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Health Technology Clinical Committee Public Meeting

January 15, 2016

Chris Standaert: Good morning. I am going to call our meeting to order. I am new at this. So, I may not get it all in the right order. So, help me if I go out of order. So, for the record, I'm Chris Standaert. I'm our chair. My first act as chair was to appoint a vice chair. Joann Elmore has agreed to be our vice chair. So, I thank her for that and her willingness to take on that role.

We have a new committee member, Tony Yen at his first meeting. Tony is a hospitalist at Evergreen. I'm very happy to have him here, as well. We have two topics today, and we have to discuss some of our prior minutes, as well. We do that after the program updates . . .

Josh Morse: Right.

Chris Standaert: . . . which Josh will provide.

Josh Morse: OK. Good morning. I'm Josh Morse. I'm the program director for the Health Technology Assessment program. I'll do a brief presentation just with an overview of what will happen this morning, and then we'll move on to the previous meeting business.

So, today's topics, as you know, are Novocure (or tumor treating fields) and cardiac stents.

Background on Novocure, this was a new topic. It was selected last year. Cardiac stenting is a re-review. It was originally reviewed by this committee in 2009. It was selected for re-review in 2015 based on new literature, changing standards of practice, and development of new stent types. So, the other topics that we have scheduled in the next five months, six months, are . . . the next meeting will be looking at a re-review of the spinal injections topic, and a new topic selected last year, extracorporeal membrane oxygenation, or ECMO. Then, at the May meeting, bronchial thermoplasty for asthma and autologous blood or platelet rich plasma injections. There is a meeting in July to wrap up the review comments and finalize the draft decision from May. That's scheduled for July 8th, which is a Friday morning from 8:30 or 9:00 until 10:30 I think. Then, we have not yet selected topics for review for November 2016.

So, for those of you not familiar with the program, there are multiple ways to participate in this process. You can visit the Health Technology Assessment website. The URL is listed on this slide. You can join our stakeholder distribution list, and this is SHTAP@HCA.WA.GOV. This is the way to stakeholders or anybody interested may be notified of any program publications or meetings. We send out all of the information about draft publications and final publications and meeting dates via that distribution list. Anyone may comment on proposed topics, on key questions, draft, or final reports, and the draft decisions, and anyