specifically about the Rutjes analysis, their conclusion was that there was not a clinically relevant effect size for the intraarticular hyaluronic acid class. This actually prompted Dr. McAlindon and Dr. Bannuru from Tufts University to publish an opinion piece in nature reviews in rheumatology, and their intention was really to clarify how it is that their meta-analysis published in 2011 did detect a significant effect size and found that the class was extremely safe. In trying to determine how can two meta-analysis, which are supposedly the highest levels of evidence, reach different conclusions? They really carefully deconstructed how the analyses were

different, and the first... and I apologize, I do not have slides, but I have handed out this information, as well as actually Bannuru and McAlindon's paper.

McAlindon and Bannuru looked at the actual trajectory of treatment effect so that they evaluated the effect of the IHA class based on its actual treatment trajectory. The Rutjes analysis looked at a time point that actually corresponds probably with the waning of the treatment effect for IHA. So, they're likely to come to different conclusions, because they're looking at actually when the effect is dropping off, not at its peak. Secondly, they also, the Rutjes analysis included papers that had active comparators, meaning it wasn't simply a saline-controlled study with IHA, it was an active treatment arm, including things as divergent as arthroscopy and physical therapy. So, if both arms have active interventions, there is likely to be some impact on both so a between-group difference is going to be narrowed toward the null. They weren't comparing apples and apples. They really mixed those groups to the point where they really confounded the result they came up with.

In addition, they included unpublished data that is not available for peer review. So, therefore, no one else has the opportunity to review what those findings were or determine the quality of the study design itself that generated that information. Ultimately, their inclusion of information that is not available really clouds the transparency of their review. In regards to their safety analysis, they included over... in their initial analysis of efficacy, they looked at 71 studies.

For the safety component, they only included 14, and in 10 of those, the serious adverse events that were reported by those investigators were determined by the investigators not to be related to the treatment. However, Rutjes included that in their safety analysis anyway, and those included things like breast cancer, macular degeneration, that had no biologic plausibility and actually from a time perspective could not really have a causal relationship, but that was included in the overall safety assessment, and I just simply want to wrap up by saying reducing the number of treatment options for patients with this disease does not benefit the patient, the physician, or the payer, and to disregard the body of evidence that has been accrued over the past 20 years regarding this class in favor of a flawed meta-analysis does not serve the patient. Thank you.

Craig Blackmore: Thank you. And we have one more individual who has signed up, Brad Bisson.

Brad Bisson: Again, my name is Brad Bisson. I am the manager of scientific medical affairs for DePuy/Synthes Mitek sports medicine. That is my disclaimer, and again, I would like to thank the panel here for the opportunity to speak briefly, if only for three minutes. My comments were about, again, the Rutjes, which actually started a lot of this process within here and within the U.S., etc. What I would like to make sure that everybody is well aware of is if they actually just simply Google, or in the case of the Northwest, Bing with Microsoft, the Rutjes article, you will see that there are basically numerous rebuttals that have been done about it.

The rebuttals have all been against or not in favor of what Rutjes actually stated. The ones in favor of it, I have not yet found one. So, that stated, I just want to read what our brief synopsis was that we actually did have published in the Annals of Internal Medicine. The data and conclusions of the meta-analysis by Rutjes et, al. on the conclusions and the treatment of osteoarthritis viscosupplementation raised several questions.

From the efficacy standpoint, we expected, upon review of their data, the author's summary of the efficacy across the 71 studies to provide benefit of the patient population. As you saw from some of the earlier slides, the efficacy did seem to lean towards the treatment of osteoarthritis being in favor with viscosupplementation. In particular, out of the studies that reported the effect size, 60 showed an effect size favoring hyaluronic acid; 49, 71%, showed the effect size greater than 0.176, which is the equivalent to 0.44 cm on the scale. In addition, the authors used a clinically important difference between the treated group and the control groups on a 10-cm scale to assess the efficacy of viscosupplementation. This cutoff was very strict given the between placebo and various differences of first proven line treatments. Their values represent the incremental and meaningful benefit of therapy across after subtracting from placebo and other nonspecific effects.

What I really want us to talk about also was related previously about the safety. They did talk specifically about the safety of hyaluronic acid being in question. They talked about six cancers in one of their analyses, as well as cardiovascular and GI risk. Of those six cancers, I was in personal communication with Dr. Baroff who was actually for those six cancers and he was a little bit chagrined, to say the least, that the Rutjes article would actually list these, because in his own words, they did not read the article. They read the abstract. The abstract had listed those, as what a lot of abstracts do, but the actual article, if you went down to the conclusion, stated clearly that there was no relationship between those. It was very clear that the efficacy, or excuse me, the safety was these cancers were discovered between 17 and 72 days upon treatment of hyaluronic acid, and I'm sure that since many of the panel here are very medically inclined, are well aware that cancers do not assimilate that quickly. That's pretty much what I have to say, and I thank you, very much, for your time.

Craig Blackmore:

Thank you. Is there anyone else here who did not have a chance to sign up that still wished to address the committee? Then, we will also need to go to the phone, Christine, and see if there is anyone who has dialed in who wishes to speak to us. What do you need Christine? Did anybody see the instructions on how to un-mute the phone? If you have called in to the Health Technology Clinical Committee meeting and wish to address the committee about the hyaluronic acid viscosupplementation question, could you please identify yourselves at this point? Okay, not hearing any responses, we will mute the phone once more and continue. Okay, I will close the public comment period. Next on the agenda is the agency utilization and outcome.

Robert Mootz:

Hi, I'm Bob Mootz. I'm one of the associate medical directors at Labor and Industries, and I do have slides if I could have those up, please. Okay, well this is our first, I believe this is our very first re-review and so I will start with a little background here. The osteoarthritis of the knee is a fairly prevalent condition. It affects over 10% of older adults. It involves, as you have heard, damage to articulate cartilage and subchondral bone changes that can be actually excruciatingly painful. The usual care for this involves physical therapy, occupational therapy, assistive devices, NSAIDs, analgesics with refractory cases, steroids, and aspiration become some of the choices. The issues, as you have heard, with things like NSAIDs and steroids is there are very significant side effects over the long-term usage of them. So, intraarticular hyaluronic acid injection is an alternative aimed at assisting lubrication and improving cartilage repair. Just one comment, too, is that the approval for this intervention in the FDA as a device, it is not as a drug. So, the rigor in drug testing to get that FDA approval is not there. The agency concerns, initially when we first brought this to you in 2010, we did not have much of a safety concern. The efficacy issues, the mechanism was not clear, and there was unstudied duration of care and duration of effect, and cost issues, we were seeing a fairly rapid increase in use at that point in time in our agency data. This year, as we were looking at it again, the safety concerns seemed to be persisting with some side effects. So, we upped that a little bit, stimulating the review.

The efficacy concerns were essentially the same, but there are some new studies available. The cost issues, we went down a little bit, because the costs did escalate initially and then leveled off, as you will see in a minute.

The decision you made in 2010 was essentially authorization for treatment of osteoarthritis of the knee when patients did not have an adequate response to usual care, and it is limited to two courses a year with at least four months in between.

The safety issues, it looks like localized adverse events appear to be more common than with comparators, such as placebo or saline injections. Serious adverse events, such as pseudosepsis, are rare and can usually be resolved. So, as we looked at the data, the safety issues are not that big of a concern.

Effectiveness, however, it looks like there are statistically measurable improvements in pain and function that have been reported in placebo trials. What is up for discussion and what we are hoping you will look at carefully in the literature reviews that are presented in the vendor report are what is the clinical significance and meaningfulness of this? The larger, if we call your attention to larger, better designed clinical trials, tend to show smaller effect sizes that are clinically insignificant. Benefit may be greater in less severe cases and younger individuals. The evidence suggests, also, that in terms of quality of life, there does not appear to be any massive effect. So, even though we may be postponing surgery, the evidence is not speaking very clearly, very persuasively that postponement of a couple of years is actually a substantially

increased quality of life compared to alternative treatments. The alternative treatments, of course, have some effect, as well. So, when we talk about pre-post studies and that sort of stuff, we are thinking about regressions to means and other issues that you are all aware of. The effects identified from viscosupplementation appear to be longer than that of steroids, and there is inadequate evidence comparing viscosupplementation to other conservative measures, glucosamine, chondroitin, and various forms of exercise.

Cost issues: Our agency experience suggested rapid initial growth that's leveled off. There may be some tradeoffs. Some products may cost less per course but may have increased risk for side effects with multiple injections, whereas more expensive single-dose courses may actually have a lower total cost. The published studies on cost, of course, are of variable methodology and have mixed conclusions, which is why when we've got this kind of issue we bring it to you guys for your input.

Just some agency information. This is just a slide for reference to give you an indication of what treatment costs are for various products. It is not a huge per treatment cost. If you look at the public employees benefit utilization, over the past seven years, they have spent about \$3.8 million on it. Medicare it is about \$1.8 million, and L&I utilization is about \$2 million. So, this illustrates going back to the by-product comparison. That just illustrates the point I made earlier that's the single dose injections may actually have a lower cost for the course than the multi-injections that appear to be cheaper by cost.

In PEBB, again, this just illustrates some of the total cost, the duration and number of courses that we have seen in our data. It looks like, on average, about 1.5 injection courses per treatment intervention.

So, I would like to call your attention to some other coverage decisions that have been made. NICE, in 2008, recommended against coverage for this emphasizing the small effect size and cost issues. Oregon Health Evidence Review Committee this past year also made a noncoverage decision based on the same evidence that we have reviewed. Guidelines that have come out since 2010 have actually diminished in their strength of recommendation, some of them that are called out, the American Academy of Orthopedic Surgery did not recommend hyaluronic acid and did not recommend for or against in 2010, and again, the minimal clinically important difference is part of the issue there. The American Academy of Rheumatology made no recommendations for hyaluronic acid, and this was a change from their 2000 recommendation, which was similar to the HTA coverage decision, inadequate response to conservative intervention.

So, our issues as an agency are based on a reasonable level of clinically important difference. Evidence does not appear to show significant superiority to placebo or sham by type of product, cost, or number of injections. It does appear to postpone the delay in doing total knee replacement surgery.

However, observing the course of that, doing physical therapy and other interventions, also delays the course of surgery. So, part of what the challenge is, as you go through this evidence, is to try and dissect those issues out. Professional societies have dialed back some of their recommendations and other well-done evidence reviews have made noncoverage decisions.

So, in being consistent with our original recommendation in 2010, we are asking you to consider making a noncoverage decision for this. The meaningful, clinical effect on pain has still not been demonstrated, and little evidence is available on other patient outcomes in the published literature. The harms are relatively minor, but they are still there. If the committee finds that the evidence is still suggestive of a net health benefit, consider continuing the coverage conditions that you have outlined previously and maybe consider adding age as one of the conditions, which was not in the original decision, and that's it.

Craig Blackmore: Do committee members have questions for Dr. Mootz? I guess I'll ask a question just for clarity. Several slides you present us on utilization.

Robert Mootz: Mm-hmm.

Craig Blackmore: And, just clarify for me average injections per patient versus average injection courses per patient, slide 9, 10, 11.

Robert Mootz: 9, 10, 11?

Craig Blackmore; Yeah, so there.

Robert Mootz: Okay, there...

Craig Blackmore: So, we've got average injections per patient and average injection courses per patient. So, this is, I assume, relating to...

Robert Mootz: Oh, yeah. It's, it's...

Craig Blackmore: ...some requirement [inaudible].

Robert Mootz: ...one course, if a multiple injection project or intervention requires three injections, that would be one course, whereas a single injection product, one injection would be a course. So, that's just distinguishing between those two.

Craig Blackmore: And so, when we relate that back to the cost, we have average paid for procedure, then, is that procedure a course or is that an injection?

Robert Mootz: That's an injection.

Craig Blackmore: That's an injection, okay.

Robert Mootz: Right.

Craig Blackmore: And then our previous decision was a maximum of two per year, and that would be courses.

Robert Mootz: Right.

Craig Blackmore: So, that's why the number is less than two.

Robert Mootz: Exactly.

Craig Blackmore: Just wanted to run it through, yeah.

Robert Mootz: Yep, correct.

Craig Blackmore: Okay, thank you.

Richard Phillips: Yes, I have a question.

Robert Mootz: Sure.

Richard Phillips: Do you have any data on the patients who underwent total knee arthroplasty, as to what their utilization of these injections were before they underwent the surgical procedure?

Robert Mootz: We have not done that.

Richard Phillips: So, as far as you know, it's not clear that they're the same population of patients, then.

Robert Mootz: Right, and that, we don't know that from our data.

Richard Phillips: Okay.

Robert Mootz: Yes.

Craig Blackmore: Other questions from the committee? Alright, we will continue, and next we have our evidence report. Maybe while we're queuing that up, I will take the opportunity to introduce Dr. Chansky. So, as part of the committee's procedure, we always invite a clinical expert to ensure that the decisions that we are making are in the appropriate clinical context, since the committee members may not have personal experience with the technology at hand. So, Dr. Chansky, I will ask you to sort of introduce yourself in a moment and tell us who you are, but just to explain the role a little more, the committee is charged with making decisions based on the best evidence, and our primary source of that evidence is going to be the vendor's report, though of course we also hear the public comments. So, we will use you, if I may say, in helping us to understand

the clinical context, and we do not have you specifically on the agenda, but there, inevitably, will be a number of questions, and we will direct them to you and ask you to help us to understand that. So, can you just share with the committee and actually before you do that, we have to speak into the microphones, because we record everything, so.

Howard Chansky: I am an orthopedic surgeon. I'm the chief of orthopedics at the University of Washington Medical Center and also at the Puget Sound VA, and my clinical expertise is in total joint arthroplasty and orthopedic oncology.

Craig Blackmore: Thank you.

Teresa Rogstad: Would you like me to begin?

Craig Blackmore: Yes, please.

Teresa Rogstad: Thank you. This, of course, is a re-review of the topic. A report on hyaluronic acid was presented to the committee in May of 2010 and Hayes prepared that report, as well. The approach that we took to this re-review, upon advice from the agency medical directors, was to consider the overall body of evidence at this point in time and to do an integrated assessment of that evidence rather than to just assess the new evidence and kind of provide an add-on to the old report.

The next couple of slides are just for your reference. Here's a definition of abbreviations, and then this slide lists the phrases that we use in a shorthand manner throughout the report to refer to the various systematic reviews that are included and defines the content of those reviews. 2010 report means that previous report that was presented to Washington HTA in 2010, and then update report is just another phrase that we use, it means this current re-review report.

Knee osteoarthritis is the most common form of osteoarthritis and has a prevalence of about 10 to 12% in American adults who are over the age of 60. You've heard some good presentations on the various treatment options and the problems that are associated with them. So, hyaluronic acid injection, or viscosupplementation, was developed as another alternative. HA stands for hyaluronic acid.

Other terms for this compound includes sodium hyaluronate and hyaluronan. These products actually replace a naturally-occurring hyaluronic acid in the synovial fluid and cartilage. It's a viscous elastic substance that serves as both a lubricant and a shock absorber for the joint. There are about 20 hyaluronic acid products worldwide. Only six of them have been approved by the FDA and one of those on the list, Gel-One, was not commercially available at the time of the last report. Most of them are designed to be delivered in a series of three to five injections, but Gel-One and a variation of the Synvisc product can be

delivered in single injection. They differ according to the source that the compound is derived from, but more importantly, they differ in chemical structure and molecular weight. Synvisc and Gel-One are created by cross-linking the hyaluronan chains so they have the highest molecular weight.

The previous report concluded that hyaluronic acid injection results in lower mean pain scores and improved mean function a few weeks after treatment with the effects peaking at about three months, but the magnitude of benefit may be too small to be clinically important. Since that time, three new systematic reviews with meta-analysis have been published, and one of them that you've heard a lot about already, the Rutjes review, raised some new safety concerns about serious adverse events. Another impetus to the re-review was the fact that professional groups for orthopedic surgery and rheumatology have produced new practice guidelines, since the last report, and their recommendations are more negative, and then lastly there is still no national CMS policy.

The PICO statement specifies that the report addressed the use of viscosupplementation in adults with osteoarthritis of the knee and the appropriate comparators were any nonsurgical treatment, the outcomes of interest were pain, function, quality of life, and adverse events. The key questions followed the typical pattern of effectiveness, safety, effectiveness by subpopulation, and cost implications. We searched from December, 2009, forward to collect new evidence, and our last updated search was in July of this year. Systematic reviews and randomized controlled or comparator trials were eligible. We also considered observational studies for the safety and differential effectiveness questions.

This slide summarizes the evidence that is included in this re-review with the red font denoting the new evidence. So, you can see that the answers to key questions one through three come from a combination of old and new evidence, but we found no new economic evaluations or cost studies, and in general, the conclusions of the previous report were reinforced by the new evidence, but the new evidence does allow us to do a little bit more nuanced assessment.

I should explain when you're reading through the report that different numbers of systematic reviews might not seem to tie out exactly. Part of that is because of this 2007 AHRQ technology assessment, which we call the Samson review. That was a main source of evidence for the last report, and it actually consists of a review of six previously-published meta-analyses, the largest of which was a Cochran review published in 2006 by Bellamy and colleagues, and so to represent that older data, we have highlighted estimates from the Bellamy review, as it was, by far, the largest of the meta-analyses in that 2007 AHRQ report.

So, these slides give you a preview of the findings with respect to key question number 1-A. We found moderate quality evidence showing an improvement in pain and physical function and moderate quality evidence showing essentially no impact on quality of life. I do have to qualify that conclusion a little bit, which I will when we get to the detailed. There was low quality evidence suggesting that a repeat course of treatment is equally effective with the initial course. We will talk about the clinical relevance of those improvements in pain and function, but not quite yet.

Continuing with our preview, some of the studies reported findings in terms of responder rates. A responder rate is the proportion of patients who improve according to a prespecified definition of clinical relevance or clinical response. So, 11 placebo-controlled trials reported responder rates and two pragmatic trials. The findings were generally positive. There were some problems we found with the placebo controlled evidence. Comparator trials showed that hyaluronic acid injection has equivalent efficacy with NSAIDs and that compared with steroid injections, the benefit is longer-lasting. That evidence was considered to be of low quality because of the study quality, and then there was no evidence comparing hyaluronic acid injection with glucosamine or chondroitin.

Before looking at those findings in detail, I wanted to give you some idea of the typical patients who were in these trials. These data were taken from the 22 RCTs that had at least a sample size of 200, and as you can see, generally patients had osteoarthritis for several years and the severity fell at 2 to 3 on the Kellgren-Lawrence scale. According to the source we found in the literature, a KL grade of 3 represents moderate osteoarthritis and 4 represents severe bone-on-bone osteoarthritis, but very few patients had disease at the 4 level. Baseline pain was usually in the midrange of whatever scale was used. Most of the studies did not give information on the history of NSAIDs use, but those that did showed that the vast majority of patients had tried NSAIDs. Several of the studies did not allow a steroid injection within the previous three months, but unfortunately, none of the studies gave any history of whether steroid injections had been used prior to that washout period. Most of the studies allowed concomitant pain medication, but often that was restricted to acetaminophen, so NSAIDs were often not used during the study period. The studies gave no history on trauma or whether patients had been compliant with previous treatment recommendations.

So, to represent the most pertinent data, we have focused on findings at three months, and the reason is that three different systematic reviews showed that pain effects peak right about at three months or just a little bit before, and the two newer systematic reviews focused on effects at this interval. So, for pooled effects that were reported in terms of a weighted mean difference, the pooled estimates were 10 and 11 on a scale of 100 points.

Other data were reported in terms of a standardized mean difference, also called an effect size. In the Bellamy review, they calculated an effect of 1.0 for WOMAC pain. There is actually an error on that slide. That was for overall pain not just weight bearing pain. They only found seven RCTs that would allow this calculation according to their analytic methods. The Rutjes review calculated a pooled estimate of 0.37. That was based on 68 RCTs. It is true that some of those trials in the Rutjes review included comparison with an active control rather than placebo, but 54 of those 68 trials were with a placebo control, and 50 of them were published as full journal articles. There was moderate heterogeneity in the Rutjes estimate, so to explore that heterogeneity, they did quite a number of stratified analyses where the studies were divided according to some type of study characteristics, such as sample size, publication status, whether there was patient blinding and so forth, and the only two study characteristics that were statistically associated with effect size were whether or not the study had at least 100 patients per group and whether or not adequate assess or blinding was clearly reported. So when they took the 18 trials that met those two criteria, the pooled effect size fell to 0.11. It was still statistically significant and it favored hyaluronic acid, but it was quite a bit smaller than the effect size for the overall set of studies.

So, we also are highlighting physical function at three months. There is no clear pattern regarding peak function effects, so that it's comparable with the pain effects. That's what we're focusing on, and that's what the Rutjes review and the Colen review also focused on. We have results expressed as effect sizes here. They are slightly smaller than the corresponding effects for pain at three months and again when the Rutjes review did an analysis based on those trials that had larger sample sizes and adequate assessor blinding, the pooled effect was quite a bit smaller.

So, let's talk a little bit about clinical relevance. This slide summarizes the various definitions that we found in the literature reviewed for this report. The language varied somewhat and the definitions varied in terms of whether they were expressed as absolute improvement on a scale or relative improvement for baseline, and you will see that some of the definitions were composite definitions that also took into account improvement in physical function, as well as pain improvement. What seems to emerge from these various definitions is that a 20-point improvement on a 100-point scale, or something equivalent to that, or a 30% improvement relative to baseline would be considered by all sources to be a clinically important difference or improvement, and an improvement on the order of 10 on a 100-point scale would be considered at least clinically noticeable.

Now, these definitions are all based on research having to do with individual improvement or mean improvement within a group of patients who all receive the same treatment and as was alluded to in the earlier testimony, there is some controversy about whether those definitions are applicable to a trial effect, which represents a between-group difference. The impact group

published a second consensus statement in 2009, in which they contended that a clinically important difference in a trial might not, maybe should not be required to meet the same standards as a clinically important difference in a group of patients undergoing the same treatment, because a trial effect represents a downward adjustment for placebo effect. So, they advised that responder rates are really a better approach to analysis in trials.

The Rutjes review did define a minimal clinically-important difference for a trial effect for a between-group difference, but the research that they cited did seem to be based on studies looking at individual or within-group improvement. So, they may have committed what the working group considered to be a fallacy. Nevertheless, that effect size of 0.37 does correspond to a fairly lenient definition of a clinically-important improvement in individuals, and if that number 0.37 looks familiar, it's because coincidentally, the effect on pain at three months was exactly equal to their pre-specified definition of an MCID.

So, just comparing those pooled estimates with clinical relevance, we see where that was expressed as a weighted mean difference. It met the, sort of the lowest threshold of clinical improvement. The Bellamy review concluded on the basis of their findings that hyaluronic acid was effective, but the Colen review with very similar results concluded that clinical relevance is debatable, and the Rutjes review, although their main outcome equaled their pre-specified MCID, in their conclusions they focused on the fact that effect size was clinically irrelevant in the larger trials with adequate assessor blinding.

There was no definition of clinical importance that was specific to physical function, but the effect sizes were very similar to those for pain and again, the Rutjes review concentrated on the smaller effect in those larger trials with assessor blinding.

So, we did identify 11 sham-controlled double-blind randomized controls with results reported in terms of responder rates. The response rates were higher in the hyaluronic acid arms than in the placebo arms, and in nine of the studies, results favored hyaluronic acid with an absolute difference of 3 to 16 percentage points depending on the follow-up interval and a number needed to treat of 7 to 16. Two of those trials had results that actually favored placebo, but the difference was very small. We considered the evidence to be of low quality because some of the studies had statistically nonsignificant results or did not clearly report statistical significance.

There were two pragmatic trials that reported responder rates and by pragmatic, we mean trials that are conducted to assess the effectiveness in real world practice. So, in these studies, viscosupplementation was considered an add-on to usual care alone and was compared with usual care rather than with a placebo injection. Again, the response rates favored the hyaluronic acid arms. They were statistically significant in both of the studies with absolute differences in the range of 15 to 27 percentage points, and a corresponding

number needed to treat of 4 to 6. We considered this moderate quality evidence. The main deficiency with the trials was that being pragmatic trials there was no patient blinding. There also was no assessor blinding, which you might consider a deficiency, although they were a patient-reported outcomes. There is a question about the generalizability of these pragmatic trials. They are over ten years old, and they were not conducted in U.S. settings. One of them had industry funding.

So, there were other results that speak to the question of effectiveness. Six sham-controlled trials suggested that there is no impact on quality of life. In the interest of full disclosure, I have to acknowledge that I realized in preparing for this presentation that we neglected to mention here the quality of life data that was collected by the pragmatic trials. They collected utility values or functional status along with the efficacy data, and they did show a slight difference favoring hyaluronic acid, but the difference was nonsignificant in one of those studies. For repeat courses, three RCTs that had high dropout rates between the first and second course of treatment suggested that the efficacy was equivalent between the two. Comparator trials suggested equivalent efficacy, although it should pointed out that hyaluronic acid injection is not typically offered as a complete replacement of NSAIDs. The goal is to reduce the use of NSAIDs. Other comparator trials, according to a systematic review, showed that initially the benefit from a steroid injection is greater, but the trend reverses at about one month and at 17 to 26 weeks, there is a peak effect favoring hyaluronic acid injection with an effect size of 0.39.

So, to recap, there was moderate quality evidence suggesting efficacy with respect to pain and physical function, either no impact or a very small impact on quality of life, equivalent efficacy for repeat courses of treatment, positive evidence with regard to responder rates, equivalence to NSAIDs, some advantage over steroids, and no evidence regarding comparative effectiveness with glucosamine or chondroitin.

The take-home message about clinical relevance is that the main pooled estimates either equaled or slightly exceeded the review author's definitions of a minimal clinically-important difference, but in the Rutjes review, when they looked only at the larger trials with clearly adequate assessor blinding, the pooled estimate was less than that definition of clinical relevance.

Key question number 1-B had to do with effectiveness by product. Three systematic reviews reported pooled estimates that favored hylan over the non-crosslinked products, but the estimates were statistically nonsignificant, and they were small. One of those reviews reported that the risk of adverse events is almost doubled with the use of hylan compared with other products. This evidence was considered to be of low quality because the studies were rated as poor. There was also inconsistency across the studies in terms of direction of findings and imprecision in the pooled estimates. There was some analysis of

molecular weight as a continuous variable and no association was found with efficacy.

Regarding safety, we considered the evidence to be of high quality showing that hyaluronic acid is safe in the short-term, although as you've heard, there was an estimate in the Rutjes review of a small increase in serious systemic events, but there are some problems with the interpretation of those data, which I will get into in a little bit. There was insufficient evidence regarding long-term safety because of mixed findings regarding the safety of a second course of treatment, and the lack of data on adverse events occurring beyond one year.

The Rutjes review estimated that there is no increase in overall risk of adverse events and that Cochran review by Bellamy and colleagues in 2006 reported similar findings. This represents mainly a comparison between hyaluronic acid injection and placebo. So, what this shows is the hyaluronic acid product itself does not seem to increase the risk of adverse events but, of course, there are risks associated with any injection, even with the placebo injections.

Perhaps a more meaningful source of evidence about the risk of the adverse events would come from large case series reporting absolute rates. There were some large case series that were covered in that 2007 AHRQ review. They only used hylan, and they reported absolute rates of 5 to 8% per person or 2 to almost 3% per injection. A more recent large-case series that used a non-crosslinked product reported an incidence of 0.8% of any adverse events per patient.

The Rutjes review showed that the risk of local adverse events does increase with the use of hyaluronic acid mainly compared with a placebo injection. These are events, such as pain or swelling and effusion in the joint. They are generally transient. There is a very rare possibility of a reaction called pseudosepsis, which is a local noninfectious reaction that mimics a systemic sepsis, and there were no cases of pseudosepsis mentioned in the trials or the more recent systematic reviews, but it does show up in mod reports, and it was mentioned in the 2007 AHRQ review. So, we identified a review, the Goldberg review published in 2004 that attempted to document all published cases of pseudosepsis. They identified 28 that had been published as of 2004 and we found another case report, since that time. Of those 29 cases, all but one followed a hylan injection, and these can be severe reactions, sometimes even requiring hospitalization.

Here's the controversial safety data. The Rutjes review reported a rather alarming 40% increase in the incidence of serious adverse events. These were systemic events. As you can see from the detail there, cardiovascular events, cancer, musculoskeletal disorders were all more common in hyaluronic acid arms than in control arms. Gastrointestinal events were actually less frequent in the hyaluronic acid arms. The authors acknowledged that they could not explain the causal relationship between these events and the treatment and, in

fact, the duration of follow-up in these studies is really too small to assume a connection. Because the authors did not report a risk difference, we calculated a crude, overall rate of 0.9% incidence that's combining both arms. So, a risk difference would be smaller than 0.9%.

Also, to get a better handle on this issue, we looked at 22 randomized controlled trials with large sample sizes, and some of those trials did report the type of serious event that was documented in the Rutjes review, but in every case, the authors said that they did not believe the event was attributable to treatment. Among the three case series that were reported in the Samson review, and that represented almost 10,000 injections, there was one serious event that involved large effusion with synovitis. In a more recent trial that used a non-crosslinked product, the incidence of serious events was only 0.8% of patients, and I'm sorry, there's another error on this slide, as well. The product was Hyalubrix, I think is the name, not Hyalgan, and it is not an FDA-approved product.

So, in other comparisons, hyaluronic acid injection was found to be associated with fewer systemic adverse events compared with NSAIDs versus usual care. One of the pragmatic trials reported that adverse events were fewer in the hyaluronic acid arm. In the other trial, they were more frequent, but even in that Kahan trial, gastrointestinal events were less frequent in the hyaluronic acid arm compared with usual care. Two RCTs with extension studies found that the incidence of adverse events were equivalent in a second course of treatment compared with the first. However, two large case series found that for patients who were undergoing a first-time injection, adverse events were considerably less frequent than for those patients undergoing a repeat course, so there's conflicting evidence there.

So, to recap, we felt there was high quality evidence of short-term safety, but insufficient evidence to draw conclusions about long-term safety. The only conclusion that can be made about the comparative effectiveness, according to patient characteristics, is that there seems to be greater benefit in patients who are younger than age 65 and who have less severe osteoarthritis. This was the result of one of the meta-analyses covered in that 2007 AHRQ report. For every other factor, there was either no evidence or conflicting evidence between two trials or evidence from only a single small trial, so no conclusions could be made.

Regarding cost-effectiveness, we looked again at the four economic evaluations that were available at the time of the previous report. Two of them were based on the two pragmatic trials that we've already talked about, and the Canadian study computed a very favorable cost per QALY ratio of about \$10,000 Canadian dollars per QALY that applies to 1999 costs. If you convert that to U.S. dollars, in 2013 that's very roughly \$11,000 per QALY. So, a very good cost-effectiveness ratio. The other study found that costs were comparable between hyaluronic acid and usual care alone. The other two cost-effectiveness studies drew their

estimates of effectiveness from placebo-controlled trials. The Taiwan study was a modeling study and they used a placebo-controlled trial from 1998 as their basis of assumptions regarding effectiveness, and that trial was fairly representative. The effectiveness in that trial was pretty similar to, for instance, the pooled estimate in the Rutjes review. What this study concluded was that hyaluronic acid was not an affordable alternative compared with either of the two NSAIDs that they looked at, not affordable for Taiwan. Looking at the numbers there, you can see it might be considered cost-effective in a U.S. setting, and that study was another older one that was conducted in 2004. The UK study was a very informal analysis that was performed to support the 2008 NICE guidelines. They took two placebo-controlled trials and calculated cost-effectiveness ratios based on that placebo comparison. In one trial, the ratio exceeded the national health services threshold, and in the other trial, placebo was both more effective and less expensive. That is a rather unusual analysis, because in a cost-effectiveness analysis, the comparison is usually between two real treatments, not comparing with placebo.

The deficiencies with the cost-effectiveness evidence are that there are only a small number of studies that may not apply to the U.S. The more meaningful studies are more than ten years old. We have no cost-effectiveness data that is applicable to single injection treatments and no data for hyaluronic acid compared with steroid injections.

Of the four current guidelines that address viscosupplementation for knee osteoarthritis, the current practice guidelines for orthopedic surgery and rheumatology do not recommend osteoarthritis for the knee, or actually they say that they cannot make an evidence-based recommendation for viscosupplementation. The NICE guidelines recommend against the OARSI guidelines. OARSI is a research group. They do identify hyaluronic acid injection as an option for knee osteoarthritis, but the recommendation is rated as relatively weak, 64 on a 100-point scale. It's also interesting to note that the American College of Rheumatology guidelines make an additional recommendation that hyaluronic acid injection may be offered to patients over the age of 75 in lieu of oral NSAIDs, but that is offered as sort of a clinical expert recommendation and they do acknowledge it is not evidence-based.

Of the four payers that we looked at, only AETNA had a coverage policy. Hyaluronic acid injection is covered when other treatments have failed for at least three months. Regence and Group Health do not have coverage policies, per se. However, it was brought to our attention that their medication policy suggests that hyaluronic acid is covered with prior authorization and it is limited to two courses of treatment per year. The Oregon HERC recommended against hyaluronic acid injection based on the 2007 AHRQ report and the reports prepared by Hayes in 2010.

So, to summarize, efficacy has been demonstrated, but the magnitude of placebo adjusted benefit may be too small to be clinically important for many if

not most patients. However, in terms of effectiveness in practice comparing with usual care alone, there is some evidence of a clinically-meaningful benefit in terms of responder rates. The effect appears to be longer lasting than the effect of steroid injections. Efficacy by molecular weight is uncertain. There is an increase in local reactions, but those are generally transient and not severe. There is a reduced risk of gastrointestinal events and efficacy may be greater in younger patients with less severe disease. Cost-effectiveness has not been studied in a U.S. setting.

There are several gaps in the evidence. A very important one is the lack of responder rate data and cost-effectiveness in a U.S. real world practice. Also, the differential effectiveness, according to patient characteristics and previous treatment history needs to be further investigated. Thank you, that concludes my presentation.

- Craig Blackmore: Thank you. Questions from the committee members related to the report?
- David McCulloch: Thank you. Nice report. I noticed that you could not conclude that, and whether or not body mass index affected outcomes or not.
- Teresa Rogstad: Right.
- David McCulloch: But I did notice on slide 15 that virtually all these trials take body mass index between 29 and 33, which is somewhat overweight, no question, but my guess is that in clinical practice, a whole lot of people that get these are a lot heavier than that, and I don't think we do, so we don't really have data on how effective it is in the short-term or long-term in people who are a lot heavier, is that right?
- Teresa Rogstad: Did you say no data on people who are not overweight?
- David McCulloch: No, on people who are more overweight than...
- Teresa Rogstad: Oh, more overweight, than...
- David McCulloch: ...the studies include 29...
- Teresa Rogstad: ...oh, no.
- David McCulloch: ...to 33 BMI, which is overweight, but...
- Teresa Rogstad: Right.
- David McCulloch: ...we see many, many, many patients BMI is 35, 40, 45, 50 and above, and I... my guess is in routine clinical practice a lot of patients who get these will be heavier than a BMI of 29 to 33, and we don't have evidence for what the short, medium, and long-term benefit is in that setting.

- Teresa Rogstad: That's right. We didn't find any data specific to that population.
- Seth Schwartz: And more of a, just a basic question. I always wonder about this when we have almost as many systematic reviews as we do primary articles, and so I am just wondering if there was a lot of crossover in terms of what the different meta-analysis we're looking at. Were they looking at a lot of the same articles and, if so, were they looking at them differently or do you have any comment about that?
- Teresa Rogstad: There was quite a lot of overlap in the studies that were included. There were some differences in how, for instance, which outcome measures were selected to be included in the pooled effects or how three-month results were identified, because not all studies reported at exactly that interval. They are pretty consistent in both the direction and the magnitude effect though.
- Michelle Simon: It seems that much of this re-review is spurred by the recent publication of the Rutjes meta-analysis, and for me, the most concerning thing that they have presented is the safety data. So, if, on your slide 34, it talks about the serious adverse events and then I really appreciated you going ahead with slide 35 and trying to pin down what those adverse events were, and it seems that the adverse events really cannot be tied back to the treatment. I mean, this is very perplexing to me about the meta-analysis. So, I guess my question is, do you have any explanation for this? Or did you, and/or, did you look at the potential for publication bias in either any of the meta-analysis or any of the individual RCTs?
- Teresa Rogstad: Well, the Rutjes review did find what they considered to be evidence, some evidence of publication bias among the trials that had efficacy data. I would have to look to see if they analyze publication bias in... they only found 14 trials that reported safety data, and I would have to look to see if there was publication bias there. We actually tried e-mailing the authors of that review to see if they could explain these findings, and they did not reply. They do acknowledge in their discussion that they cannot explain the causal relationship with these events, and was there another question that I'm not responding to?
- Michelle Simon: I guess I was curious about your interpretation of who published Rutjes and where it came from. Is there any potential for publication bias in that meta-analysis?
- Teresa Rogstad: Oh, you mean, a bias on the part of the authors?
- Michelle Simon: Correct.
- Teresa Rogstad: Oh, well, they are, I did not think about that. I'm trying to tell you where they're, where they're located. I think they're in Belgium.
- Joann Elmore: They were supported by an ARCO Foundation, whatever that is.

- Teresa Rogstad: Switzerland, sorry. I have no information on which to judge that.
- Marie Brown: Could you comment please on the inclusion of nonpublished trials in their meta-analysis versus only including published data?
- Teresa Rogstad: Well, they included about 15 or so conference abstracts and five completely unpublished studies, but the Bellamy review also included any study published or unpublished, and the Colen review only included studies that were fully published as a journal article and still had similar results. So, it is true that there were unpublished studies included in the review, but they were not particularly influential on the results and, in fact, in their stratified analysis where they collected, I mean, where they calculated effect size for the fully published studies, the conference abstracts, and then the unpublished studies, there was no statistically significant difference across them, although the effect size was larger in four of the five unpublished studies, but they couldn't demonstrate there was a significant difference.
- Craig Blackmore: So, if I understand what you just said, they included some essentially nonpublished studies, but those nonpublished studies actually made the hyaluronic acid look better.
- Teresa Rogstad: Correct.
- Seth Schwartz: I just had one more question related to the effect size data. It seems the way a lot of this is reported where they were looking at VAS scales and things like that and then doing means of the groups and then looking at a minimally clinically important difference across the entire group, but I am wondering if any of these studies, or if there are any studies that look at percentage of patients who achieved a clinically-meaningful difference.
- Teresa Rogstad: Yes. That's what the responder rate data are. That's exactly what they are and those studies did show positive results favoring hyaluronic acid. Out of 11 placebo-controlled trials with responder rate data, 9 of them reported results favoring hyaluronic acid. So, more patients in the hyaluronic acid arm than in the placebo arm had clinically-meaningful improvement, and then the two pragmatic trials also showed a greater proportion of patients with a clinical response in the hyaluronic acid arms.
- Chris Standaert: They had big ranges in the responder rates, though, yes? Like 30 to 80 or something like that?
- Teresa Rogstad: Well...
- Chris Standaert: I can't remember which slide that's on.
- Teresa Rogstad: ...in the pragmatic trials...

- Craig Blackmore: Slide 22.
- Teresa Rogstad: ...it was something like 60 to 80 in the hyaluronic acid arm. It was quite a bit wider in the placebo-controlled trials.
- Craig Blackmore: Slide 22.
- Chris Standaert: Yeah, 30-80. Doesn't the placebo... the RCTs it was 30 to 80 for hyaluronic acid and 27 to 68 for the placebo.
- Teresa Rogstad: Right.
- Chris Standaert: I mean, those are big ranges.
- Teresa Rogstad: Yes. Yes, they are, and that's part of the reason that we characterized that evidence as low quality, but, you know, the pragmatic trials are, perhaps, more meaningful, because they are looking at, you know, how it is actually used in practice, and those...
- Chris Standaert: But they were also, they were totally unblinded, though, from what you told us.
- Teresa Rogstad: Correct, yes they were.
- Marie Brown: And it sounds like the outcomes were mainly pain. There weren't even that many that looked at outcomes of function, and then you also included quality of life, and I'm surprised to see that there's very little data about quality of life that most of this we're talking about is improvement in pain.
- Teresa Rogstad: Yes. There was a fair amount of data regarding physical function, so the function of the knee, but in terms of overall functional status or quality of life, that has not been well studied and where it has been, the differences have been negligible or small.
- Marie Brown: Okay.
- Michael Souter: Yeah, if you look at page 60 of the evidence report itself, at the bottom of page 60 it gives how the pain and function changes were scored.
- Marie Brown: Could you speak a little more clearly in the mic? We couldn't understand you.
- Michael Souter: Oh, I see. Okay. I was just saying if you look at the bottom of page 60 under pain and function changes.
- Craig Blackmore: 60 of the actual report?

- Michael Souter: Of the actual report. It says pain and function change scored differences at follow-up that favored viscosupplementation but they were small.
- Chris Standaert: Another couple of questions. Did you, so in terms of the, when we talk about osteoarthritis of the knee, but osteoarthritis of the knee is variable. So, I know it looked at like an AETNA policy that specifically excluded patellofemoral coverage for example. They don't cover patellofemoral osteoarthritis. They cover, I assume, tibiofemoral osteoarthritis, and the Kellgren-Lawrence stuff does not really, the stuff I read does not really talk about which compartment we're talking about, but are we, these studies are largely... are there studies that specify whether they're talking about patellofemoral osteoarthritis versus tibiofemoral osteoarthritis?
- Teresa Rogstad: I don't recall coming across any discussion of that. I can flip through some studies and see if I find that. I don't recall that information was provided or that there was any analysis according to that.
- Chris Standaert: And my other question was on, we had a lot of comments about medication stuff. Is there, I know there are a couple of studies that excluded the use of NSAIDs during the study trial, but are there studies that really look at effects on medication use of doing the viscosupplementation, so a study that looked at three months out, six months out, a year out, medication rates, self-administered medications.
- Teresa Rogstad: The randomized control trials did not tend to look at that, but the case series that we found that was published in 2011 did show that NSAID use went down, you know, in a before and after comparison.
- Craig Blackmore: Without a control group, is that right?
- Teresa Rogstad: Right, right.
- Richard Phillips: I have a question about getting into these trials and the severity of the osteoarthritis, I did not see anything there that really provides anything about the stage or the disease. In other words, when somebody comes in with pain, my biggest question would be, well, what level of disease is there? If there is severe disease, maybe I would just go to the orthopedic surgeon and have a knee replacement, but is there, is there a way in which this is defined, which way you go with therapy, and I didn't get that from the studies that it indicated that. It just sort of said, well you have osteoarthritis.
- Craig Blackmore: So, maybe, maybe we could ask our clinical expert to comment on A) the relationship of the Kellgren-Lawrence scale to symptomatology, how well it relates, since that seems to be an inclusion criteria and sort of where arthroplasty fits in, in terms of Kellgren-Lawrence and severity of disease. Is that, is that sort of what you're getting at?

- Richard Phillips: Well, you hit the nail on the head, 'cause I was gonna ask for the, our clinical expert, but I was wondering if there is anything in the research, the literature, that's...
- Craig Blackmore: Okay, please, because I didn't mean to...
- Richard Phillips: No, and I'm happy to have him respond now, if he would.
- Howard Chansky: Sure. So, Kellgren-Lawrence and other scales we use, Macon scale, they are more frequently used by rheumatologists. Typically, orthopedic surgeons combine our sort of innate sense on the severity of the radiographic findings, but really, more importantly, when you're considering somebody for total joint replacement, you know, you're not really treating x-ray findings. You're treating the symptoms, and all of the scales, you know, they somewhat correlate with the severity of clinical symptoms, but I think everybody that sees patients, you know, whether it's primary care, rheumatology, orthopedics. I mean, we all know that there is not a great correlation between radiographic findings and pain severity for reasons I don't think anybody is certain of, whether it's related to the degree of inflammation, you know, in that particular patient's osteoarthritis. Does that answer your question?
- Richard Phillips: Well, I would ask maybe, maybe you could answer, is it true that bone on bone, for example, is a strict contraindication, for example, to using these kinds of therapies, or is indeed there a role for it? And I guess I'm trying to figure that out, you know, where this fits in, if at all.
- Howard Chansky: Yeah. So, I think that's a clinical opinion question and I think, again, most of us would agree that when a patient has bone on bone arthritis, there is probably no medical treatment that we have available that, you know, significantly alters their symptoms. You know, you can try on loader braces, canes, nonsteroidals, intraarticular steroids, but when I'm counseling patients that come to me with bone on bone arthritis, they typically have already failed those more conservative measures, and I will tell them, you know, I'll try anything you want, but my gut feeling is it's not going to work, and if you're healthy enough and there are no medical contraindications to surgery, you're probably gonna be best helped by joint replacement.
- Kevin Walsh: Just to follow up on Richard's question, then. If you were... if an orthopedic surgeon was looking to stratify patients within a research study, are you saying that they wouldn't use these scales? Or, I mean, how would you, you know, what would you use as a comparator of the level of disease?
- Howard Chansky: So, I would, I would first say that, you know, I am not an expert in clinical study design, but the important things for me, you know, we have to have objective criteria and there are pain scores. There are the, you know, evaluations of the radiographic severity of the arthritis. In my particular practice, this is purely anecdotal, but I have convinced myself that patients that have a greater degree

of rest pain, I think, have a greater component of inflammation and, in my opinion, those are the people that might actually get some long-term response to intra-articular steroids or nonsteroidals if they can take them, and I think that the patients that actually have more of a component of activity-related pain may be the people that are more likely to respond to viscosupplementation, but again, that is just my gut sense, not based on any data.

Richard Phillips: Dr. Chansky, I was just curious, what criteria do you use on selecting a course of treatment? What are the spaces between the injections and what criteria you're using to decide on the next, you know, the next procedure. Is it done basically on pain, or is it done on function or some other criteria?

Howard Chansky: Yeah, I mean, I, you know, as these studies do, I think it's harder in a clinic visit to get a sense on somebody's quality of life, you know? The most direct, I think, most important thing to people is reducing pain. So, for me, again, the decision on, you know, how often I'm going to treat them whether it's viscosupplementation, intraarticular steroids, or surgery really depends on what their relief... what their improvement was with the last treatment I gave them. If it doesn't work, you know, move onto something else. If we sort of run out of options, and again, they're a reasonable surgical candidate, that's when I would do surgery, but I counsel patients, even for total joint surgery that the surgery is primarily designed for pain relief. There are definitely functional improvements. There are quality of life improvements well documented, but the main predictable thing is improvement in pain. So that's, that's, you know, what I would typically go by with a patient.

Richard Phillips: Thank you.

Chris Standaert: I had another question. If we talk about the issue of osteoarthritis and severity and all this sort of thing and age and how, where these things, whether they may or not play a role. So, if you had somebody whose 50, it's not always easy to tell why their knee hurts, either by MRI or x-ray or whatever, because they don't... by 50, they often don't have normal anything. So, I'm pretty close there myself, I'm casting aspersions on my own peers.

Howard Chansky: Close on the high side, right?

Chris Standaert: Yeah. So, did these studies talk about how they really defined osteoarthritis and how they identified the patients that they really use in the RCTs? So, in these larger RCT's, if we go back to sort of the... the bigger RCTs, how they define their patient population. How do they define somebody who's having osteoarthritis knee pain? Is it generic knee, is it knee pain with some changes on x-ray, and that's the definition? Is it some other clinical definition or criteria they have to decide that really is the problem so we know who we're talking about?

- Teresa Rogstad: Well, where that was, part of the enrollment criteria, it was usually something like grade 2 to 3 on the Kellgren-Lawrence scale or radiograph. Some studies said radiograph evidence of osteoarthritis.
- Chris Standaert: Just that with knee pain?
- Teresa Rogstad: With knee pain.
- Chris Standaert: Yeah, that's like everybody. Yeah, that's like everybody over 55 years old.
- Marie Brown: Well, these are probably people with knee pain.
- Teresa Rogstad: With knee, with knee pain, right, right, and evidence of osteoarthritis in the knee.
- Chris Standaert: Right.
- Teresa Rogstad: I also wanted to say something else in response to your question about the use of NSAIDs. There were three sources of evidence showing that gastrointestinal events were lower in hyaluronic acid arms, which implies that there maybe was less NSAID use, and then in one of the pragmatic trials during this study, they did find that 79% of the patients in the usual care alone group used NSAIDs compared with 65% in the group that got the hyaluronic acid injection.
- Craig Blackmore: That was before, after, or both?
- Teresa Rogstad: That was during the study. So, they followed patients for a year, one group had access to usual care. The other had access to usual care and hyaluronic acid injection if they wanted. So, during that year, the group that had access to the hyaluronic acid injection had a somewhat lower use of NSAIDs.
- Craig Blackmore: But again, is that a change or is that a difference in base line...
- Teresa Rogstad: No, it doesn't represent a change. It's just during the study period.
- Craig Blackmore: But is that...
- Teresa Rogstad: I mean, I don't know...
- Craig Blackmore: Were they like that before they got the injection or were they like that after the injections or both?
- Teresa Rogstad: That I don't know.
- Craig Blackmore: Yeah.
- Teresa Rogstad: It's not reported.

- Chris Standaert: We also have no idea if they're taking it for their knee or their shoulder or their back or their something else, too.
- Teresa Rogstad: Right, right.
- Richard Phillips: I thought some of those randomized control trials did not allow the use of NSAIDs.
- Teresa Rogstad: Right. The placebo, a lot of the placebo-controlled trials did not. This was the compared with usual care trial that I was talking about.
- Richard Phillips: Okay.
- Michelle Simon: I have one more question for the clinical expert. So, where are we at with joint replacement for the knee? What's the expected life of that these days and what is... what does it entail to get a new one?
- Howard Chansky: So, the, I'm not sure I understand the second half of that, but, the answer to the first question. So, there are, you know, now good national registries, particularly in Europe and we often, you know, are referred to the Scandinavian registries, and probably the biggest advance in total joint replacement in, you know, the last 20-25 years is the quality of the plastic, the polyethylene, we have, you know, our bearing surface. A new, well-done total joint replacement, whether it's a hip or a knee, I will tell patients that they can, in general, expect that starting at about postoperative year five to fail at somewhere around 1% per year. So, even at 20 years, you know, you're expecting at least 85% of those implants to still be working. I mean, that's affected by age, you know. Youthful patients have shorter longevity of their implant, obesity, but in general, at 20 years 85% or so survival.
- Michelle Simon: So, can we expect the patient, in their lifetime, to be able to get two or more knee replacements, or is that not reasonable?
- Howard Chansky: No, it's not necessarily a good thing to have your second or third joint replacement. They get technically more difficult to give the patient a good result with your revisions, but certainly, I think any busy total joint surgeon and major centers, you know, there are patients that have had five, six, even seven revisions, but at some point you exhaust those possibilities, but maybe what you're asking, you know, has the age at which we're willing to give people joint replacements decreased, and, you know, it has. I mean, the literature bears that out and, you know, again, if you ask the other orthopedic surgeon or surgeons in the room, I'm sure they'll tell you that we are, you know, gradually dropping the age, and for me, that is particularly due to the quality of the implants we have now, the polyethylene we use.

- Joann Elmore: I have a question for our clinical expert. What is your perspective on the definition used in these studies defining clinically significant differences given some of these scales that are used?
- Howard Chansky: I would ask you to be a little bit more specific and maybe I'd ask Terry to just refresh my memory at what they were.
- Joann Elmore: On 100-scale, a change of 20, is that clinically significant?
- Howard Chansky: Yeah.
- Joann Elmore: The change of 36, clinically significant?
- Howard Chansky: So, as I was reading the review and then some of the primary articles, you know, that is the question I had myself and, again, I am... I am not here as an expert in, sort of, clinical study design. It, you know, all I could go by was what those studies reported as being their meaning, you know, meaningful clinically or minimum clinically important difference. I don't really have any, you know, independent opinion. I would just go back, again, and say, you know, for treating patients, it's basically when they tell me that all the things I have at my disposal have left them with night pain, you know, they're unable to do their jobs, unable to take care of their families and the risks of the treatment are worth it to them. So, ultimately, it's that sort of global picture that I use.
- Joann Elmore: Does our vendor have any comments on that? On the definition of a clinically significant difference in pain?
- Teresa Rogstad: Well, those definitions are based on some empirical research where they, you know, and I'm not an expert on the methods of validating these kinds of scales, but there is some empirical evidence to support the fact that it shows an association between a 20-point improvement and some other measure of patient satisfaction or improved function or whatever.
- Marie Brown: Right, so these are not patient evaluations of their improvement, the significance of their improvement, it's a statistical evaluation to talk about clinical significance.
- Teresa Rogstad: Right. It's not the patients saying I had significant benefit. There is some objective measurement of whether or not it makes a difference.
- Howard Chansky: I would just add that when these studies are designed and they come up with this scale, though, that is based on sampling large groups of patients and asking them, you know, what constitutes an important difference.
- Chris Standaert: I mean I think that...
- Teresa Rogstad: Self-reported objective, right.

- Chris Standaert: The terminology is tricky. I mean, there's the MCID, which is the numbers you put out, minimal clinically important difference, which you had numbers ranging from 10 to 20 to up to 30 or whatever and maybe 30% instead of an absolute number of 10 to 20. That is not the same as clinically significant, though not the same as a patient's perception as significant. There is minimally clinically important difference. That's the minimum. So, there are different, there are different terms for how people measure this and how patients measure it and perceive it.
- Teresa Rogstad; Right.
- Chris Standaert: And so then the only numbers we have that you put up and that people are referring to are the two MCID, which is the minimal, that's the word, minimal difference, minimally clinically important difference, as perceived by patients, but there are other phrases for what a patient perceives as substantially different, you know, substantial improvement. I think there are other terms out there, but I didn't see them in the report.
- Teresa Rogstad: Well, well...
- Chris Standaert: I don't know if that that helps, or no?
- Teresa Rogstad: ...the ORC definitions do differentiate between minimally clinical important difference, that's the 10-point improvement, and clinical importance at 20 points, and then substantial improvement, which was 50% from baseline, I think.
- Seth Schwartz: I just had one other question for our, I guess for our clinical expert. I was a little bit surprised, quite frankly, by the practice guideline recommendations based on the data that we've seen, how nice and particular and the American Academy of Orthopedics basically made recommendations essentially against using this product, and I'm curious what the perception is amongst orthopedic surgeons with that recommendation and whether that's taken seriously or what, how that's been handled.
- Howard Chansky: Yeah, so, so I can get censored if I say anything negative about those notes. So I can, you know, tell you my opinion on that and sort of the gestalt talking to my colleagues, but, you know, we all use viscosupplementation in our practices, but I would say we already, in my group at the University, you know, use them relatively sparingly. They are used typically in patients that cannot take nonsteroidals for renal disease, or they're taking anticoagulants, or they have cardiac disease. So, the Academy guidelines, I don't think they're going to push people, most people to say, oh, I'm never going to use them again. I think we will all continue to use them judiciously. Again, this is just my personal feeling. There are patients I am quite certain they help. I don't know how to predict in advance, you know, which patients will respond to it, but, you know, we see a

lot of patients. I think, as somebody mentioned in one of their talks, that cannot take nonsteroidals, cannot take Tylenol, you know. I have really liked intraarticular steroid injections. Not everybody responds to those, and I won't do them more than every four months. So, there is a population of patients who also can't have surgery for whatever reason that I will still use them, but I will use them sparingly, and the Academy guidelines, you know, they'll be in the back of my head, but it's not really gonna change my practice. I think my colleagues would pretty much agree with that.

Carson Odegard: I have a collateral question that goes along with this, because I was thinking the same thing that these Academy guidelines, had anything changed, I can't remember what they were before when we went through this process, of what the Academy guidelines were, but...

Howard Chansky: Well, they...

Carson Odegard: ...did anything change since the, you know, the last...

Howard Chansky: ...well the last, the last time they came out, it was basically a neutral recommendation. There was, you know, they thought the evidence wasn't sufficient to go one way or the other, and the thing that has changed is just, you know, some of the analyses and primary studies that we talked about today.

Carson Odegard: So, they have changed, just since those reviews? Okay.

Howard Chansky: Yeah. I mean, I think the last one came out in 2010 maybe.

Carson Odegard: Mm-hmm. Okay, thank you.

Craig Blackmore: So, if I, if I'm looking at slide 10 and if I understand this correctly, there have been four new randomized trials, basically, since we made our last recommendation, which was about 2010. So, I think the attention is focused on the meta-analysis, but there is more actual data if I'm reading this correctly.

Teresa Rogstad: Some new trials, you mean?

Craig Blackmore: Yeah.

Teresa Rogstad: Yes.

Craig Blackmore: I mean, since, everybody's talking about the new meta-analyses, and of course, if it's a new meta-analyses of the same trial, what's, you know, what's the big deal, but, tell me if I'm wrong, but it looks to me like there have been four new, or maybe three new, four new randomized clinical trials since this committee last looked at the question three years ago.

- Teresa Rogstad: Well, actually there has been a little bit more than that, because there have been trials published that did get captured in the Colen and the Rutjes reviews, but we didn't analyze them separately. The three on slide 10 are those that are not represented in any systematic review. I can either tell you how many new trials there have been, but it's less than half a dozen, I think.
- Craig Blackmore: Okay, so a handful.
- Teresa Rogstad: Right.
- Marie Brown: And they showed positive results.
- Teresa Rogstad: Yes, they did.
- Seth Schwartz: They showed positive results. They showed minimal positive results in pain, very little in function, little to zero in function.
- Teresa Rogstad: Qualitatively, they are not different from the conclusions of the systematic reviews.
- Craig Blackmore: And then I guess I would ask an expansion of that question and when looking at slide 16 in the Rutjes analysis, they did a sub-analysis on sort of the better trials, if you will.
- Teresa Rogstad: Mm-hmm.
- Craig Blackmore: The trials with larger sample size and better or adequate assessor blinding, and they found in those trials that the effect was even smaller and maybe when we take a break, maybe you don't have this off the tip of your tongue, but do you know if these larger sort of better trials are among the more recent, particularly ones since the previous guidelines or if those are older trials that haven't changed? Do you understand my question?
- Teresa Rogstad: I'll look...
- Craig Blackmore: It's a little confusing.
- Teresa Rogstad: ...I'll look that up, but I think only, maybe only one is a trial that's been published since the last, but I'll... I'll look that up.
- Chris Standaert: The Rutjes trial has an interesting table in it, Figure 3 in the actual document that has this whole plot of all these different factors they looked at, which I find interesting to look at. I have, I don't know if everybody else has, but it basically stratifies these things, and it shows you the relative sort of ranges of effect size based on different characteristics of a trial blinding, nonblinding, industry funded, no industry funded, and it has all these different things that were just

pretty interesting to look at. I don't know if you, you can maybe find that and put it up on the board maybe.

Marie Brown: That would be helpful.

Joann Elmore: I was impressed by that figure, as well. It basically showed when you add in methodological quality...

Chris Standaert: Everything goes...

Joann Elmore: The potential impact is lessened.

Chris Standaert: Right. Everything, every measure of a higher-quality study shifted to a lower effect size, but I don't know.

Craig Blackmore: So, I'm going to, it seems like this is a good time to take a break, and, so we'll take 15. It's 10:30 now. We'll come back at 10:45 and we can talk about maybe we can figure out if we can get that on the screen to share, or we can just have the committee members download, and we'll resume.

Alright, we are back in session, and we will continue with the committee sort of questions aspect of this. We are working on bringing up the actual tables from the Rutjes analysis. Hopefully, we'll have that soon. Are there any other questions from the committee members for discussion? Are you, are we still looking? We're still working on it? Can we help?

Marie Brown: I have a question for our vendor? Could you talk a little bit about, in terms of methods, the differences we would expect? I mean, we've talked about it already, between a group of studies that used as the sample responders and pragmatic approaching to sampling, as opposed to the placebo controlled trial? Or as opposed to other samples. How would a study differ if you looked at the outcomes based on before and after pain comparisons?

Teresa Rogstad: The difference between studies that reported results in terms of a pain difference and those that reported responder rates or the difference between placebo control and usual care control.

Marie Brown: The former. The former.

Teresa Rogstad: The former...

Marie Brown: Uh-huh.

Teresa Rogstad: ...comparison? Well, it, it's not either/or. It's just that some studies, in addition to reporting the main difference in pain score between groups...

Marie Brown: Right.

- Teresa Rogstad: ...also reported how many patients improved according to some definition of response, and I didn't deliberately look, but I'm not aware that there's something distinctive about those studies...
- Marie Brown: Okay.
- Teresa Rogstad: ...that reported response rates.
- Marie Brown: So, they had similar... if you looked at just the response, the before and after, they had similar outcomes when they did a subanalysis of that.
- Teresa Rogstad: Right. In terms of the mean differences in pain scores...
- Marie Brown: Yes.
- Teresa Rogstad: ...that were reported. They were similar to the whole body.
- Marie Brown: Okay. That was my question.
- Teresa Rogstad: I gotcha. Sorry, okay.
- Craig Blackmore: I guess I'm also a little focused on the responder rate issue, and I think we covered this a little before, but if you could help me understand. The trials that gave us response rates rather than sort of mean scores, were any of those trials in the high-quality end with... particularly with adequate assessor blinding?
- Teresa Rogstad: Yes. Some of them were. It would take me a minute to...
- Craig Blackmore: Right.
- Teresa Rogstad: ...tell you which ones, but yes, some of them were, and you had asked earlier if the trials with larger samples sizes and adequate assessor blinding were older or newer. They are dispersed over time.
- Craig Blackmore: Thank you. So, I'm looking at this for the first time, but presumably the dotted line is no effect and the blue on each side would be sort of where one has to be for clinically important difference.
- Teresa Rogstad: The shading represents the area of clinical equivalence, smaller than minimally clinically important difference.
- Craig Blackmore: Okay, and then the subanalysis is studies that either did or didn't conform to one of these quality measures. So, we could look at concealment of allocation. If it was adequate concealment, the mean is much closer to no effect than if there was inadequate or unclear concealment of allocation.

- David McCulloch: Six or seven dots down [inaudible] or blinded out [inaudible]...
- Craig Blackmore: Right.
- David McCulloch: ...adequate or inadequate. [inaudible] trial size. Small trials.
- Craig Blackmore: Can we scroll down?
- David McCulloch: Yeah, can you scroll down a little more? Stop, stop. Another thing is interesting that the fourth dot down, unpublished much closer to mean. We only had 14 published. I mean, most journals have a biased towards, they'll only publish it if looks exciting and positive. So, including unpublished data is a good thing if the studies were reasonably well done. Can you scroll down a little more?
- Marie Brown: What is crosslinked?
- Craig Blackmore: It's a different type of molecule that you're injecting.
- Marie Brown: Okay, yeah.
- David McCulloch: Thank you. That was helpful.
- Joann Elmore: While you have that up, why don't you go down a page to the adverse effects, figure four, and I think on here, I think a point can be made if you go down towards the middle of this. It was mentioned, oh, can cancer be an adverse effect, especially if it's diagnosed a month later, and I agree with that comment, but if you look here towards the bottom, it says any local adverse event in the injected knee, all trials and large trials with blinded outcome assessment, both of those favor the control and both of them are statistically significant. So, that has nothing to do with cancer or other adverse events that one might think, you know, how could that association even exist.
- Craig Blackmore: Any other questions or comments from the committee? Okay, well at this point, what we usually try to do is to ask one of the members of the committee or maybe more than one member of the committee to summarize where we are or not necessarily with a yes/no decision but more what the issues are and where the evidence is and use that as a starting point for discussion. So, can I ask someone to start us off? David?
- David McCulloch: I mean, I'm strug-, since I wasn't here in 2010 on the committee, my first impression, having looked at this objectively, I'm surprised that we voted for coverage with criteria back in 2010, because I mean, a couple of things are clear. Having a really painful knee is a terrible thing. The placebo effect is huge. I mean, you know, come in with a nice, big injection by some benevolent doctor in a white coat injects your knee. The placebo effect is huge, clearly statistically significantly you can move the effect size with hyaluronic acid, but those things struck me. The other thing that struck me, as I mentioned earlier, these studies

are a lot more careful to use patients who are not that overweight, etc. I think in clinical practice, again, the tendency to say these poor patients, I want to do something for them. I'll try NSAIDs. I'll try a steroid injection. I'll try a hyaluronic acid injection. I'll do another one. I'll keep going until the doctor says enough, replace my knee joint. I mean, so, all of this sort of emotional arguments and arguments about, I think you have to try and cut through that by saying where's the most objective data with unbiased observations of outcomes and then, I'm struck with by the time you do all that, it's a very trivial improvement in outcomes beyond placebo effect and some evidence of harms. I'm just surprised that this is something we would cover at all.

Craig Blackmore: I guess I would, I would just add one thing to that, and I think we always talk about placebo effect, but the other thing that we shouldn't overlook is regression to the mean. You're doing these injections when people are feeling their worst, when they've had a bad week or a bad month, and though arthritis is a condition where you have pain maybe all the time or maybe always when you're walking that the severity of the pain fluctuates, and we see that with all the sort of chronic pain issues that we deal with, and so one would expect the condition, on some level, to wax and wane, and we're gonna capture that as regression to the mean. So, again, I think it just gets at the idea that before and after doesn't work, as a measure. You have to have some sort of comparator group and then we can argue about what the appropriate comparator group is, etc., but I wanted to make that point. Does anybody want to speak to David's comments from the other perspective or have a different slant or different take on the whole thing? Seth or Richard?

Richard Phillips: Yeah, I was struck that the data that was presented to us really doesn't answer the questions I want to have answered and that is, let's just say we do not cover this entity. We don't cover the injections. Then, basically what you're saying to a patient is that this is no longer one of your options. When you get to this point, you can't use NSAIDs anymore. You have to have surgery, and that seems to me to be the wrong thing to do, because I think that it fits a role in there. We don't have the data. We're not comparing this technology versus surgery. That isn't what this was all about. We're basically looking at comparing it versus placebos and then getting the systemic reviews. So, the question that it's asking isn't the one that really hits me clinically. So, I have a problem, I guess, in canceling out the therapy based on the data we have, because it didn't answer the questions we needed.

Kevin Walsh: I'd like to respond to that. I take care of a lot of patients with this condition, and it's difficult. Whatever treatment you offer them, it's difficult. At best, they get some pain relief when they get a knee replacement, but if their BMI is excessive, the amount of time they're going to enjoy that replacement is limited. I don't think you're... I understand the question you're asking, but I disagree with it. I think the question we're being asked is, should we pay for this or not? Does it work or not? Not in the larger picture of the patient with the problem, gosh, if we take it away there's one less thing to offer the patient. While that's true, it

seems to me that the information that we're looking at says if this benefits patients, we can't demonstrate it.

Richard Phillips: Well, see, I disagree with that. I think it does help some people. The thing is, I don't think it's appropriate to offer this to somebody who needs a knee replacement, you know. As a person who needs a knee replacement, I would never take this kind of therapy, but I would say that I think there's a group of people that isn't defined by our studies that probably would fit in there that might benefit from it. I don't know if they have the most severe or least severe, but I don't see that, you know, and that's based on the data that we have. Some people get short-term benefit, and I don't know.

David McCulloch: Some people get short-term benefit with saline injections. Some people just get short-term benefit by coming in and having somebody do something whether it's regression to the mean.

Richard Phillips: Oh, yeah. I saw that in the data, too, you know?

Seth Schwartz: I'd like to respond a little bit to what David said, which I think, I think David gave a very valid point looking at this. I have a slightly different take on it, which is that I look at all these systematic reviews over all these different articles, and what we see fairly conclusively is that in the well-controlled trials, there still is a significant difference. I think there's some difficulty showing what's a clinically-important significant difference. So, that's the differentiation. There is a statistical difference. I don't think there's a lot of argument about the fact that the patients who got hyaluronic acid did a little bit better. The question is, is that difference enough to be clinically meaningful, and that's where I struggle a little bit with the lack of granularity in terms of looking at the variable patients, because when we look at the real-world question, so we have that for effectiveness, but I want to know what's happening in the real world, but when we look at the real world trials, they show a little difference, but they're bad trials. So, we discount that evidence, and we sort of have to. Then, I also want to know about separating out some of these patients. So, maybe the patients who really have less severe disease or who are younger may benefit a little bit more, and maybe those are the ones that have slightly more clinically important difference, but we don't know that data. That's the data that we don't have, because it's just not there. So, my sense of this is that I think there's a real benefit to this in terms of it does something. Is that enough to pay for? Probably not in all patients, but are there some patients where it may be beneficial? Maybe, probably, but I can't sort that out based on the data, and that's what I'm struggling with.

Kevin Walsh: And neither can the people who use the injection.

Chris Standaert: So, I think a couple of comments. One on Richard's point. I mean, I think in some ways the discussion of management of osteoarthritis of the knee has been overly distilled. When I talk to patients, it really isn't, well, I can inject you or I

can operate on you, or you're hosed. I mean, that isn't it. There are questions about activity modification and diet and weight loss and exercise and pools, or, you know, there's all sorts of other things you do to help people adjust to an arthritic joint that aren't, frankly, have not been part of the conversation at all or anything we've really heard, and that's an important part of managing these patients, and so the discussion really, it isn't really well I can inject you or I have nothing for you or you get a knee replacement. That's never the conversation I have. There's other things you talk about, and we didn't study...

Richard Phillips: I didn't mean to oversimplify that.

Chris Standaert: But it's been oversimplified the whole discussion. The whole morning has been oversimplified, frankly, and we didn't talk, we didn't hear studies versus exercise versus a rehab program versus appropriate activity modification, you know. We have somebody you just tell them, no, you can't do high-impact things. You don't go trail walking, you go walk on a treadmill. You get on a bike instead of out walking. We didn't talk, there's nothing like that. That's one comment. The other thing, when I look at the data, I'm sort of struck of what it says there. There does seem to be an effect, and the question in my head is, is it really worth it and if so, in whom, and can you find them in a way that's reasonable, and I, you know, we talked about this years ago, and this was a difficult decision years ago for me personally when we agreed to this. This was a difficult one, and this is one of the few that I had rattling in my head for three years for whatever reason, personally. That's my own personal take on it, and I still have that same conundrum that, well Seth, that you guys were talking about. Is it really worth it and can we find these people [inaudible].

Seth Schwartz: Is that what that rattle is in your head?

Carson Odegard: Well, I think we're kind of stuck with the same situation we had last time. You know, to answer David's questions, I mean, we were driven by data that was primarily the Bellamy review and Samson review and they clearly said it's effective. So, if we're talking about effectiveness, even though the margin was small and now we find that the margin is even smaller, as far as clinical effectiveness or improvement, we are still 5 to 13 weeks is 28 to 54% relative pain differences in the Bellamy report. So, it favored hyaluronic acid.

Marie Brown: I agree with Carson that we have, most of the time in our conversations with past decisions, we have talked about is there... does the data support that there's a positive, significant difference, and today it's, we keep forgetting that yes, the data shows there is a significant difference, and the discussion is more about clinical, is it clinically significant.

David McCulloch: I guess the data also shows that there is a statistically significant increased adverse events in all the proved data. So, there's a statistically significant small improvement that we're debating whether it's clinically significant, and there is also an increased risk of adverse events. So, we're paying for this?

- Seth Schwartz: Can we talk a little bit more about that adverse events thing? Because I mean, that's kind of why we're here right now. We're talking about this, and I'd just say, I wasn't struck by, or convinced that there was really any significant additional risk to doing this over conventional therapy. So, if we, you say that there's a statistically significant difference, but that seems to be kind of has been discounted based on what was included in the calculation of that. So, I'm just curious if anyone has any other perspective on who was convinced by the safety data, because I wasn't convinced by the safety data that there is any significant risk there.
- Joann Elmore: That's why I asked that figure 4 be put up on the screen, because when I heard comments about oh, a cancer diagnosis a month later, how could that be related to injecting the knee? I would agree with that question, and I would like to look at the data. So, I ask that figure 4 be placed up on the screen in that they showed all 'serious' and who knows whether a cancer is really associated with it, but they also showed different types of outcomes, and one of their outcomes was local adverse event in the injected knee, and that was statistically significantly increased with this agent compared to controls, both in all trials, as well as the higher quality larger studies.
- Chris Standaert: The safety stuff, some of what they talk, I mean, the cancer thing is tricky. Three months cancer stuff, but they talk about cardiac events, you know? Maybe there's something we don't know. Cardiac events are an acute issue. They're not... that could be from an acute intervention. It's hard to walk by that one. If you kept seeing it, if I kept seeing that over and over again, I'd have trouble walking by it. Seeing it once, I don't know. And these issues of joint inflammation and, I hadn't heard the term pseudosepsis. I'd seen this before. I had a patient who had this happen. The whole knee swelled up and worried about infection and ER visits and all this... you have to do all this stuff when that happens, because they get an acute inflammatory reaction of the knee, and you can't tell they're not infected very easily, and that's a real phenomenon. I have... the number..., data on frequency is really hard to come by, because people aren't really reporting... a lot of these studies aren't reporting complication data very well, which is a problem, but I mean, that is a real phenomenon. It does happen and it is a bad thing, short-term anyway.
- Craig Blackmore: I think for me, it all boils down to whether it really works, and we've heard sort of both sides of that and I still think we're, we're a little, we're a little hooked on the statistically significant versus clinically significant, and looking at a P-value and saying this works, I struggle with that, because the minimal clinically-important difference is the minimum difference that a patient would care about. So, if somebody is having less of an effect, then that means it's not something a patient would care about, and so, why do we care about it? But the flip side of that is, these are average effects.
- Joann Elmore: Right.

- Craig Blackmore: And so an average effect of 0.1 might mean one person had 0.5 and everybody else had zero. So, this is sort of Seth's point, you know? Is there a minority of people that we can't identify who had a clinically important difference, and that's why, overall, we see a clinically unimportant difference, meaning no difference, and I don't have an answer to that, but that, for me, is the struggle.
- Seth Schwartz: This seems like familiar territory, and what I'm struck by is the fact that the people who do the research don't click to the fact that maybe it would be helpful to do this kind of research when there's minimal difference, to find, to further delineate what specific subgroup of patients might respond more favorably.
- Chris Standaert: And that's where my question before about sort of the cause of knee pain and the measuring away and looking at x-rays is really not so easy, and how you, even in my own head, how do you define these. How do you distinguish it so that everybody whose 50 whose knee hurts for, you know, a month or two who has a 50-year-old knee on x-ray, do they all, I mean, is this what they should all get? It's, that's difficult for me to say, and the data doesn't have, you said nobody, I don't understand why people aren't sorting through it either trying to find responders and relative risks and different things and all that. That would be very helpful. Increased granularity would be very nice if we had it. I completely agree.
- Marie Brown: It sounds like that's what our clinical expert opinion said was, if there was a subgroup of people who responded, but he couldn't predict who they were.
- Michelle Simon: I don't think the data we've seen since our last review on this topic persuades me that we need to completely revamp what we thought the first time. I don't think the safety data, really, given the discussion we've had here, suggests that this is something very dangerous. It doesn't seem like the utilization is extreme in the state, looking at the agency data. They say that their cost concerns have actually come down, since the last time we reviewed this topic. It seems like there is a subset of patients in which this is a useful, according to our clinical expert, procedure if they can't stand corticosteroids or, you know, have blood thinners or something, and the safety data on corticosteroid injections, as well as on NSAID use, no one's talking about that, but good grief, that's not wonderful either. That profile is quite concerning. So, I think for me, I think it's something we do need to consider and look at maintaining availability with the state people.
- Craig Blackmore: I struggle with that comparison, too. I guess if we had alternatives that were perfectly safe, this would be easier, but in my mind, the question isn't really how bad are the alternatives, it's are we doing any good, you know? I don't really... there's no point in having it if it doesn't work whether the alternatives are good or bad become sort of irrelevant. So, I mean, it, it still gets down to that, that same decision we were having. We're giving people another option,

- but if we're giving them another option that's not doing anything, why are we giving them another option?
- Chris Standaert: It may be safer than NSAIDs, but if they're still taking NSAIDs anyway, then it didn't really get you very far.
- Michelle Simon: But it sounds like, in some of the studies anyway where they actually looked at that, there was decreased use of NSAIDs. Now, whether that's attributable to knee pain or some other pain, I don't know.
- Chris Standaert: Yeah, there's just that one study, but it wasn't even a decrease, it was just a relative rate.
- Marie Brown: What...
- Chris Standaert: So, the question of NSAID use...
- Marie Brown: ...I didn't hear.
- Chris Standaert: ...you said there was one of these.
- Teresa Rogstad: Oh.
- Chris Standaert: The, the sort of...
- Craig Blackmore: Not a, not...
- Chris Standaert: ...nonrandomized in...
- Teresa Rogstad: Case, case series, yeah, before and after.
- Chris Standaert: ...case series. No, you didn't give us, you gave us comparison data. You said that, you looked at two different arms, the arm that got the injection. This is the in-practice group.
- Teresa Rogstad: Oh, oh, the, right...
- Chris Standaert: [inaudible] other, but nonrandomized, noncontrolled injectable end group not the other. They weren't blinded, anyway.
- Teresa Rogstad: And that was...
- Craig Blackmore: And we don't know...
- Teresa Rogstad: ...during the treatment.
- Craig Blackmore: ...what they were anyway.

Chris Standaert: Nonrandomized, yeah.

Teresa Rogstad: They were, it was a randomized trial, no blinding...

Chris Standaert: They weren't blinded, right.

Teresa Rogstad: It was NSAID...

Chris Standaert: Sorry, I correct that.

Teresa Rogstad: ...use during the study.

Marie Brown: During the study.

Chris Standaert: Right.

Teresa Rogstad: And it, it did show decrease.

Chris Standaert: But they didn't give us pre-injection NSAID use and post. You gave us...

Teresa Rogstad: Right.

Chris Standaert: Right. So, we don't know...

Teresa Rogstad: So, we don't know if it changed.

Chris Standaert: We don't know if it changed.

Teresa Rogstad: Right, right.

Michael Souter: I tend to agree with Michelle, that I'm not persuaded that there's a great deal of data to persuade me one way or the other from where we were before. You know, I look at the Rutjes report, and to be honest, I find it a little bit conflicting in itself. It talks about, you know, the serious adverse events in one sense. It talks about the other adverse events in another. It then talks about, you know, there being insignificant differences when you look at, you know, to try to nail that down in a little bit more detail. The... and it's a meta-analysis, and, you know, meta-analysis is only a sum of what you plug into it. It's an imperfect tool in itself, and I think we have to be cautious about that. The, you know, there are some more randomized controlled trials. I like trials that, you know, have got some pragmatic base and there are concerns about the two openly pragmatic trials. There is another one just on flipping through the evidence tables there, the [inaudible] trial, which was actually double-blinded and is, you know, actually assessed as more likely to be more like a pragmatic trial, just because of the way they have structured it. They included repeat injection of any active treatment of one year. So, that makes it more like an effectiveness

trial than an effects trial, and you do see, you know, reports there in terms of improved pain.

Seth Schwartz: But they didn't compare, they didn't compare the saline group when they reported the improvement. They only reported improvement in the group that was treated.

Michael Souter: No, I thought the important... they compared it with the saline group. I mean, it was, you know, there was the combined and there was the other mixture of the molecular weight groupings in there. The saline group discontinued the study at 52 weeks. They still... I thought my reading of that, that they did actually talk about that being, they did compare the groups, I thought...

Teresa Rogstad: Um, I actually mis-...

Michael Souter: ...but none, nonetheless, it's just, sorry...

Teresa Rogstad: ...oh, finish, go ahead and finish.

Michael Souter: ...no, carry on.

Teresa Rogstad: I...

Michael Souter: Were you going to say something about...

Teresa Rogstad: ...on a different point, so go ahead and finish.

Michael Souter: Okay, so anyway, I've... I think that we were not talking about making this available to anybody and everybody. We're... we put limitations on its use previously that you actually had to have a failure of conventional therapy. I think that was appropriate. I still think it's appropriate. If there are benefits there, then let them be proven in the patient groupings by seeing them fail the conventional therapies and then see whether or not this gets any improvement. If this does not display an improvement, then we're not allowed to, or rather, the practitioners aren't allowed to go in and repeat it on the basis that another dose might improve it. I mean, those were the limitations we put on there before. So, I'm... I'm thinking that we just stay with where we are.

Teresa Rogstad: I just needed to correct something I said earlier about change in NSAIDs use in that pragmatic trial. I just realized there were baseline data. So, in the group that had access to hyaluronic acid injection, they went from about 94% using NSAIDs to 65%, and in the usual care alone, it went from about 84% down to 79%. So, there was a change. Sorry about that.

Seth Schwartz: Michael, I just want to, look at page 111 of the study at the bottom.

Michael Souter: Mm-hmm.

- Seth Schwartz: It talks about the [inaudible] Study and in column four, the improvement in mean walking pain, saline is not listed as one of the modalities that's compared. It's all the different molecular weights of hyaluronic acid products that are compared. While it was a good study, they had an N of 200 and the saline group was 50. I mean, it wasn't an equal group, 150 and 50, and it didn't even look at improvement in pain in the saline group, so there's not a comparator.
- Michael Souter: Well, I'm reading it differently. I'm looking at improvement to mean walking pain and differences from baseline were significant for all hyaluronic acid groups. Outcomes of saline group was NR. What's NR? Not reported.
- Teresa Rogstad: But remember, there could be a placebo effect, and there could be regression to the mean.
- Michael Souter: Yeah, but it's a long placebo effect, though, 52 and 104 weeks.
- Joann Elmore: As a clinician who cares for patients with terrible knee pain, I do want to help them, and I don't want to hurt them. As a scientist who does clinical research, I want to rely on good quality data I can trust. I have four points after listening to the presentations today and reviewing the material in advance. The first is, the placebo effect is truly remarkable. When you look at data from 11 randomized clinical trials that were placebo, double-blinded, double-blinded randomized clinical trials, more than 4,000 patients, the placebo effect ranged from 27%, so one out of four got better with placebo, to 68%. So, more than half got better on the placebo arm. So, number one, this is impressive, this placebo effect.
- Number two, I don't know what to really make of the risk data. I think that it looks like it's slightly higher, you know, what is a local reaction in the injected knee, but it does look slightly higher. You know, we do need to, first, do no harm. So, I'm not certain that's weighing heavily on my mind at this point, but there was data, especially in the larger studies, that there was slight increased risk, at least of problems at the local injection site.
- The third point has to do with quality of the studies, and this, I found concerning in that, when you look at the results, almost everything shifts to less statistically significant, less clinical significant. When you pull out quality metrics, such as, only look at the larger size or only look at the sham, or only look at, you know, double blind. That, to me, I think is important, and we need to pay attention to.
- The fourth and final point is something that I don't have an answer, and it worries me, which is, will this help my patient? I want to help my patients. I want to give them a clinically meaningful improvement and I have not seen that from the data, because the data defined used these scales and while there may be a statistically significant difference, things are still in that grey zone, according to the investigators and scientists who have said, in talking with patients, how much of a movement on this little research scale is important to

you? Will you even notice this, and while most patients would want an even bigger movement, some have defined this, you know, 20-point movement as something that at least would be relevant to the patient, and we did not see that in these studies, and that worries me, and I think, Craig, you articulated this the best in that I want to support technology that is beneficial to the patient and that will help my patient, but according to some of these summary results, there are no overall clinically meaningful improvements for the patients, if I'm interpreting this correctly, and Craig can you follow up on that?

Craig Blackmore: I mean, clinically, minimally-clinically important difference is the difference that makes a difference to a patient. Below that, it is not either identified by the patients as present or that it's not enough for them to care, and that's minimal. So, that would mean saying, alright, that's a little bit. That's not a big help. That's a little bit of a help, but I can sense that, and what we're seeing is a range from the different societies and the different research panels who have tried to look at it, but the results that we're seeing, particularly the results of the better performed studies, are below what a patient would notice. So, we say this thing works, what does it mean for it to work? Certainly, it does not work for the patients if it's not clinically important to them, but it works for the statistics. So, on average, I would say the data tells us that it does not work, at least from the standpoint of the patients. That doesn't answer the question of, are there are a few patients out there, and we don't know who they are, that might benefit, but on average, it's a clinically unimportant difference. At least that's how I would interpret it.

Chris Standaert: It's sort of tricky. I mean, the last time we said this. We used the criteria failed conventional therapy. It's a very vague term. Is that Tylenol? Is that somebody that said I took Advil? It didn't work. I mean, that's sort of what you hear, but would that qualify? That's very vague. But then, we had a conflicting thing. I think we said patients had to be considered candidates for knee replacement, which, mostly, is actually the study data that we're looking at. Most of the severe osteoarthritis, the category 4 are the ones that are going... they are the bone on bone who are going to need...

Michael Souter: No, we didn't say [inaudible]. We just said knee replacements.

Chris Standaert: We said candidates for, didn't we?

Craig Blackmore: No, I don't think so.

Chris Standaert: What did we say? Where is it?

Craig Blackmore: Number of courses and [inaudible].

Michelle Simon: We did, and the discussion had always been that this works better, as we understood it, in mild cases.

- Chris Standaert: Yeah, yeah. I guess I struggle with how to define these people in whom it might work in, and if you can't define them, do you define a population where this would be the best choice for them, because other choices are bad? They're on Coumadin. They're on something else. They have heart disease. They can't have surgery anyway. They can't... we always have these outliers in our medical group, but then you can't tell which of them would respond to this, which becomes the problem, if any.
- Michael Souter: Yeah.
- Chris Standaert: And our data hover around, they hover around that MCID. They're not clearly passive. In all... when you really... this thing of distilling it down to better studies, you drop clearly below it is troublesome to me. There's an effect there, but it gets very small when you look at very well-done studies, the more well-done study.
- Kevin Walsh: I'd like to just make a response to one of the things that Michelle said. It doesn't look like much money. I agree. It's \$8 million a year.
- Craig Blackmore: No, not quite. A million a year.
- Kevin Walsh: No, a million a year. Is that over a couple years?
- Carson Odegard: Yeah.
- Kevin Walsh: Oh, okay. I'm just thinking, in my patient population, I've got a large percentage of patients who are undocumented. The state used to have a program to provide cancer screening for those patients, but with the Affordable Care Act, it's going away. This could buy a lot of fit tests. It could buy a lot of mammograms. So, we're not, I mean, we can decide on what's the benefit of MCID, you know, for this subgroup of patients, but it's not like that's not a significant amount of money somewhere else in the health budget.
- Craig Blackmore: I guess I'll... I'll expand on what I said before, talking about average benefit versus benefit in a few individuals, and I said that, but remember that that's a theoretical construct. That what we're seeing, again, what my interpretation of what we're seeing is a small, not clinically important difference overall, which could be that there is a clinically important difference in a couple of people or a minority of the people, and it's averaged out to become unimportant, but that's a theoretical construct, and there's no evidence that that is the case. So, if that were the case, I could make an argument to pay for it, because I know at least somebody is benefiting, but I don't know if that's the case, and the evidence doesn't support that. So, again, I'm circling back to, therefore, I don't have evidence of effectiveness.

- Seth Schwartz: Craig, I'm struggling with that same thing, but I won't say that, I would disagree with you when you say there's no evidence, which I completely agree with that, that construct...
- Craig Blackmore: There's no good evidence, yeah.
- Seth Schwartz: ...but there's no good evidence, but I mean, but in the per... in the responder trials they did show a difference. So, again, that's worst data, I agree. Those studies weren't as well done, and you're trying to extrapolate. So, I don't know what it means, but I wouldn't say there's no data. I think there's some support for that concept.
- Craig Blackmore: I think that's fair. It's not clear-cut, at all. Anybody we haven't heard from want to chime in, if there is anybody we haven't heard from? Marie, do you have any other comments? Richard, you've been quiet for a while.
- Richard Phillips: This reminds me a lot of the TENS, the TENS decision we made where, you know, there it was only like \$75 per unit, and we voted against approving TENS because really, the evidence was very sporadic and it was plus/minus, and yet we all knew that there were individuals that had tremendous benefit from it and it's the same kind of thing, you know? We really don't have strong evidence one way or the other. I don't know if I have any, I really don't discredit what you've, what you've said. You said it very nicely, and I really agree that the effect could be explained a lot by placebo. For me, it's just a, you know, I think, I see covering this with a lot of restrictions, but it wouldn't hurt my feelings, you know, if we went the other direction on it, but maybe we ought to just get on with it.
- Craig Blackmore: We can get on with it. Anybody want to say anything else before we get on with it? Okay.
- Chris Standaert: I just don't want to hurt his feelings.
- Craig Blackmore: So, I think we're at a point now where we need to start to formulate some decisions and the way that has worked for us in the past is to sort of go through kind of a straw vote process and kind of narrow things down. I'm not voting yet. You can put your cards down, just to kind of go through kind of a straw vote process and narrow things down and then drill down. So, in this, we have three options: noncover, cover without limitations, and cover with conditions, and my sense, and please tell me if I'm wrong, my sense from the deliberation is that the committee is leaning away from a decision to cover with unconditionally. I want to sort of see if I can, in kind of a straw vote, put aside. So, is there anybody who... how can I phrase this? Nods of heads, should we focus on no cover versus cover with conditions? Does that seem like a fair way to go?
- Marie Brown: Yes.

- Carson Odegard: Agreed.
- Craig Blackmore: Okay. So, then the next thing that has worked for us is to talk about what those conditions might look like and use that as a framework to proceed to a vote, in this case versus no cover or cover with conditions. So, this is where we get...
- Richard Phillips: Well, Craig, I think if we have enough people here who want no cover, we've got it settled. We don't need to go through that step. So, don't we really... wouldn't it make more sense to go, find out.
- Craig Blackmore: I mean, that's the other approach, and I'm, I'm happy either way. Maybe, why don't...
- Marie Brown: Although it may change, I don't know if there's anybody that it would change their decision to look at what the conditions are. Sometimes that really does help with decision making.
- Craig Blackmore: It makes it tricky.
- Richard Phillips: Yep, fair enough.
- Craig Blackmore: It makes it tricky, and it goes both ways, you know?
- Marie Brown: Yeah, yeah.
- Craig Blackmore: You might be looking at the conditions and say no, or you might say yes, or...
- Marie Brown: Right, exactly.
- Craig Blackmore: Well, I mean, I think both approaches are valid. Maybe we will pick up our cards then and go through our tool and then get to the first nonbinding vote and see where that seems to lead us. So, the tool we use is our coverage and reimbursement determination analytic tool and the committee is very familiar with this tool. It describes the committee's charge. Is it safe, is it effective, and does it provide value and underlying principles. The determinations are evidence based. They result in health benefits, and we use evidence as the basis for the coverage decision and then also we reconcile our decision making with CMS national coverage decisions, as well as local decisions and societies and payers, etc. The first action piece in the tool is whether we have identified... is for the committee to delineate the outcomes that they deem important, and in my binder anyway, pages 6 and 7 are switched, just sort of for your information. So, on page 6, the safety outcomes that we're concerned about, and this is prepopulated, is there any safety outcomes we haven't talked about that need to be added to this? We talked about the concept of pseudosepsis. That is certainly a consideration, and under efficacy, effectiveness outcomes, we also talked about decreasing use of NSAIDs and, of course, narcotics, as well, as potential outcomes of interest. Okay, any other comments on that?

So, the next piece of this is the nonbinding brown cards, and this is, again, this is meant to lead to more discussion if we feel the need, and I'll ask the committee members to vote with their cards on whether the use of hyaluronic acid injection, tell us if there is sufficient evidence under some or all situations that the technology is more, less, or equivalent in effectiveness or if it is unproven. So, if you believe there is evidence that it is more effective under any circumstance, you should vote yes. Does that make sense?

Marie Brown: Under any circumstance?

Michael Souter: More.

Craig Blackmore: You should put more, I'm sorry, yeah. That's, under some or all situations. So, we will assign the more if you think it is effective under any situation, basically.

Josh Morse: Okay, I see seven more, two unproven, and two equivalent.

Craig Blackmore: Alright, and now, the safety issue. So, if you believe it is less safe under any circumstance, now, so it's the reverse, if you believe it is less safe under any circumstance you should vote less. Otherwise, you should use one of the other categories.

Michael Souter: Say that once more. If it's less...

Craig Blackmore: If you believe it's less safe under any circumstance, you should vote less.

Josh Morse: Eight less, three unproven.

Craig Blackmore: And then finally, cost effectiveness.

Josh Morse: Eleven unproven.

Craig Blackmore: Okay. So, in looking at sort of the straw vote, I'm not sure what's going to happen. So, I'm going to ask the committee, basically, to help me. We can either go straight to vote and then if conditions are chosen, decide on those conditions, or we can go to conditions now and then vote on coverage under conditions or not with the conditions predefined. Either way is... either way has merit. I'm just going to ask the committee which one they want and then go down that path. So, how many want to vote now? So, I think that was about seven. Okay, so then, we'll proceed to a vote and if the vote is coverage with conditions, we will figure out what those conditions are subsequently.

Chris Standaert: So, if we, I have a question of order. So, if we vote cover with conditions, have we accepted that as a vote, and then we have to define conditions, or could we vote cover with conditions, put the conditions up, and then if people decide they don't want those conditions and they vote against it, and so it, I mean,

that's what, we're voting for cover with conditions, but I don't know what I'm voting, if that's my final vote, I don't know what I'm voting for. So, I have trouble with that.

Craig Blackmore: Yeah, that, that's why, that's why I was asking the question, because...

Chris Standaert: If there, I guess if there is a majority that already know they're not gonna cover it, well it's easy, but if people are on the fence and we have cover with conditions and some may find them acceptable and some may not, that may shift the vote to no cover after we've already voted to cover with conditions, and are we screwing up our process by doing that?

Craig Blackmore: There, there is, there is no, the process is not predefined, and we have done it both ways in the past, and there are advantages and disadvantages to both approaches. If we vote now and then decide on the conditions, then the conditions we've come up with may have caused people to regret their vote on some level, right?

Chris Standaert: Mm-hmm.

Craig Blackmore: But at the same time, if we decide on conditions now, then that may cause people to vote... that means that the people that are sort of in the no-cover group are affecting the conditions that define the overall vote. So, that might push us into a different category altogether than we would be in the other way, if, if I've explained that properly. So, there's no, you know, I don't think there's an answer. That's why, and, and maybe after that explanation we should raise our hands again and make sure we still are where we were, because again, there's not, there's no preconception with this. So, again, do we want to vote first or not vote first? So now, see, it's changing. Okay, so now I'm seeing we're not gonna vote first. We're gonna decide, oh sorry, we're, we're redoing this because I want to make sure that people understood what we are doing, and I don't know that they did the last time. So, what we need to do is, give me hands if you want us to vote first and then decide on conditions, if indicated. So, a show of hands vote first. So, how many is that?

Josh Morse: Six.

Craig Blackmore: Half five, six.

Carson Odegard: Okay, because we had a split vote last time, seven to three last time, right? So, I can't remember if we did this... did we go over conditions first last time?

Chris Standaert: You know what, six is the majority.

Craig Blackmore: Six is the majority. I don't, I don't, we've done it both ways. I've done it both ways. Okay, so we'll vote and, right. So, this is, so based on the evidence about

the technology's safety, efficacy, and cost effectiveness, your choices are to cover unconditionally, to not cover ever, or to cover under certain conditions.

Josh Morse: Four no cover, seven cover with conditions.

Craig Blackmore: Alright, so the committee has decided to cover with conditions. Now, our task is to come up with conditions. I will ask Christine or Margaret to put up... if we could start, I think, with what we did last time for frame of reference and then we will... we will decide to keep or add or subtract. They are gonna work on getting that up there for us.

Chris Standaert: I guess I'm gonna say that I voted for cover with conditions so that I could see if we could come up with conditions that would make sense, but I still may switch if we can't do that. I don't know if we can do this. My concerns here, though, I don't think, frankly I don't think every 35-year-old with patellofemoral syndrome who has some demonstrable change on x-ray needs hyaluronic acid, and they're all going to have pain off and on forever, because their knees are bad and they're aging and their knee is going bad, and they have to manage it, but I don't think that's an indication to do this twice a year for the next 40 years, and, and I somehow don't think that should happen, and I think people, you know, this idea that if you can find the space where this fits well where it's worth the extra sort of intervention and invasiveness and everything else and cost and all that, then that's okay, but very blanket everybody under 65 with any sort of osteoarthritis and knee pain who did not do well with Tylenol, I don't quite, I'm not comfortable with that.

Craig Blackmore: So, what do you suggest?

Chris Standaert: I don't know. That's a good question.

Seth Schwartz: I guess I have a couple of thoughts here. I think one is, one of the ways we've handled this in the past when we have a sense that there is a chance there may, it may be beneficial under the circumstances are difficult for us to define. We've kind of left it up to, we've put more generalized constraints and then left it for the conditions to decide when to use it. So, that's one thought. In line with what was said with the previous coverage decision, I think it basically does that. It says, we're not going to, it's not going to be used egregiously. We're going to try and select the patients that included their other alternatives first and then if none of that works, then we'll leave it to the clinician's discretion to use or not use, which sounds like is basically what's happening in clinical practice, particularly given that their guidelines with some of these groups are helping to guide us to some extent.

Craig Blackmore: I don't... I don't think we know what's happening in clinical practice. I don't think we have any data on that, whether it's being used appropriately, whatever that is, used not used.

- Seth Schwartz: So, my second point is, so that's one perspective on what the limitations could, or what the, what the conditions could be. The other perspective is that there is this group where clearly the other alternatives are not an option. So, you have these patients who aren't candidates for surgery and aren't candidates for NSAIDs and aren't candidates for steroids for various other medical reasons and whom you basically have no other option. So say maybe that's the condition is patients in whom there is no other options, it should be at the discretion of the clinician to decide if this is something they want to use in that setting. So, in my mind, those would be the two different options for conditions. I don't know what the right answer is, but it's just where I would... how I see it.
- Craig Blackmore: Okay, any other sort of general thoughts before we try to drill down?
- Michael Souter: Our previous conditions relied on a filter being on patients who have not had an adequate response to known pharmacological conservative treatment. I think that's probably been unduly soft. I would like to kind of raise the bar a little bit there, and so I would actually, you know, change that to patients who have not had an adequate response to nonsurgical treatment and allow the intervention there of anti-inflammatory and appropriate group. I agree with Seth about injecting a caveat there so that condition would not apply to patients who cannot tolerate those kinds of interventions, but I think that we need to raise the bar a little bit from where it previously was.
- Marie Brown: And to emphasize what Chris was talking about is, there is a variety of other treatments that no matter what else you were doing pharmacologically, you want to work on these other issues, which are, people call the placebo effect, which I could the therapeutic effect.
- Michael Souter: But, I think if we... if we fall short of surgery, then I think that then leaves the, you know, leaves more scope for the practicing clinician.
- Craig Blackmore: I'm, I'm sorry. Say that again.
- Michael Souter: So, nonsurgical, instead of nonpharmacological conservative treatment, I would just change that to patients who have not had an adequate response to nonsurgical treatment.
- Craig Blackmore: So, who, who do you think, let me ask this a different way. Who, who should be getting this? Is it people who NSAIDs aren't working? Is it people who the NSAIDs are contraindicated? Is it people who, you know, are too young for surgery? Is it people who are too sick for surgery? I mean, can we define the group in whom we think there might be a benefit, meaning we can define the people in whom we don't think there's a benefit, and that would be our condition.
- Michael Souter: I think, well, at the moment I think, you know, you could actually argue for all of the above in those groups that you outlined.

- Craig Blackmore: And that, and that may be. I mean, I'm asking you what you...
- Michael Souter: And that, and that's the way I tend to think of it as a, you know, what I do want to do is to avoid this being used too egregiously, as was vocalized earlier on. I think, we don't want, you know, people to, for this to be too easy an option and standard. So, I think if, if you've got a failure of nonsurgical treatments, to me, that, that gives enough. You know, you could argue, do we need to be more specific than that? You certainly don't want it to be that you've tried Tylenol and it hasn't worked for you. There needs to be a little bit more than that.
- Craig Blackmore: Okay, other thoughts? Sorry, I'm kind of stalling.
- David McCulloch: I mean, with respect, Mike, I don't think, that's not a condition at all. It's putting words on a page that will make us look better. I mean, any patient and doc who want to do this says, 'oh, I've tried all the painkillers and I can't take this, and I can't do this and I can't do that. I just want the shot.' I mean, you can meet those criteria by just saying you meet those criteria.
- Michael Souter: But if you take that approach, then any of our conditions we have ever applied in any of our decisions will fail.
- David McCulloch: Well, and that's a generalization. We've had such much more specific conditions for other things. I don't, don't, I'd just say that's not really a condition. There's no way to define it other than the patient and the doctor agree that everything else hasn't worked, I want the shot. It's not really a condition. I can't tell from any of this data that we've looked at conditions that actually would define somebody that will benefit, so that's why I can't come up with anything.
- Marie Brown: I think our healthcare training is such that we don't... when someone says this hasn't worked for me, nothing has worked for me, that we're trained to do in-depth assessments of what that means. How much have you taken? When have you take it? So, I think it's less arbitrary than, I mean, I think we do assess what and why something might not be working and look to see if those... we can help the patient think of those ways... of other ways to make those things work.
- Richard Phillips: You know, I think that, I tend to agree with Michael's point there about the, expanding a little bit. I think it would be important to say it like the orthotic options, therapy, behavior modification like weight reduction. You know, if somebody doesn't achieve weight reduction as part of their therapy, it's hard to believe that they would be a candidate for hyaluronic acid injection. I mean, in other words, it seems to me it has to be one of the, the last alternatives in a situation where the patient is not a surgical candidate, and my personal thing is that the patient cannot undergo surgery either because of clinical condition, age, whatever, but probably meets criteria for it otherwise. So, I would like to think that it would be restricted to, you know, a set of people where, you know,

maybe it's, as our clinical expert mentioned, there's maybe a small number of people that maybe it will meet some goals. It's impossible to really predict who's going to achieve and who is not going to achieve, but I think it would be good to expand that talk to include the higher list with an expectation that hyaluronic acid injection only goes if you don't achieve those goals.

Marie Brown: I'd like to expand beyond the nonsurgical candidate, because I think a delay of surgery for two years or one year or six months is a worthwhile outcome for...

Chris Standaert: But we...

Craig Blackmore: But we, we have not seen any data. I mean, I know we were shown some slides by one of the... one of the speakers here, but I mean, there is no data that this delays treatment.

Marie Brown: Okay.

Craig Blackmore: The data that was presented was that patients who have a longer delay to their arthroplasty get more injections. Does that mean the injections caused the delay or they didn't want to have the surgery so they got more injections? I mean, you can't make any inference from that.

Michael Souter: Mm-hmm.

Craig Blackmore: So, I mean, we have no idea if this delays treatment.

Chris Standaert: One of the... some of the very frustrating things about the data we do have is, it does not include good data on timing of surgery and influence on subsequent treatment, and it does not include quality of life.

Marie Brown: Right.

Chris Standaert: And so, we have all this data on pain with this hovering little data point, but these bigger questions of, does it delay surgery, does it improve quality of life, does it improve health outcomes...

Marie Brown: Right.

Chris Standaert: ...we don't have anything, which is problematic.

Marie Brown: Agreed.

Michelle Simon: So our... our discussion right now is around conditions, I'm gathering. So, I don't feel compelled that we've seen evidence for us to really make a change in the decisions that we made in the past regarding this, and I think if we do we're guessing, because we don't really know, based on the evidence, who the perfect patient is for this. If we delay it and make it a very small group of people who

have failed absolutely every possible measure, then we're talking about people that probably have advanced osteoarthritis and this is probably a patient population, which it is not going to work very well in. So, I'm cautious about making those types of changes from our previous decision.

Chris Standaert: Our condition, actually, is the exact same language in the FDA indication for Synvisc, which must be where we got it, because it's exactly what that says, and, you know, if you're going to tighten these things, you know, typically with policies like this, you do things like months of treatment, you throw in specific things, you throw in exercise, activity modification, and you say behavioral, advice on behavioral modification. I mean, you throw in specific things and you throw in timelines, and that's the only way to really modify the scope of what you're defining as nonoperative care, and by switching to nonoperative, which even includes the idea that you could do a corticosteroid injection. That would be the big expansion of changing that language from nonoperative to nonsurgical.

Michelle Simon: Nonpharmacological.

Chris Standaert: Nonpharmacologic to nonsurgical, you get into injections, but is there a way to change this language so you can more clearly specify what you mean as what you... if you're trying to get at the... like Craig's question before, who, who is it? Who is the person for this? Is it somebody who has tried activity modification, has tried exercise, has tried safe oral medication, been compliant with it, just not done well, really not bad enough to be thought of for a total knee yet but is hampered by this in a way that's functional. Is that the person in whom you try it?

Craig Blackmore: See, I...

Chris Standaert: Logically, I think of it that way, but I don't have the data to tell me that's it.

Craig Blackmore: I would argue it completely differently. I would say, the benefit here is basically the same as all the other treatments. If there is a benefit, it's the same as placebo. It's the same as NSAIDs. It's the same as anything else. So, the only people that I would make eligible for it are the people that can't get NSAIDs and that can't get... maybe can't even get surgery, the ones in whom the other treatments that are equally effective can't be used, and then we need to offer them something and we're not sure this works but, you know, at least they get the placebo benefit, and, and I would make it, I mean, obviously I voted no cover, so I'm not convinced by the data, but I would make this restrictive and I would say, look, you know, maybe if we can't give them NSAIDs, because, you know, they have gastric bleeding or whatever it is, kidney problems, then this would be an option, but if they're eligible for these other things that work as well, they should do those.

- Seth Schwartz: One of the things we've done before when looking at this, we looked at what were the, you know, debating whether the trials really showed effectiveness but, you know, since we're here they must be, you know, at least some of us think that they do. We've looked at what were the entrance criteria for the trials. So, maybe we should ask our evidence vendor, you know, was there anything beyond just knee pain and radiographic evidence of arthritis that allowed these patients to be entered into these trials?
- Teresa Rogstad: No.
- Seth Schwartz: Did they have to have, you know, trials?
- Teresa Rogstad: It was typically a minimum pain score and evidence of osteoarthritis. There wasn't anything like they've tried...
- Chris Standaert: Did they have an age range?
- Teresa Rogstad: ...six weeks, weeks of exercise or three rounds of physical therapy or anything.
- Chris Standaert: Did they have an age range? Did they say over 50, over 40, people, they'll take all comers? They'll take 30-year-olds, they'll take 70-year-olds?
- Teresa Rogstad: They were generally all adults. I would have to check that out. I'll double check on that.
- Carson Odegard: I have a question about the third point. On why we decided on that particular condition when isn't it, you know, are these courses done when there's no clinical benefit?
- Craig Blackmore: Well, they could be.
- Michael Souter: Well, it was to stop... it was to stop that very circumstance, if somebody...
- Carson Odegard: Yeah, I mean in...
- Michael Souter: ...continued to get injections...
- Carson Odegard: ...clinical practice...
- Michael Souter: ...on the vague hope that somewhere sometime one might work.
- Chris Standaert: I hate to be totally cynical but it's hard to imagine you haven't seen people who had ongoing care that has been absolutely futile towards treating their problem in any meaningful way, not necessarily harming them, but not really helping them either.
- Carson Odegard: Right.

- Chris Standaert: I see this every day in my practice.
- Carson Odegard: Sure.
- Chris Standaert: I don't deliver, I know, I hope, but I see it every day. I see people who have had it every day. So, I hate to be, but yet I'm sure that I would, you know?
- Craig Blackmore: And then the... I mean, the other question is, is that really a barrier?
- Carson Odegard: Yeah.
- Craig Blackmore: Looks good.
- Carson Odegard: Right.
- Michael Souter: I think it's a barrier.
- Joann Elmore: I've been quiet, because I don't feel that there's evidence to base the conditions upon, so I'm hoping that you all will come up with something that seems clinically reasonable, but I do want to point out that since the committee voted in 2010 with these conditions, there has just been a slight increase in utilization of the injections in PEBB and in Medicare. In other words, it didn't go down after 2010 per capita. It's gone up slightly.
- Michael Souter: Maybe that restricted it going up.
- Joann Elmore: In other words, it slowed down the usage?
- Michael Souter: Yeah.
- Joann Elmore: Oh, okay.
- Craig Blackmore: Any other thoughts?
- Marie Brown: I don't see any compelling reason to change what we have. I don't see any data to help us change what we have.
- Craig Blackmore: Okay. So, I'm going to... I'm going to... so one choice would be to keep this. I'm going to put an alternate out there and see if there's enthusiasm among the panel, and that is what I said before, which is to restrict this to people who have a contraindication, and we can talk about how to define that, a contraindication to the other nonsurgical interventions. So, it would only go to patients who, for whatever reason, cannot get the NSAIDs or, you know, the other nonsurgical treatments. So, I'd.... I'd like a show of hands if there is support for that as a restriction and then we will talk about some of the others. So, who, who thinks that would be an appropriate condition?

- Joann Elmore: I'd need a few more studies.
- Chris Standaert: I would be more supportive of that than this.
- Richard Phillips: Did you just say nonsurgical?
- Craig Blackmore: So, I'll back up. So, I am proposing, in lieu of the first three bullet points that we would use the fourth bullet point. I guess we would also use the second, but basically starting from scratch using a new one that says we will only allow the use, or will only pay for the use of this in patients who have a contraindication to other nonsurgical treatments and, and we can refine that. This is straw vote, right? So, it would basically be people who can't get NSAIDs or can't get Tylenol or for whatever reason were not able to use the other tools in the armamentarium.
- Marie Brown: How does that language deal with the physical... with PT and other lifestyle change things?
- Craig Blackmore: I guess what I'm talking about, really the pharmacological.
- Joann Elmore: And what about a patient that's not a surgical candidate at all and cannot undergo surgery, what about them, Craig?
- Craig Blackmore: Well, that, that would be another condition.
- Chris Standaert: Well, that's Michelle's point. There are people who need a knee replacement who can't get it, they aren't the ones who are going to, they're not even the ones in the studies. They're not the ones people are talking about benefiting, which is tricky. And there are, I mean there are people who...
- Craig Blackmore: It's all tricky.
- Chris Standaert: ...yeah, it's all tricky. There are people who can't really go to PT, and there are people who really are not medically stable to benefit from exercise. There are people with bad cardiac disease, people who have other bad things where they really can't go to an exercise program that is going to help their knee. So, those people you probably could call out also. The PT benefit, now that's a different question, but that issue of people who, due to other medical comorbidities, cannot rely, cannot effectively access an appropriate exercise program.
- Craig Blackmore: So, this is not as simple as I thought it was going to be is what you're telling me.
- Chris Standaert: You thought it would be simple?
- Carson Odegard: So what... what about the people that actually failed conservative treatment and now they're becoming contraindications?

- Craig Blackmore: I don't, I agree, I agree with David. I don't think failed conservative treatment is meaningful. I don't think it says anything. I mean, there isn't a person who comes to the doctor who hasn't had knee pain for three months, and they, and they tried something, and they failed it, right? And so saying that is just basically saying, you know, open season.
- Carson Odegard: I agree, but what I'm saying is, the people that have failed, they're not in our description but now they've become contraindications because they failed treatment.
- Craig Blackmore: I don't know.
- Chris Standaert: I think the people who have tried an appropriate exercise program, modification then lost weight and tried NSAIDs and tried Tylenol and still have pain.
- Carson Odegard: Mm-hmm.
- Chris Standaert: Right? I mean, the truth is that... the trouble is, I agree with you. That's what I was pointing out. So, we get these, Seth brought this up before. You have the two camps. You have the people who can't have something else that might expect it to be helpful, cannot have the other comparators that seem to be equally as effective, or you have the people in whom they have not worked and this is some other step, but then the trouble comes down to, the data doesn't tell us that in those people, this is particularly helpful, as a population. That gets to be the tricky part. So, you've hit the end, but it's one more thing. You've already tried five things that haven't worked. So, is the next thing going to work, you know? Is this the next thing that's going to work in that population? And we don't have the study to say that it is, which is the problem.
- Craig Blackmore: Or is that a population in whom nothing is going to work?
- Chris Standaert: Right.
- Craig Blackmore: So, I mean, I am trying to figure out how to word this to people who... so that it's not just used sort of on everybody but would be used on people who had some reason they couldn't get an equivalent treatment, meaning Tylenol, NSAIDs, and then the whole question of physical therapy and weight loss. So, I guess I would say restricted to patients who have a contraindication to other or to pharmacologic treatments, perhaps.
- Chris Standaert: To pharmacologic treatments or unable to... or have medical contraindications to exercise modification or exercise approaches, or something.
- Craig Blackmore: But they could still get Tylenol.
- Chris Standaert: They have to have both.

- Craig Blackmore: Right. Well, I was, yeah. We can do both or I'm just saying, as a replacement for the NSAIDs and the Tylenol and...
- Richard Phillips: What about the nonresponders? You have just the contraindications to them...
- Craig Blackmore: Yeah.
- Richard Phillips: But what about those who didn't respond?
- Craig Blackmore: I'm intentionally excluding the nonresponders. I'm saying if... I'm proposing, and the committee may not agree, but I'm proposing that this be limited to the people who can't get the other equally-effective treatment.
- Kevin Walsh: I would ask, if you're going to do this, that you include physical therapy. So, and not limit it to pharmacologic.
- Craig Blackmore: So, contraindication to pharmacologic therapy and...
- Kevin Walsh: Because there was a study...
- Craig Blackmore: ...contraindication to physical therapy?
- Kevin Walsh: ...there was a study that they, or a trial that was described that found no difference between hyaluronic acid and home exercise.
- Chris Standaert: Yeah, and I guess I would use exercise opposed to PT, because you run into people who don't have good PT coverage and can't do that, but you can still tell them to, you know, walk exercise, get to a pool.
- Richard Phillips: Does PT, does that include orthotics?
- Chris Standaert: No.
- Richard Phillips: That's a separate thing altogether.
- Seth Schwartz: And I guess I, my only...
- Chris Standaert: Well, PT is a hodgepodge, but no, I wouldn't count DME stuff in PT, but...
- Seth Schwartz: My only problem with pharmacologic is, you know, they might not be able to take steroids, but if they take 100 mg of morphine, their pain is going to go away. That's pharmacologic but still a terrible idea.
- Richard Phillips: Yeah.
- Chris Standaert: So, appropriate pharmacologic.

- Craig Blackmore: Say nonnarcotic, I mean, you know?
- Chris Standaert: Say appropriate pharmacologic care. Haldol for treatment of knee pain.
- Craig Blackmore: Alright, so I'm hearing restricted to patients who have a contraindication to a nonnarcotic pharmacologic and exercise treatments, is that what I'm hearing? I would leave off the exercise personally, but...
- Kevin Walsh: I would just, I'm, I'm just saying, scratch the nonnarcotic... scratch the pharmacologic descriptor in there to just nonsurgical treatment. That could include other pharmacologic treatment. It could include physical therapy, home exercise, you know, magnets, whatever else you want to try.
- Marie Brown: Well, now we're, we're back to Michael.
- Chris Standaert: So, contraindication to all forms of all nonsurgical treatment.
- Craig Blackmore: Is it single or is it all?
- Chris Standaert: Yeah, so they can take NSAIDs, but they can't go to PT, they can go to, they can exercise but they can't take NSAIDs. So, they're, they can exercise but they're on Coumadin. Even then, that's indefinitely. You get them off the Coumadin and stick a needle in their knee, which is a whole other ballgame, but.
- Seth Schwartz: Why do you always do this to us?
- Chris Standaert: Because things are rattling around in my head.
- Richard Phillips: Can I ask a question? One thing that I'm concerned about is that we're, it becomes a nightmare to try to validate this from the agency point of view, wouldn't it? I mean to try to find out all of these particulars, small issues?
- Craig Blackmore: I mean, I...
- Seth Schwartz: No, that's, but historically they say, we can't do that. It's going to be left up to the provider. So, you can either give people a carte blanche and say, hey, give it to everybody, or we can try to put something in there that...
- Chris Standaert: How about, how about...
- Seth Schwartz: ...implies that patients...
- Chris Standaert: ...we say patients who have a medical contraindication to other appropriate forms of nonsurgical care?
- Craig Blackmore: Write that down. Did anybody capture that?

- Marie Brown: Yeah.
- Chris Standaert: Patients who have a medical contraindication, so it has to be a defined medical condition, to other forms... to.... medical contraindication to other forms of nonsurgical care. Even for the people who medically, for some reason you don't want to, you can't do the other things, that's who you're looking for. That's what this says, anyway.
- Craig Blackmore: Well, it might limit a little. Alright, thoughts on the wording on number... the second choice here?
- Marie Brown: Limited to two courses per year?
- Craig Blackmore: Yes.
- Chris Standaert; And the third bullet point, the evidence... you have to prove it worked if you're going to do it again.
- Richard Phillips: I'd like to add another category in there if you would, and that would be the patients who are nonresponders who are not surgical candidates in the patients who have not responded to medical therapy, not contraindication but just have them respond to medical therapy but have no other alternative.
- Marie Brown: Wouldn't that be...
- Craig Blackmore: Well, I think that would be covered, wouldn't it?
- Richard Phillips: Mm-hmm.
- Craig Blackmore: You have... you can't... you have medical contraindication to other forms of nonsurgical...
- Richard Phillips: Not medical contraindications. Say they've, now they're...
- Chris Standaert: He's saying they're nonresponders...
- Richard Phillips: ...they're nonresponders to medical therapy...
- Chris Standaert: ...he's saying the people for whom nothing else works.
- Richard Phillips: ...are candidates for surgery, except for the fact that they're, you know, I mean, they need surgery but they aren't candidates for surgery because of their comorbidities, essentially.
- Joann Elmore: So, they've failed.

- Richard Phillips: Yeah, like somebody with stage 4 heart failure or something like that. I don't know, this...
- Craig Blackmore: Can you make that a second [inaudible]...
- Richard Phillips: ...if we end up parsing this, it might be, so maybe it's too much, but I.
- Craig Blackmore: So, this would be, um, if you can't have the surgery, even though we think you need it, we would allow this whether, you know...
- Richard Phillips: If the provider believes that the patient has an opportunity to do the surgery, then I think that surgery should be offered rather than the injections.
- Chris Standaert: But surgery...
- Craig Blackmore: That's not what it says.
- Chris Standaert: Surgery's really, you're hitting this end-stage people.
- Marie Brown: Yeah.
- Chris Standaert: And they're the ones in whom this isn't, if the people who are lined up for surgery aren't, not the ones who really...
- Craig Blackmore: They're the ones we don't think it would benefit. Those are going to be the bone-on-bone.
- Marie Brown: I think that there was data that mild... it was more effective in people with mild-to-moderate osteoarthritis than more severe.
- Richard Phillips: Yeah.
- Craig Blackmore: Other thoughts?
- Joann Elmore: [inaudible]
- Craig Blackmore: We can move that down.
- Marie Brown: Move that down, too, so we have three.
- Chris Standaert: We could... we could change it to add a clinical benefit in terms of pain and function, and we could make people not just sort of say, oh they were better, but actually prove that they hurt less and could do more.
- Joann Elmore: What's your definition of improve?
- Chris Standaert: Didn't you ask that before?

- Craig Blackmore: Okay, there it is.
- Chris Standaert: Clinical benefit in terms of pain and function.
- Richard Phillips: That sounds very reasonable.
- Marie Brown: Mm-hmm.
- Craig Blackmore: Okay, so, then Margaret I would ask you to add, in terms of pain and function to the third bullet point above, as well, so they are the same. Yes.
- Seth Schwartz: Not to be nit-picky, but shouldn't it be pain and/or function? I mean, we've heard that pain may be improved. Their function may be no different, and pain is what they care about, or if their function is better.
- Marie Brown: And improved pain is, in itself, an important outcome.
- Craig Blackmore: So, why do we have pain and function there at all? Just say clinical improvement.
- Chris Standaert: You don't get the, oh, it's a three today. I think we can do a...
- Seth Schwartz: He's trying to stop the rattle in his head.
- Chris Standaert: I know the data is on pain. That's one of my problems with the data. Pain is fuzzy, you know? It's sort of, you see people in there with a three one day then a four the next, you know? What's, and then we get into this, what's significant pain as opposed to saying can you actually, is it... I'd like to see does this make your life better in some way, and that's a harder thing to measure... the quality of life measure isn't as routine. People measure pain and function, that's why I threw it in, but I could go either way.
- Craig Blackmore: Alright, do we keep pain and function or not?
- Marie Brown: Yes. I mean, it makes it more stringent, and that's what we're looking at.
- Craig Blackmore: Okay, so there's... there's two proposals for conditions on the board. Should there be a third? Is there another proposal that we haven't heard?
- Joann Elmore: No cover was the third.
- Michael Souter: No, we've already covered that.
- Joann Elmore: No, we can still vote no cover.
- Chris Standaert: People can still vote no cover if they want.

- Joann Elmore: That's still an option for voting, obviously.
- Richard Phillips: Yeah, I think so.
- Craig Blackmore: We're in new territory. I don't know if it is or not. Now that we've seen the conditions, are we allowing a no coverage vote? I can't have a three-way vote. Alright, we'll do this. We'll vote on the conditions, and then we'll go back and vote again on whether people accept the conditions or not, but first, we can't have three choices, because then we won't have a majority, right?
- Joann Elmore: Right.
- Craig Blackmore: But, but after understanding what the conditions are, we'll give people the opportunity to decide if they're going to go that way or they're going to go back to no cover.
- Marie Brown: I like that option. It's the most cautious and the most group oriented.
- Craig Blackmore: I'm getting comments from Gary.
- Gary Franklin: I just have a question. Is there anything on the degree of severity by some measure, by some osteoarthritis score? I know we heard, you know, don't do it for bone-on-bone, but is there kind of a, a range of severity that you would want to see? You wouldn't want a tendinopathy kind of thing, like you said before. So, you don't want like nothing, but, so do you want some kind of medium-to-severe score on how bad the osteoarthritis is?
- Chris Standaert: The first paragraph, if you scroll up, that's where we used the phrase osteoarthritis: with osteoarthritis of the knee. So, radiographically evident?
- Craig Blackmore: I mean...
- Chris Standaert: You know, or did it matter?
- Craig Blackmore: Don't you think osteoarthritis is osteoarthritis? I mean, if somebody has osteoarthritis of their knee and the pain is from the tendonitis, we can't come up with a criteria that differentiates that, right? We're not...
- Gary Franklin: Well, aren't they graded, though, in terms of...
- Michael Souter: [inaudible] from the evidence vendor was that...
- Gary Franklin: Arthroplasty is...
- Michael Souter: ...there wasn't...

- Gary Franklin: ...done, aren't there grades of it?
- Michael Souter: No. Not that they provided in our data.
- Craig Blackmore: The Kellgren-Lawrence has four grades plus, you know, a zero meaning no osteoarthritis and it... it corresponds, not incredibly well, with symptomatology and...
- Chris Standaert: But no routinely used clinically. I mean, you don't read x-rays that have... this is a Kellgren-Lawrence 2 ever.
- Craig Blackmore: Well, I do, but most people don't.
- Chris Standaert: I know, reading my x-rays reports. So, that's not what it says. So, it's... well, since Craig's left I don't read that, but it's... I don't know that those are wide, as Dr. [inaudible] said before...
- Craig Blackmore: It is not widely reported.
- Chris Standaert: There are multiple scales...
- Craig Blackmore: It is not widely reported.
- Chris Standaert: ...out there and picking the one scale we think has to be documented, I think, would be tricky for us, because we're redefining the standard of practice there.
- Michael Souter: So, the attempts to try and, you know, an adequate response there was, I think, to try and give some metric of severity there.
- Seth Schwartz: Or, the question more about if you have somebody with really mild osteoarthritis, should you be doing an injection? So, there's, you, we may not even have to define how it is, but just say moderate or severe osteoarthritis or moderate or severe symptoms of osteoarthritis and you can't do anything else.
- Craig Blackmore: I mean, I'm, I'm happy...
- Seth Schwartz: I'm not saying we have to do it. I'm just saying that, I mean, aren't...
- Chris Standaert: If you go with the second one, not this set but the second one, they're pretty restrictive. You have to be medically contraindicated to other treatment, so then you just have osteoarthritis and you can't have anything else.
- Craig Blackmore: It would still be very mild osteoarthritis. You know, I think, I think we can put those words in. I'm not sure they mean anything, but they might. I mean, they might. Moderate? I mean, what's going to help with implementation of the rule? We can give you the intent of the committee, but we have to phrase it in a way that you can operationalize it, right? So, there's...

Gary Franklin: Well, if you say moderate to severe. I mean, so that's what the FDA just did on long-acting opioids. They changed their labeling from moderate to severe pain to severe pain. So, they didn't say what scale you had to use or whatever, but it was a huge change in how people are going to look at, how opioids might be used for pain, for chronic pain. So, I think it would be helpful. It couldn't... maybe we end up using some instrument or something, I don't know, but.

Craig Blackmore: Okay.

Gary Franklin: That guidance would be helpful.

Michael Souter: I would be happy with moderate to severe if we catch it with an original set of conditions. If we are going to use the more restrictive conditions that Craig has supported, I would not support moderate to severe.

Marie Brown: Right. I agree.

Craig Blackmore: Really?

Michael Souter: Yes.

Craig Blackmore: Okay. Okay, then... so then Margaret, we need you to take what you just wrote, moderate to severe, and put it, not the whole thing, just the parenthesis moderate to severe, and make it a new bullet point above the word in patients who have not had, does that make sense? Yes, and then write osteoarthritis after, no, yes, you're good. Sorry. After the word severe, write osteoarthritis. Okay, is that...?

Michael Souter: That's okay, and then remove it from the paragraph above.

Craig Blackmore: Yes.

Michael Souter: Okay, and I would still, in that original paragraph, I would still support, or propose, that we change nonpharmacological to nonsurgical.

Craig Blackmore: Right. So, that nonpharmacologic... yes, right there, becomes nonsurgical.

Michael Souter: And then we can vote and see.

Craig Blackmore: Can we get rid of the word conservative?

Marie Brown: Yeah.

Michael Souter: Get rid of conservative.

- Craig Blackmore: You got that Margaret? The word conservative after, the word conservative right there, yeah, get rid of it. Okay, other comments? Alright, so we're going to do a hand vote on which of these sets of conditions are most appropriate, and then we're going to follow that with a vote on accepting the coverage with conditions or going to one of our other two options.
- Marie Brown: Do we want to leave simple analgesics on the top?
- Craig Blackmore: I'm sorry, did I miss something?
- Marie Brown: Nonsurgical treatment. Do we need simple analgesics on that?
- Michael Souter: Yeah, okay, no that makes sense if you take that out.
- Marie Brown: Yeah.
- Michael Souter: The only reason we injected it in before is because we were talking about nonpharmacologic, but nonsurgical treatment embraces all of it. It might embrace just [inaudible]
- Craig Blackmore: Hopefully, nonsurgical treatment includes simple analgesics. Okay, let's get rid of that.
- Seth Schwartz: One other thing I would say is, if you're going to vote for the first, you would also probably want to include the second. In other words, if patients can't try that, you want to include it. So, I think what we should be voting for is the second alone or the first and the second basically.
- Craig Blackmore: Right.
- Michael Souter: Okay, so take, let's take patients who have a medical contraindication to other forms of nonsurgical care and inject that as a bullet point at the bottom.
- Craig Blackmore: Okay, so you got it, so Margaret, the part in purple you can get rid of. The part in pink, get rid of that, and then the first bullet point under the or, if you can copy that and also include that in the upper group.
- Michael Souter: Mm-hmm.
- Craig Blackmore: That's what you...
- Michael Souter: Yeah, you can't, get rid...
- Craig Blackmore: ...were saying, right?
- Michael Souter: ...of the restricted, too. Yes.

Craig Blackmore: No, copy it. Yeah, that's fine.

Seth Schwartz: Yeah, the fourth, fifth bullet point on the top.

Craig Blackmore: Yeah.

Seth Schwartz: But get rid of the restricted to. Say, it should be or in patients.

Craig Blackmore: Or... or in.

Chris Standaert: Then you want the other requirements back.

Seth Schwartz: So, fourth bullet point.

Craig Blackmore: Bullet point... not the fifth.

Chris Standaert: Take it up one more. No, no, no.

Craig Blackmore: Yeah, that's fine. Just move that down below it, either way.

Seth Schwartz: But it should be the third, shouldn't it?

Chris Standaert: It should be the third.

Seth Schwartz: It should be the third. It's still going to be limited to two courses a year.

Craig Blackmore: Oh, I'm sorry.

Chris Standaert: Move it up one more.

Seth Schwartz: Move it up one more.

Chris Standaert: So, the or patients before is limited to two courses per year.

Craig Blackmore: It goes right there, not even as a bullet point. It's part of the same sentence. Yeah, right there without, there it is.

Richard Phillips: Take the semicolon out.

Craig Blackmore: Okay, so... so I'm going to go again with a show of hands on which set of conditions we are going to opt for. So, first the... the first set up there. How many people would vote for the first set of conditions?

Josh Morse: Five.

Craig Blackmore: Alright. How many people would vote for the second set of conditions?

- Josh Morse: Three.
- Richard Phillips: I'll vote for that, too. I will, I'll vote for either.
- Craig Blackmore: Alright.
- Josh Morse: So, everybody has to vote on these two.
- Craig Blackmore: Everybody has to vote. You have to pick either number one or number two, and the difference is just number one is a little broader and allows, you know, it's just a little broader. So, again, how many people would favor the first of those as the conditions? If I could have hands, please.
- Josh Morse: Five votes for number one.
- Craig Blackmore: Okay, so how many people would vote for number two?
- Josh Morse: Six for number two.
- Craig Blackmore: It's a close vote. Okay, and we're going to proceed to the final vote, and this will be no cover, cover with these conditions, or cover unconditionally.
- Josh Morse: Eight cover with conditions, three no cover.
- Craig Blackmore: Alright. So, we are required to see if our decisions reconcile with Medicare national and local coverage decisions, and I'm looking in my packet. There is no national coverage decision. There are practice guidelines, and we are less restrictive than the American Academy of Orthopedic Surgeons, and we're different than the American College of Rheumatology. They don't really have a recommendation. We are less restrictive than NICE, and there is no local coverage decision. Okay, and our reasons for disagreeing are based on the most recent evidence, which we've talked about, the recent meta-analysis, but more importantly, the underlying trial data that goes with it. We've also considered... well we drilled down on the data, some of which is recent. Okay, lunch is here. It looks like lunch is here. We resume at, we'll resume at 10 of 1:00. Thank you.
- Alright, I am calling the meeting back to order. Alright, we have a quorum. We have a quorum. We are back in session. A request has been placed for coffee and we're gonna track some done.
- Richard Phillips: Caffeine is good enough.
- Craig Blackmore: Okay, next topic for the afternoon is hip resurfacing. It's a re-review. The first item on the agenda is scheduled and open public comments. We have no prescheduled public comments. Do we have... and we have nobody who signed up. So, anybody who's here in the audience, if you'd like to address the committee on hip resurfacing, please let us know. I'm not seeing any hands

raised. We will go to the phone, if we can. Christine is looking for coffee, so we will hold off on the phone comments. On our schedule the public comment period goes to 1:15, so I'll make sure we check back at about 1:15 and check the phone people and also check the audience, but in the meantime, we'll move on to the agency utilization and outcomes.

Steve Hammond: Hello. I'm Steve Hammond, chief medical officer Department of Corrections and as soon as we get the slides up, I'll proceed. When I use a pointer, I'll use the screen at the end of the room where the food is, so my apologies to those whose back is to that screen.

Craig Blackmore: Can I ask you to point at that screen instead so I can see?

Steve Hammond: Well, you know, actually that might make sense.

Craig Blackmore: Thank you.

Steve Hammond: Because this morning I was thinking there was a larger audience, but okay, we'll do it that way once we have something to point at.

Craig Blackmore: And the meeting grinds to the halt, as soon as Christine steps into the hallway.

Steve Hammond: Yeah, I'm, I'm afraid I'm lost without the PowerPoint, so.

Craig Blackmore: I'm the same way.

Richard Phillips: Why don't you give us a lecture on diabetes?

Steve Hammond: Okay, so as Craig mentioned, we are doing a re-review of the hip resurfacing assessment. This topic was reviewed in 2009. At the time it was selected, the criteria for selection gave medium weight to safety concerns, high weight to efficacy concerns, and low weight to cost concerns. In 2009, the HTCC decision was to cover with conditions, those being hip resurfacing could be used for conditions of osteoarthritis or inflammatory arthritis when there was a failure of nonsurgical management, and the patient is otherwise a candidate for a total hip arthroplasty, and the device used would be FDA approved.

Let's see. Here we go. So, the re-review was prompted primarily by reports that were related to safety, largely coming from registries, and our criteria for selection then were high safety concerns raised by the reports of complications and frequency of revisions required in the experience subsequent to 2009. Concerns about efficacy were there related largely to the relatively high rate of premature revision required in hip resurfacing procedures, and there were also concerns about cost, again related to management of complications and surgical revisions, although when we saw the utilization data, we saw that it has been decreasing. So, that somewhat mitigates cost concerns. So, it is primarily a concern about safety.

So, a little background. This is a typical hip resurfacing device. This happens to be the Birmingham device, which is commonly used. I think it is the most frequently used, but this is just an illustrative example to see the nature of the device, and this contrasts the hip resurfacing procedure with the total hip arthroplasty and you see that with hip resurfacing, the acetabular component, the cup, is placed and then the femoral head is reshaped to accommodate the femoral component with a stem that goes into the femoral neck. This is in contrast to a hip arthroplasty, in which the femoral neck is replaced by this metal prosthesis, and that comes into play when we look at the most common or most serious complication of hip resurfacing, which is femoral neck fracture, and this is an illustration of that. The first panel shows the prosthesis placed. The second shows a propagating fracture, and the third shows a completed fracture, and again, with the arthroplasty, this does not occur. I do not believe that ever fractures.

So, the safety concerns, again, revolve to a large extent around the significant rate of femoral neck fractures that occur following hip resurfacing, again not seen with arthroplasty. Also, there is concern about a fair number of local complications, including pain in the area of the resurfacing procedure and pseudotumor, which is an inflammatory mass that sometimes develops in the area related to, subsequent to that procedure. These problems have resulted in significantly higher rates of revision required after hip resurfacing procedures. Also, there is growing concern about all metal-on-metal arthroplasty systems and these, some of the complications that have been attributed to metal-on-metal are local hypersensitivity reactions related to metal fragments around the area of the prosthesis and then there is concern about possible consequences of systemic metallosis. The actual consequences are not well understood, but it is known that measurable systemic levels of metal ions are significantly higher in metal-on-metal prostheses. This is important for hip resurfacing because all of the hip resurfacing prostheses are metal-on-metal. It is also a concern for metal-on-metal arthroplasty systems.

So, in 2009, the clinical committee found hip resurfacing to be equivalent in efficacy with arthroplasty, except that there was expert opinion provided at that time that revision after a hip resurfacing would likely be less technically difficult than revision after a hip arthroplasty, and then the decision in 2009 was made despite a recognition by the clinical committee that there was some evidence that suggested a higher revision rate required after hip resurfacing than after arthroplasty. That evidence, though, has accumulated and become more weighty subsequently.

So, the updated review, again, shows equivalent efficacy in terms of pain and function outcomes, that is, if you are not considering the requirement for premature revision, and safety evidence goes both ways, but generally favors total hip arthroplasty. Again, higher... there are substantially higher revision rates, and I don't remember the exact ratio, but I think we'll be hearing about

that from... in the evidence report. It's something like three times, three or four times the revision rate for resurfacing procedures. This is a relatively new procedure, so follow-up data greater than 10 years are scarce. Again, there is a significant incidence of femoral neck fracture associated with hip resurfacing procedures, which is not seen with arthroplasty. However, with arthroplasty, there is greater incidence of dislocation and deep infection. Again, the metallosis is a concern with all metal-on-metal prostheses systems.

So, one of the questions, a new question we asked to be reviewed in this technology assessment was evidence relating to the greater efficacy or safety of revision after hip resurfacing, as compared to arthroplasty. Unfortunately, the evidence remains sparse and of low quality, although there was one study that showed similar outcomes after revisions of hip resurfacing and arthroplasty procedures.

So, getting at a question that came up in this morning's discussion, what population might particularly benefit from hip resurfacing, and the answer is somewhat in the reverse of that question. There is good evidence that hip arthroplasty appears to be more effective and safe in cases of hip dysplasia, female patients, and patients with smaller femoral head, and so the question remains, is there some ideal setting for hip resurfacing and this is in the realm of theory at this point. There is not really good evidence to demonstrate this conclusively, but it appears, given the safety concerns, that younger patients who have favorable bone geometry, structure and quality, that is good bone density and strength, plus the geometry is, to an extent, related to the size of the femoral head and also the angle, the femoral neck. So, that usually equates to being male patients for whom remaining physically active is a high priority and who would be expected to outlive an arthroplasty. So, that is theoretically a population that might benefit from hip resurfacing.

So, how effective is it, or how cost effective? Basically, the cost utility studies that were reported in the tech assessment were quite heterogeneous in their conclusions related to assumptions about efficacy and safety and essentially given their widely-varying conclusions and methodologies, the medical directors did not find it particularly helpful.

So, current coverage policy is that it is covered by all of the state agencies per the 2009 decision. All of the agencies, except Medicaid, exert prior authorization, and Medicaid is covered without prior authorization.

There is no national coverage decision from CMS on hip resurfacing, and there are a variety of coverage policies from other private payers, which, as you can see, specify certain conditions that have already been mentioned in the previous discussion about for whom this might be a suitable procedure, and I won't go ahead and read all of that.

These are the agency utilization data, since 2005, and we see a couple of interesting findings here. Now, the high bar here is for arthroplasty procedure. So, what we see here, I think, is the march of the baby boomers, and maybe with a little bit of inhibition related to the recession, but anyway, definitely growing utilization and that may help explain why despite the coverage decision for viscosupplementation we still see rising trends. It is just the prevalence of arthritis in our population, which is undoubtedly rising, but we also see here then, in comparison to arthroplasty, is the frequency of hip resurfacing procedure, so much less common. Here are the patient counts, and we also see that it peaked around 2009 and there does appear to be a pretty convincing downward trend in utilization subsequently.

This, again, shows similar data, procedure counts for hip resurfacing and arthroplasties, both total and partial, and you can see that arthroplasty outnumbers hip resurfacing substantially, and you can see the downward trend in numbers for hip resurfacing to vanishing in 2002 in a couple of the agencies. So, the utilization is of its own accord declining.

These are the costs over the past four years. Again, we see that there is a very substantial cost for hip arthroplasty, but in comparison the cost for resurfacing procedures is relatively small, and these are the average prices paid, and we can see the hip resurfacing, the cost or price of hip resurfacing. These are amounts paid, which is not quite the same as amount allowed, but basically the costs are pretty close for hip resurfacing and arthroplasty procedures.

So, this graph is, I admire this a great deal. I thought the person who put together this graph was very creative. Let me try to walk you through it. This is looking at hip resurfacing procedures for the past four years, looking by age, and it is comparing hip resurfacing with arthroplasty procedures and looking at it broken out by gender. So, the hatched part of the bar is arthroplasty procedures. The kind of intermediate one there is a partial arthroplasty, but the hip resurfacing is the solid bar at the top or the bottom. So, what you see is that these are much more commonly performed in patients under 55 years old and more commonly performed in men than in women, which is really in accord with safety considerations that we mentioned before.

So, the state agencies will recommend that hip resurfacing be not covered, but that if it is covered it be restricted to a group with the highest likely benefit and lowest risk, again osteoarthritis or inflammatory arthritis in the setting of favorable bone structure, geometry, and quality, which would usually be men, who want or need high levels of physical activity, perhaps less than 55 years old, and that concludes.

Craig Blackmore: Questions for Dr. Hammond? Alright, thank you. So, I just want to circle back. We're at the tail end of the public comment period. So, I wanted to respect the fact that people may think we're gonna be actually on the agenda on schedule. So, is there anybody here who had wished to address the committee about hip

resurfacing who hasn't had the opportunity? Then, Christine, could I get you to unmute the phone, and we will see if there's anybody who has called in who wishes to address the committee. So, this is the Health Technology Clinical Committee, and the discussion is around hip resurfacing and if there's anybody who has called in that wishes to address the committee on that topic, this is your opportunity. Please identify yourselves. Alright, I'm going to close the public comment period, and we will move in with our... with our evidence report.

Christine Masters: Just give me a second to [inaudible].

Joseph Dettori: Okay. While she's bringing those up, let me just acknowledge my colleagues in this report, Dr. Hashimoto who gave the first report. She was the PI for that, and then Katy Moran from our company has also helped me with this, and I asked her to come to keep me straight, so. Where do I point? There. Thank you.

Okay, so I'd like to present the data in three sections if I could. One will be a background for the update to provide a context of how we got from our 2009 report to now, and if you'll allow me to use the word update instead of re-review, it's the... it's the arc language and I, that's... that's what I did. Then second, the second section I'll present some of the data, and then the third section, I want to sort of summarize some conclusions in the context of the strength of evidence and how the data differ from our original report, so hopefully you can see what it was and what it is now.

Okay, so the first section, why? Why an update, and I think that the key to this has to do with the bearing surfaces and so, if we look at data up to our report, the years just preceding 2009, the bearing surfaces of all hip systems, both total hip and hip resurfacing, there was a growing popularity for metal-on-metal bearing, and if you look at that in America, I have some data for 2006 that shows about a third of all systems were this metal-on-metal bearing. That's both total hip and hip resurfacing. So, I'm talking about the bearing surfaces now, in general. Then, not only in America, but also internationally, this is data on the right from Australia and it shows an increasing use, also, of metal-on-metal bearing systems.

Because it is more popular, more patients were being treated by it, some reports about safety about these systems started to come in, in the peer-reviewed literature, and also in the public news, as well, and there seemed to be some issues with those systems, metal-on-metal, and that came out just about the time we gave our report. Shortly thereafter is when these reports on metal-on-metal safety started coming out.

So, in 2011, the American Academy of Orthopedic Surgeons, again, I'm talking about all metal-on-metal systems with this slide. They came out and reviewed all the metal-on-metal, and they were very concerned about higher revision

rates with metal-on-metal, concerned about the metal debris, some of the things that you just heard, and then the FDA subsequent to that did their own evidence report, again metal-on-metal had some of the same safety concerns.

So, now I'm switching back to specifically hip resurfacing, okay? So, we had three technology assessment groups, as a result of the safety concerns that we've been hearing about, decided to do their update to re-review their Health Technology Assessments and so we have the California Technology Assessment Forum. They did their re-review in 2011, and they essentially... I don't remember what their first decision was, but they changed their decision to not cover hip resurfacing, felt it did not meet their standard, primarily because of safety issues. Ontario Health Technology and Canadian Coordination Office, again, safety, all focused on the safety and potential safety issues of hip resurfacing.

So, this is the same slide I showed you earlier, except I continued on. I cut the first one off at 2008, and now this goes to 2011, and you can see that similar to the kind of graph that the agency director showed you for the State of Washington utilization, but you've got to remember, this is all metal-on-metal systems, both total hip and hip resurfacing.

So, we're going to move into that. So that's... that's the reason why this got bumped up to us to re-review, to see what the safety issues are. Now, I'm going to present some of the data. These are the key questions. I'm just going to highlight that this middle key question is a new key question. It was implied in the old report. We actually addressed it a little bit in the old report, but we sort of co-defined it as a key question this time, and basically one of the theoretical advantages of hip resurfacing is that if it's done in a younger patient, when it's time to have their revision, now we can revise the hip resurfacing to a total hip. It's easier. It's better, as opposed to them having the total hip then having the revision. So, the question is, is it really better? We don't know if it's really better. So, that's the purpose of that question.

So, just to kind of catch everybody up again on the vocabulary, we are using revision, we put revision in the safety outcomes area. Some people... some reports use it in the efficacy. We're considering it safety, and the last time we did this report there was interest in us presenting the report in terms of short-term, mid-term, and long-term, and our clinical experts at the time defined for us those timeframes, and so we will continue with that as, as we did last time.

Okay, so key questions one, two, and four are the safety. I'm sorry, the efficacy, effectiveness, the safety and the differential efficacy and safety, and you can see we added two randomized control trials. They are small randomized control trials. We added three nonrandomized control trials to answer this, and then three registries. These are not new registries. These are the same registries, but they are new reports. There is new data. We have four and five-year data in addition to what we had last time.

If you read the report, you may have missed... there was a little section in there where we said, we identified 13 or 16 publications that published from the registry, and we did not include that in the report proper. We abstracted the data, put in the appendices, and we decided rather than that, that we were going to look at the latest registry data instead, because all of those reports took earlier registry reports, and so those numbers are going to change a little bit. So, we encompass all of their information by sort of taking a fresh look at the registry data with respect to revision. All of these were with respect to revision. We looked at five nonrandomized trials for this new key question three. Only one had a direct comparison, and I'm going to show you the results of that and then we had two new studies on cost effectiveness.

So, the big... the big player for this report, with respect to safety, which is the key issue here for this re-review, are these registries. So, I just want to say one short thing about these registries. They are all international registries. The Australian Joint Replacement Registry has the longest follow-up. It has an 11-year follow-up for hip resurfacing. Of course, it has longer for, for other total joint systems, but somebody is going to need to correct that one for me.

If you look back in the appendices, if you're interested, you can look back in the appendices and see that we actually evaluated the quality of the registries, and these three actually have very high quality. They have all taken steps to validate their data. It is all prospective data. These are all registries that were created for the specific purpose of looking at total joints and so they are high quality sources of data, and registries can, just like any other source of data, can have their problems, but these, in particular, are good sources of information.

Okay, so we'll... we will move to key question one. I'm just going to show you a small sample of the data from key question one, because the results of the data do not change from the prior report with respect to efficacy and effectiveness. They are very short timeframes, one in two years is all. We have no midterm or no long term results, and the two randomized trials that were added since then had really no information with respect to efficacy and effectiveness for the outcomes I am going to show you here, okay. They report, they report some different outcomes. I'll just mention them when we get there, but, but this will look similar if you sort of remember the prior report.

So, the first one is going to be a patient reported joint-specific outcome, the WOMAC score. We had three randomized trials. The bottom line is that there was no statistical difference between those two at one to two years. We looked at... there were a few studies that looked at the SF-36. I'm just showing you now the physical SF-36. There was a metal component, as well. No statistical difference between the two groups. Again, a very short time period.

There were a couple of studies that looked at different activity scores. The one that was used the most is the UCLA activity score. That score is a scale that has

10 statements on it, and each statement is supposed to provide a higher level of activity. So, at the very bottom a score of 1 would be, I don't do any physical activity at all, and 10 would be I compete in competitive sports, and you're supposed to... and it's graded up through there, and you're supposed to pick the one that sort of best fits your lifestyle, you know, moderate housework, severe housework or whatever. No statistical different. Severe housework, I guess. Any housework can be severe housework.

Then, so there are a couple of other activity scores that have maybe one study. All of them show similar results with respect to efficacy, and that is that there is no statistical significance. You might say that it does seem to move a little bit to the right there, but it's not statistically significant. The clinician-based outcomes, here's an example, the Merle D'Aubigne score. Again, no statistical significance. Okay, maybe a little to the left favoring total hip, but it's not statistically significant.

So, that's all the data that we have. I mean, we have more of lesser import in the report, but that's all I am going to show you here. I am going to move onto effectiveness, and we added one study. We have a bunch of cohort, nonrandomized trials that we included, and we added one, that's the Costa study, and you can see that the Harris hip score, which is a clinician-based score, is the one that's used most in these, similar. This is the UCLA activity score. We added one study to this. You see it on the right, and on this score, you can see that it tended to favor the hip resurfacing. That's possibly confounded a bit by age, because people who get the hip resurfacing in these nonrandomized trials tend to be younger, and so they tend to be more active and so there's potentially confounding by indication there.

Okay, so that's, that's the efficacy. Effectiveness is very similar to what you've seen in the past, and it's all short-term data. Now, let's take a look at the safety of hip resurfacing. We are going to look at three outcomes, revision, complication, other complications, and metal ions, okay? Okay, so, randomized trials for revision, we had two of them, and you can see that there is no difference in the short-term revision rates from randomized trials, and this is a good example of why, in some cases, randomized trials are not the best trials for safety information, especially if... if safety outcomes are... pop-up long-term. Randomized trials usually are short-term in nature, just because of the cost of the trial. So, you have to look for nonrandomized evidence, and we are going to see that really clearly in this particular technology. So, if we look at the nonrandomized cohort studies, their follow-up is a little bit longer, between two and five years, and you can see that the summary estimate moves a little bit towards favoring total hip arthroplasty.

But, it is really... it's really when we get into the midterm revision rates and we look at all of the... the registries, and we are going to see that is where the story is told the clearest. So, you can see with the Australian registry, we have both... they presented both five- and ten-year data in their latest report. England and

Wales five and eight-year data, and then the Swedish registry was five- and seven-year data, and you can see in all there, there is a separation between total hip and hip resurfacing. Now, the data I'm showing you when I make these comparisons, the total hip that I'm making the comparison to is metal on polyethylene. It's the... it's the standard total hip. It's the conventional total hip. There are total hip bearings out there. There's ceramic on ceramic. There's metal-on-metal, we already talked about that. These comparisons aren't with those. They are comparing with the standard of care, which is the metal on polyethylene and that occurs... if you'll look at the... if you'll look at the registries about 90%+ of total hips are those bearing surfaces. Then, of course, Australia has one more year. I told you they had 11-year data. So, the long-term data is still in favor of the total hip.

There are other complications. I'm presenting six other complications that are all statistically different. They're... there's another handful of complications that are reported that are not statistically different there in the report. These are... the ones in blue favor hip resurfacing. The ones in red... I'm sorry. The ones in blue favor total hip. The ones in red favor hip resurfacing, okay? And so, femoral neck fracture, avascular necrosis, neither of those can occur in a total hip. The femoral component loosening was already mentioned. There is a nine-fold increase in the hip resurfacing versus total hip and then heterotopic ossification almost twice... twice as frequent. Dislocation, however, occurs less frequent among those who have hip resurfacing, and deep infection also occurs less frequently.

So, what I am going to say now about the metal ion safety, again, moves out of the realm of hip resurfacing, per se, and into the realm of all metal-on-metal hip systems, because that is how the data is presented, and there is ample evidence that following a metal-on-metal hip replacement, whether it be total or hip resurfacing, there is an increase, varying increases of these serum ions, cobalt and chromium, in particular, and there is concern over what is the long-term exposure of these in our system. There are a couple of things that we know. We know that if you take people who have had these procedures and you look at their ion level in their blood, that those with the highest level of ions tend to have more pseudotumors compared to those that have less ions in their blood. They also tend to have worse functional outcomes than those that have less ions in the blood. These are people who have all had metal-on-metal replacement, looking at the highest concentration and lowest concentration. We also know that for those people who are in the hip resurfacing group, if you... if they have a revision as a result of a pseudotumor, their outcome is worse than if they... if they had a revision for some other reason. With respect to the systemic effect on cancer and renal dysfunction, right now we don't have any data to show that there's an association. There are a couple of reports that are reviewed in the report that looked at that, in particular, looked at metal-on-metal systems and the incidence of cancer, and at this point there, they found no association, but it is a short period of time, and we know that if there's a

causal effect, it may take longer for it to show up. So, at this point, we can say that there's no evidence of that.

Okay, key question three is the new key question, and it has to do with whether or not a revised hip resurfacing does better than a revised total hip arthroplasty, okay? So, you have an individual who comes in. That individual has a hip resurfacing, ten years later has a total hip versus that same individual who comes in, has a total hip first, ten years later has a total hip, revised total hip. So, how do those compare, and there was only one study that looked at that. It was a nonrandomized trial, and it was very small, you can see only 35 subjects, and they didn't report any safety issues. They didn't report re-revision if you will. They only reported these outcomes here, and they found no difference.

How about differential efficacy? In our last report there was some suggestion that there was some differential efficacy with respect to these systems. So, we looked at all the ones that were suggested from the last report, and we looked at them more carefully now with the data from the registries, and we were able to identify three. The first one is the diagnosis, and it has already been mentioned that... that hip dysplasia has an effect, has a negative effect on the... on revision rates. These are rates, not risks, per 1,000 person years. So, it has a negative effect on rates. If you do a hip resurfacing among people with dysplasia, you're going to have a worse outcome versus a total hip. So, these figures I'm going to show you, these three figures, basically, are meant to show you that here's the exposure down here. So, the treatment inside the exposure is influenced by that exposure. So, you can see that these three are relatively close together and all of a sudden this one pops up. So, the interpretation of that is that this exposure, developmental dysplasia, differentially effects in a negative way, hip resurfacing.

So, we have the same thing with males and females. Females do worse with hip resurfacing. Femoral head size, that was already brought up before. The last report that we did suggested that the male/female may be a result of the head size. We tried to tease it out a little bit better. This time, it is hard to do that with the summary data that we have, but I would just say that's probably partially true, but I don't think it explains all of it, so.

Okay, what's the evidence of cost? We have two new studies. These are... these are hard studies for me to untangle. The two new ones, the second one, Edlin, makes, in my opinion, the same mistake as the three prior reports, and that is that they use a randomized trial to estimate the revision rates, and they're wrong. Those revision rates are just wrong for their assumptions. Bozic does a good job. They used the Australian registry to estimate the revision rates, and I think they do a better job of making that estimate, and they basically concluded that in young males, there may be some cost effectiveness to hip resurfacing in young males. I think the ICER for that was 28,000, I think.

Okay, so that's a sampling of the results focusing on the safety issue, which is what brought this up to the re-review, and so let me see if I can make some concluding remarks showing you the differences between the last report and this report.

So, with respect to efficacy, we have the same strength of evidence, moderate, that there is no difference between the two in the short term. The only thing we really changed is we went from one year to two years.

Effectiveness, same, low evidence. We didn't really change anything but our vocabulary. If you look down at the very bottom, we went from very low to insufficient. Those are the same in grade, which is what we used to evaluate our strength of evidence. They use either term. They are moving away from very low to the word insufficient. We have adopted that at our company and it's... but it is the same category.

With respect to revisions, we've gone from moderate to high that in the short term, hip resurfacing has a higher risk of revision, and I put the absolute risks down there. The percentage higher goes from three to... 50% at three years and at five years between 30 and 80% depending on which registry you look at.

In terms of the midterm, we went from low evidence at seven years to what we consider is high evidence at seven and ten years, that the risk is higher, 40 to 100% higher, and the absolute risks are listed there at the bottom. Then, long-term, we went from no evidence now to what we're calling low evidence because we only had one report at 11 years, and that is the Australia.

With respect to complications, we went from low evidence concerning complications to now what we're calling high evidence. Evidence that the femoral component loosening is greater, heterotopic ossification is greater, and dislocation is less in hip resurfacing. We are saying there is moderate evidence with respect to deep infection because of the... of the number of studies that report that isn't quite as high. Then, of course, we do not make a comparison with respect to femoral neck fracture and AVN, but I give you the absolute risks there, and we feel confident that those are pretty darn close, looking at all the studies.

In our last report we said, well there's... there's some concerns about safety. In this report, we say, with respect to the ions, in this report we say, okay, there's some evidence now for all metal-on-metal bearing systems that if you have higher cobalt and chromium levels in your blood, you're more likely to have a bad outcome. You're more likely to have a pseudotumor, and if you have a revision for a pseudotumor, you are more likely to have a bad outcome, and there is no evidence at this point that there is an association between hip resurfacing or total hip arthroplasty with metal-on-metal bearings. There is no evidence or association between that and cancer or renal dysfunction.

This was the key question that was added. It wasn't in the last report, is in this report with insufficient evidence to look at the outcomes following revision hip arthroplasty, or hip resurfacing versus total hip. We went from low evidence last time to differential efficacy on dysplasia to now high evidence. We still believe it modifies the effect.

With respect to sex, it went from moderate evidence to high evidence, and then high evidence with respect to the size of the femoral head, as well.

And then lastly, cost effectiveness. We, basically, have the same conclusion that the main problem is that studies, except for this one study, studies don't use the right risks or rates of revision in their assumption, which is a significant contributor to the models. So, I'll take your questions.

Chris Standaert: I have a question. I like the comparison tables you put up by the way, comparing what you said before to now. I thought that was really helpful. The cobalt/chromium sort of question, and maybe this is for Dr. Chansky, as well, but the general views in the orthopedic community and AOS on cobalt/chromium, because all it has, you said all of the hip resurfacing are metal-on-metal, there is no metal on plastic, but metal-on-metal is, in my own clinical experience, becoming quite frowned upon now, but I don't know whether the AOS has made a statement. You said something, but I don't know. Is there an issue with cobalt/chromium in general now?

Joseph Dettori: I suspect the reason you don't have anybody from industry in the room is because metal-on-metal has become such a toxic topic and the academy has recommendations for metal-on-metal joints, and those are pretty much discourage the use of them and if they're already implanted and asymptomatic and cobalt and chromium levels, which are now... it's now recommended you check them annually. If they're not at toxic levels, leave the implants alone.

Chris Standaert: That's reassuring.

Joseph Dettori: Yeah, leave the implants alone, but if the cobalt and chromium levels are rising and... or if the hips are symptomatic with, you know, pseudotumors or whatever, then to revise them, but the... the rate of use of metal-on-metal bearing implants has plummeted over the last three years.

Chris Standaert: That's what I thought, thank you.

Richard Phillips: I thought it was a very good presentation. I thought it very... thank you very much. The question I have is, we're talking about metal-on-metal as being the only problem. In other words, if we had ceramic on polyethylene or if we had metal on polyethylene or metal on ceramic or something like that, would we be seeing this problem?

Joseph Dettori: You mean, if the hip resurfacing had a different bearing?

- Richard Phillips: Yeah, in the hip resurfacing.
- Joseph Dettori: Yeah, well, I don't know. That's, that's the question, right? There isn't any, but...
- Richard Phillips: But do they even exist? Do those...
- Joseph Dettori: As, as far as I know, the answer, you know, they used to exist and they failed, and then when they went to metal-on-metal, that's when it became popular again.
- Howard Chansky: Yeah, there are technical reasons why you really can't have alternative bearings for... for surface replacements, and that is to avoid fracturing the femoral neck. You need a big neck, which typically goes along with a big femoral head. To fit that big femoral head into the cup side, you know, that you're implanting in the pelvis, you need a big, big cup to accommodate that, and you just don't have room for anything basically softer than cobalt chrome. If you put polyethylene in, it's too thin and it just wears away quickly, and the ceramic fractures. So, for the foreseeable future, there's really no alternative for surface replacements, other than metal-on-metal.
- Richard Phillips: The other thing, thank you very much for that. The other thing I had a question about was that I was really struck by the high instance of deep infections, and if you put a severity of infections, you know, a dislocated hip, I would guess, would be a 2/10 whereas a deep infection would be an 8 to 9/10 of concern and worry, and here we have almost what, 1.8% incidence, is that right, of deep infection?
- Joseph Dettori: I'd have to go back and see about that.
- Richard Phillips: I don't recall that you, that was in the prior...
- Joseph Dettori: I think, I think that's right. That's right, 1.8%, yeah.
- Chris Standaert: It's much, it's, it's lower. It's lower resurfacing, right?
- Joseph Dettori: Yeah.
- Richard Phillips: Yes, that's what I mean.
- Joseph Dettori: Yeah.
- Richard Phillips: It's lower with resurfacing, and I was... I don't remember that being pointed out before.

- Joseph Dettori: It wasn't. The data wasn't... wasn't presented. If you looked at the comparison table, it was not on that.
- Richard Phillips: Isn't that a, a major concern, too, in this...
- Craig Blackmore: Well...
- Richard Phillips: ...I mean, am I missing?
- Craig Blackmore: ...what is a deep infection?
- Joseph Dettori: Well, I was, okay, a deep infection is anything deep to the fascia. So, it's a, you know, the classic peri-prosthetic infection, I...
- Craig Blackmore: But it's not an infected prosthesis that has to be replaced necessarily.
- Howard Chansky: Well, it is an infected prosthesis. The issue of whether it needs to be replaced is, you know, I think is a complicated question, but most of them end up having to be taken out and put back in, but I was actually going to make two comments. I don't know where the data for dislocations and infections came from. I don't quite recall, but they don't agree with the big studies that have been done that have just looked at hip replacements, not the comparison studies, and the dislocation rate of 2.8% for total hips is really higher than it should be. If you're, if 3 out of every 100 of your patients are dislocating after a standard total hip replacement, that's actually considered to be quite high, and the same for infection. Most of the big studies say the deep infection rate for standard total hip replacements is more on the order of 0.75 to 1%. So, that... that actually, you know, makes the total, makes the surface replacement look even... even worse.
- Joseph Dettori: The only problem with looking at the large studies that only look at total hips and not the comparative studies, the data that I report is actually the pooled estimates from all the randomized trials we included in our study and all the cohort studies. So, you can look in the report. When I go back over there I can dig it up and give you the... the bottom line sample size. This population is probably... those that are eligible for a trial, right, is probably a different population. For a trial for hip resurfacing is probably a different population than those who are... just get the standard total hip and don't ever consider hip resurfacing. So, so you have to be careful transferring those numbers. I think that with respect to the kind of population, the kind of activity, the age, the whatever goes into making somebody consider a hip resurfacing, that population, I would say these numbers probably reflect what's happening across the country, but we do better at the University of Washington.
- Craig Blackmore: But can I, can I drill down on this a little more, because...
- Joseph Dettori: Yes.

- Craig Blackmore: ...I think it's important.
- Joseph Dettori: Sure.
- Craig Blackmore: So, I mean, you've given us several slides that are related, 19 and 21. So, 19 is the registries and it's got time series on the failure rates, and then slide 21 is giving us these other complications, and there is no... there is no time delineation on the complications. So, I don't understand if the 1.8% deep infections, are those immediate? So, if you go two slides out.
- Joseph Dettori: Yeah.
- Craig Blackmore: You know, what, are these immediate in the first year or is it, you know, we've got a longer history on the THAs, we've got 20 years on those.
- Joseph Dettori: Right.
- Craig Blackmore: So, the rate per year might be lower, and then the second piece is, if I try to reconcile this with the revision rate, I mean, if you get a femoral neck fracture, if you get avascular necrosis, and please tell me if I'm wrong, if you get femoral component loosening, if you get a deep infection, and maybe if you get a dislocation you're going to end up with a revision. So, aren't these already captured in the revision rates? Do you understand my question?
- Joseph Dettori: I do. I do, and I'll answer the second one first, and that is that I don't know. I don't know the answer to that. I think that his comment about whether you revise somebody for something, I mean, I think some things are an automatic, maybe some are not, and perhaps, perhaps Dr. Chansky can speak to that. With respect to your first question, though, yeah, so we're reporting basically what's given to us. So, your comments an astute... or your question's an astute one. These are risks, that is, these are cumulative incidence of complications over whatever follow-up period the study has, and these... and these go from two years to five years. Okay, so this is the cumulative incidence. This is the proportion of people that have gotten this over that time period. That's different, that's...
- Craig Blackmore: So, a little bit of apples and oranges.
- Joseph Dettori: ...yeah. This is with respect, that's right, and that may be another reason why you can't really compare.
- Seth Schwartz: And not just that, but are the follow-up periods the same for the total hips as they are for the total hip resurfacings?

- Joseph Dettori: So, with respect to the... with respect to the... with respect to these data, these data are also risks at various points in time, five years, ten years. They are also cumulative incidence.
- Craig Blackmore: Right.
- Joseph Dettori: The slide I showed you that had rates are per year, and this is on differential effectiveness, and this is per 1,000 person years. So, that... so that basically says, well, that could be five people in one year. It could be one person in five years. That's the same denominator if you will. So...
- Craig Blackmore: But slide 21 has no adjustment.
- Joseph Dettori: ...not, right. Not everything, yeah, so unfortunately, not all the studies report the same follow-up period, the same...
- Seth Schwartz: I understand.
- Joseph Dettori: ...etc., etc., so.
- Seth Schwartz: No, no, but that's not what I'm asking. What I'm asking...
- Joseph Dettori: Okay.
- Seth Schwartz: ...in slide 21 where you're showing total hip arthroplasty versus hip resurfacing...
- Joseph Dettori: Yes.
- Seth Schwartz: ...is the duration... the time duration for those incidences the same for those two different groups? In other words, was the follow-up the same for each group within the studies?
- Joseph Dettori: Yeah, so, in... in the short answer to that is yes, not identical, but similar. These were all comparative studies with the same follow-up period. They might have missed a little bit, but.
- Seth Schwartz: And then the one other question I have, I think, is for our clinical expert. I'm not sure what, I mean, I can get a sense of what heterotopic ossification means, but is that significant? What does that really mean from a patient standpoint?
- Howard Chansky: Yeah, it's... it's not as significant as any of those other complications in that not everybody that develops heterotopic ossification needs additional surgery. About a third of the patients that get it, though, will eventually need a surgery to... it is basically excess bone that forms in the muscle around the hip. So, some subset of those patients it will hurt them, maybe not bad enough to need

another surgery, and then another, about a third of those patients will need it excised, and then about a third, you just forget it. It's a radiographic finding.

Craig Blackmore: So, again, sorry. I just, to... I'm trying to reconcile what looks to be worse on one hand versus worse on the other hand, and I'm trying to over-simplify and by doing so, I'm saying that basically everything but heterotopic ossification means you need a new hip.

Howard Chansky: No.

Craig Blackmore: Then tell me otherwise.

Howard Chansky: So, I'll go back to your question a few minutes ago. So, femoral neck fracture equals needing a revision.

Craig Blackmore: Yeah.

Howard Chansky: Avascular necrosis, because your native head in a surface replacement is... is covered by the metal ball, the only way to make that diagnosis is after revision you've pulled the head out and looked at it under a microscope. So, that equals revision. Femoral component loosening, at some point that needs to be revised, but there are patients who actually say, you know what, I can tolerate this for a while. Heterotopic ossification we just talked about. Dislocation, the majority are not revised, although a good percentage eventually go on to need revision, and deep infection it depends on your philosophy, but most people, as a generalization, would give the implant at least one chance to just wash... wash the hip out and not revise it.

Craig Blackmore: Okay, thank you.

Joseph Dettori: Chris, you had a...

Chris Standaert: No, I was going to say the same thing. Those top categories are the reasons for revision, the fracture, the AVN, and the loosening to a degree +/- . I'm assuming a hip replacement loosening is probably worse than a hip, a hip resurfacing loosening is worse than a hip replacement. The hip replacement is more intrinsically stable.

Seth Schwartz: Did I just... did I just...

Chris Standaert: So, when I...

Seth Schwartz: ...hear the avascular...

Chris Standaert: ...[inaudible] numbers come close, those are the reasons why they're getting revised.

- Seth Schwartz: But did I just hear that avascular necrosis is not necessarily the cause. It's something you identify when you do the revision?
- Howard Chansky: But it, it causes loosening of the implant.
- Seth Schwartz: So, it causes it... but I... but what I'm saying is... so it... that is probably captured in the evidence. Captured, well, yeah.
- Carson Odegard: Yeah, I have a question about slide 18 on revision events and on the cohort studies, I mean, it looks like the whole total is swayed by one report, and 24 events... 24 events, I mean, even though when you look at that same report for their effectiveness scores, they're almost identical. Was there something strange about that report, why there's so many events?
- Joseph Dettori: Not, not...
- Carson Odegard: Or is it just [inaudible]
- Joseph Dettori: ...not by memory. I don't remember anything particularly... nothing jumps out at me.
- Carson Odegard: Nothing that would come to mind?
- Joseph Dettori: Hm-mm.
- David McCulloch: But, as you pointed out, I mean, if you want to look at how safe something is and how often it needs to be revised, you don't want to look at randomized control trials, most of which are done at an academic center. You want to know from big national registries over the passage of time how often are these... which is why I, I think that the data in slide 19 are... are more relevant than looking at, you know, one to two year follow-ups from RCTs and things of that nature. What you see in the registries is much more real world experience of what it would be if these are done by everyone and their dog in various little hospitals.
- Chris Standaert: That's a hell of a dog.
- Kevin Walsh: Yeah, at the same time, I think it's a valid point that you may not be comparing the same thing. So, in other words, I guess what I would be curious about is, in the registry data, is there any age-matched, were the... were the original data looked at by age or was there any other kind of subset analysis to try and find out if we're comparing the same patients?
- Chris Standaert: But you, in a register, you, by definition, aren't. I mean, that's the thing about a registry, right? So, a registry is cause, cause and effect in a registry you can't do, because you're not, you don't have similar populations.

- Kevin Walsh: No, no, I understand that, but I mean, you, but you could...
- Joann Elmore: They did adjust for, for gender and age.
- Kevin Walsh: ...they did adjust for that.
- Joann Elmore: [inaudible] but the question is, are there any other characteristics? I mean, I would think that you might do a [inaudible] resurfacing in someone that you wanted to just hold off a few more years is likely the clinician's thinking, and there we would likely see more revisions like that.
- Chris Standaert: Well, that's like, well it's like Joe said. There's, there's also, I mean there are different patient populations. So, even if you control for age, you... you're going to think about putting a replacement... a resurfacing in somebody who wants to be active.
- Joann Elmore: Right.
- Chris Standaert: Who is fundamentally healthy and wants, they're not equivalent. So, however you want to stratify them, they're not going to be equivalent, because they're not randomized, and the study is showing, you know, high functional levels in the people who get resurfacing. Is that a reflection of the resurfacing being less invasive and a more functional hip, or is that just a reflection of self-selection for a younger, for a more actively-motivated population and they're the ones who want that, and it's probably more the latter I would bet, but that's where, I mean, answering that from the data is really hard from the registry.
- Joseph Dettori: But the comments are good comments because, I mean, a registry study is... is a cohort study, right? It's a prospective cohort study. So, you have all the potential for, you know, misclassification, for confounding, etc. So, yeah.
- Seth Schwartz: I guess I'm also struggling with this, the significance of this metal-on-metal issue. I mean, obviously it's, you know, captured the lay press and everyone's making a big deal about it, but I'm just... it looks like there is no data that it actually matters. So, I mean, it seems bad, but is there any data that shows it's bad?
- Howard Chansky: It's bad. I don't know if Joe was going to say something.
- Joseph Dettori: Well, we... we didn't... we didn't look at the question of metal-on-metal. I mean, where you go to find that is metal-on-metal on total hip versus conventional total hip. That's where you find that. You know, our... we were asked to look at hip resurfacing and only brought in the metal-on-metal because of the... the implications of that, but we didn't look specifically at total joint arthroplasty metal-on-metal versus conventional.
- Seth Schwartz: I mean, I think that's important here, because we're looking at these other potential, you know, reasons why, why the hip resurfacing looks bad, but there

are some questions about whether it looks bad because the patients are inherently going to have worse outcomes because they are different patients versus the joint is bad. The one thing that seems clear that is different is this metal-on-metal, and if that's bad, then that's, then that may be all we need to know. So, can you tell us more about why it's bad?

Howard Chansky: Sure, yeah. Metal-on-metal, by almost everybody now, is considered to be unequivocally really bad, and the reason for that is, as you get the metal wear, you know, you get these adverse local responses. So, you get osteolysis around the implant. So, the bone just starts being resorbed, and you can see patients with massive amounts of bone loss. The inflammatory reaction from the metal debris getting dispersed into their soft tissues can result in necrosis, you know, for example, of the abductor muscles and after that you can't have a hip replacement. Systemically, +/- you know effect on kidney function, but there have been case reports of people going blind from very high either cobalt or chromium levels. It can be cardiotoxic. So, I mean, we see mostly the local effects. I think you have to have really sort of high, high levels from somebody whose ignored the local problems for a while. The pseudotumors, which, which also arise around the surface replacements, and that's just big, persistent fluid collections with high levels of metal ions in them. So, you know, there's some evidence that some of this is operator dependent, even in total hip replacements, and everybody has put in metal-on-metal hips that have functioned beautifully for many, many years, but, you know, none of us can be perfect placing these components, and they are not forgiving, and the other side of the coin is, we have a beautiful implant, which is, you know, I don't know if Joe was here earlier, but we talked about, you know, I think the biggest advance in the last 25 years for joint replacements has been the advent of what we call highly cross-linked polyethylene and now some people are thinking that highly cross-linked polyethylene, when impregnated with vitamin E, which acts as an antioxidant, is even better. So, you know, hip replacements have been really revolutionized in the last 10/12 years because of the advent of new plastics, and you give somebody a regular conventional old-fashioned total hip that should serve them well for 20 to 25 years. So, I think that's, that in a... I think some of these studies also... it doesn't come out in the comparisons, because we've only been using the new plastics for about ten years now, and you have to have the hip for, you know, 10/15 years before you start seeing the benefits on the longevity from that. Does that all make sense?

Chris Standaert: Is there an FDA... any FDA action on the metal-on-metal prosthesis, black box warnings, recalls, things like that?

Joseph Dettori: They, there's, yeah, so they did their own report. They did their own report and they basically elevated metal-on-metal to you have to watch that they put down some, I don't remember exactly all of the specifications they have to watch for, but they discourage the use of it, but they don't ban it.

- Chris Standaert: I would assume, high systemic levels of cobalt and chromium were not part of the original plan of the manufacturer.
- Joseph Dettori: Right.
- Chris Standaert: Where, yeah.
- Howard Chansky: And you know, obviously, this is not purely correlated to medical science, but everybody probably saw, I think in the last few days, Johnson & Johnson settled their metal-on-metal implant class action lawsuit for many billions of dollars, and I think I read that they are paying each patient that needed revision surgery from one of those like a minimum of \$350,000. So, they are not going to be pushing these anymore.
- Michael Souter: I'm just looking at the FDA page here, and they say that... they recommend that asymptomatic patients with metal-on-metal follow up with their orthopedic surgeon every one to two years to check on this. That's what the FDA says at the moment. So, they would seem to discourage it, and the UK Medicines and Healthcare products issued a device alert against it. Health Canada ensued a public health recommendation discouraging it and the Therapeutic Goods Administration of Australia issued something similar in 2012. So, yeah, it all seems bad.
- David McCulloch: So, Dr. Chansky, would you do a hip resurfacing on anyone now? I mean, a young guy who... or not?
- Howard Chansky: I was told I wasn't going to have to give my own personal opinion. Well...
- Craig Blackmore: You just did.
- Howard Chansky: Honestly...
- Craig Blackmore: You can turn the mic off if you want.
- Howard Chansky: ...honestly, a patient would probably have to put a gun to my head. I don't see any reason for it, and there's too many potential complications, and the other side of it, again, I think we have great... a great alternative that I still think some of these studies do not quite do justice to. I mean, there's tens of thousands of patients in some of the British medical research studies, and we have good ideas of what dislocation rates should be and what infection rates should be and, you know, around Seattle I know of one person that will still, you know, fairly regularly put in surface replacement. There may be more, but pretty much, everybody else has stopped doing them.
- Richard Phillips: I find it interesting that the manufacturers haven't withdrawn it with that kind of a settlement.

- Howard Chansky: Well, that settlement, again, as Joe was pointing out, was not for surface replacement specifically, it was for metal-on-metal bearing hips, and some of the metal-on-metal bearing surface replacements have not done well, but I think everybody saw the data. There are still a lot of, you know, a lot of people out there that are very happy with their surface replacement, and there are some advantages to it, but again, you know, I think most orthopedic surgeons, we probably are pretty close together on the bell curve of skill, and if something is that finicky and, you know, you have to be so precise putting it in, in the end, I think you, you know, you almost have to get lucky. So, you know, in some patients, I'm sure it does absolutely great, but it's hard... it's hard to achieve that.
- Craig Blackmore: Thank you. Alright, any other comments or questions from the committee? Well, let's... let's move ahead and again, I think a good way to start on this is to have one or more members of the committee sort of summarize where their thinking is, in terms of the evidence, and then we can use that as a starting point for discussion? Does anybody want to take a stab at it?
- Michael Souter: I think we're talking about a very low frequency, you know, in terms of utilization procedure that there is not a great deal of enthusiasm for clinically and that has a significantly impressive level of problems or complications when looking at registry data. So, I don't... I think our earlier decision warrants revision, and I would favor no coverage.
- Craig Blackmore: Okay, any other thoughts? Anybody want to disagree or expand, or? Richard?
- Richard Phillips: Yeah, it seems to me, the only question I have is this issue of deep infection that Joe had pointed out in the total hip group that was higher than what, you know, I felt... I'd feel comfortable with, as opposed to what 0.4 where the hip resurfacing. Is there any reason that we should be concerned about that as a reason to maintain hip resurfacing, or is this the evidence of... so overwhelming the other way that we should never, ever even approve it. I guess that's one of the... the only issue that holds me back, right here.
- Craig Blackmore: Anybody want to comment on that?
- Chris Standaert: I mean, if that's... we don't have the total hip registry data. I mean, we also have... these are different patient populations. So, you have people with, you know, young 50-year-olds getting hip resurfacing and you have 75-year-old diabetics getting hip replacements. So, you do have this... they're not the same population. You have to look at registries for complications, but you have to be somewhat careful on how you interpret it. And I don't... compared to... I mean I look at this and say, you know, when we decided this a few years ago, you know, function was pretty equivalent, and it still looks like it is pretty equivalent. It looks like when they work in the short-term, they work pretty well. For five or ten years people are functioning well, but you start seeing this divergence of data that we didn't have three years ago. By the time you get

seven, eight, ten years out, your failure rate is getting high. All the bone problems are getting high, and then you throw in all the sort of metal-on-metal concern that has really... it's... since we made this decision, this is when it's become a big issue, and you throw those pretty substantial negatives onto this, I personally have a very hard time seeing where you would actually want to put this in somebody.

Howard Chansky: It's just, I was gonna say, it's... I mean, I think the people that are left doing it are reserving it for men that are young, under 50 typically, and they do not have inflammatory arthritis. So, it's osteoarthritis, active young men. I mean, that is the only population that I think it is still being used in.

Joseph Dettori: Let me just clarify that infection a bit, if I could. So, the estimate that we have comes from five studies. Three of them are randomized trials. Two are cohort studies. The denominator is a little over 500 for each group for the total hip and the hip resurfacing, and the relative risk is 0.2, but the confidence interval goes from 0.05 to 0.9. So, the real estimate is, I mean... the mean I gave you, which was 1.8, it could go down as low as under 1 and can go higher than 2. So, where that really lies, we're not sure, but I don't know if that's helpful to you. It could conceivably be lower than that is what I'm saying.

Richard Phillips: And if we... I don't know if I'm miss-stating your point of view on this, but I understand that the... this is not characteristic, what you see in all total hips, in general.

Howard Chansky: What is that?

Richard Phillips: What is the... the infection rate is much lower.

Howard Chansky: Well, yeah. That, those, you know, again, I understand Joe's points that, you know, they are comparing the same populations. I just know, again, from some huge studies that involved, you know, tens of thousands of patients, the typical infection rate reported for all-comers having a total hip replacement is more on the order of 1%, but I think when, again, the few surgeons that still really believe in this, and they're out there, they're not selling this to their patient because of infection rates. I suspect most are not even aware of that. They're selling it to the patients, again, because there is absolutely a lower dislocation rate. So, if you're young and you, you know, want to be very active, that is the, to me, the one clear benefit of a surface replacement. Your hip is just less likely to pop out of the socket and, you know, that is a big deal.

Richard Phillips: So, it's probably fair to say that the... taking Chris's point, that the population of the patients undergoing the hip resurfacing are probably not the group of patients, the same group of patients that are getting the total hip and that are getting the infections.

Howard Chansky: Yeah, not anymore, for sure. They are reserved for younger, healthier people.

- Richard Phillips: Okay.
- Craig Blackmore: Other comments? So, does anybody want to take a stab at summarizing where we are or what their thinking is at this point? You did. Anybody else want to expand or contract or contrast?
- Richard Phillips: I personally think I'm almost ready to [inaudible] on the vote, you know, because I... it seems to me this is pretty clearcut. Maybe I'm wrong, but that's my point of view.
- Craig Blackmore: I'm not arguing that it's not clearcut. I just, it's important that the committee sort of vocalizes what their thinking is for the record, as much as anything else, so that it's explicit why we're making decisions that we're making. So, I'm not trying to stir up controversy. I'm trying to get it all out there so we can... so we can have a train of what our thinking is.
- Seth Schwartz: I think I'm fairly in line with Michael's thinking here, which is that there does not appear to be a significant performance advantage to one over the other. I don't think we're seeing a significant difference in terms of efficacy of the approaches. I think there's some significant safety concerns related to the hip resurfacing that were not present at the last assessment. It seems like there may be some extreme circumstances where clinically people may want to use this, but that there is a good alternative for these patients even if this is not available, and I would be leaning towards no cover as well.
- Craig Blackmore: I guess I'll add my... just my two bits and then I'm trying to remember in looking at notes from the previous time we discussed this, and this expands a little bit on what you have both said, but the only, the only point I would make is that one of the reasons, I think, that we... that we approved this last time was given a similar safety profile, we were willing to accept the theoretical benefit of easier revisions, particularly for the younger, sort of more active person, and now we've got several more years of data, and that data, limited though it is, doesn't actually support this theoretical benefit of easier revision, and countering that, we have the increasing safety concerns. So, in my mind, the reasons that we approved last time haven't been supported by what's happened in the interim. So, I'm with the other comments we've heard.
- Marie Brown: Especially with the addition of our new... of number three.
- Craig Blackmore: Right, which we haven't... has not been demonstrated. The data is terrible. I mean, there's not much there, but it doesn't support it.
- Chris Standaert: But that data is insufficient. I mean, there's really no data. It's not... it's... that theory is not supported by the data. It's not really refuted by it.
- Craig Blackmore: It's not refuted.

- Chris Standaert: But it's not supported and since there's no evidence to say that this really is a good thing long-term from that standpoint, the safety data really becomes quite concerning.
- Craig Blackmore: Yeah, and there has been three or four more years to advance that hypothesis, and it is not supported yet. Any other further point? Anything people want to clarify about where they are? I mean, I'm happy to keep moving, but I wanted to get it out there.
- Carson Odegard: I don't remember in the last... our last meeting if revisions were put into efficacy or if it was in safety. I mean, the fact now that it is in safety means that everything we're talking about is safety, and I can't remember the last time if revision?
- Joseph Dettori: It was safety.
- Craig Blackmore: Okay, well why don't we proceed then? We will turn to our tool, and we have been through this before. I will just briefly run down for... for the record and to make sure we're clear in our own deliberations. I want to have you turn to page 5 and 6, and are there outcomes that we are considering in our decision making, which have not been delineated? Revision, we talked about as a safety outcome and we... is there anything else on here that we should consider under safety, efficacy, or cost? We have had discussion about special populations, and again, I think these are captured here, and any other comments?
- Okay, let's move to our first voting question. This is the nonbinding vote, and is there sufficient evidence under some or all situations that the technology is more, less, or equivalent effectiveness? So, if you believe there is sufficient evidence under any situation that it is more effective, you should vote more, and again, we have included revision as a safety outcome. So, this isn't pertaining to revision. This is pertaining to symptomatology, basically. Okay.
- Josh Morse: Seven equivalent, three more, and one less.
- Craig Blackmore: Okay. Safety, so, vote less if you believe it is less under any circumstance.
- Josh Morse: Eleven less.
- Craig Blackmore: And then cost effectiveness.
- Josh Morse: Ten unproven and one less.
- Craig Blackmore: Okay, so that forms basis for further discussion, as needed. Does anybody have further comments they want to make, further deliberation? So, I think when you have three different choices, you run the risk of not having a majority on any one and having to go through a re-voting process, but I think we will be

okay. We'll just go straight to the voting. Cover unconditionally, cover with conditions, or do not cover, and if we have a cover with conditions, we'll... we'll do the same process we did last time deciding on the conditions and then doing another aeration, but...

Josh Morse: Eleven no cover.

Craig Blackmore: Alright, we are... a part of our charge is to reconcile our decision making with Medicare National Coverage Decisions, and there are none. There is no, and we have already reviewed some of the other payers decisions and I think we do have some disagreement with some of the other payers, and that disagreement is based on the best and most recent evidence, I think particularly being swayed by some of the registry cohort studies showing the safety concerns with the metal-on-metal with the hip resurfacing. Any other comments on why we are disagreeing with some of these other recommendations, or have I captured...? We saw slides from... on different payers' policies, insurance payers, regarding... so I was commenting on them, which, I don't know that we have to, but I thought that was desirable. Is that not?

Josh Morse: Either way.

Craig Blackmore: Okay.

Craig Blackmore: The clinical guidelines. Right, so I'll just go back to those and make sure that I am... so, in terms of clinical guidelines, the American College of Occupational and Environmental Medicine gives it a C grade for certain patients. NICE includes it as an option under certain conditions and... and again, I think we are disagreeing a little bit with these guidelines, because we've reviewed the most recent evidence on safety, including the registries and cohort studies, and found that there was convincing safety concerns and no definable benefit. I believe this is a record.

It is 2:25, and we are adjourned. We have no other key questions, right? We are adjourned.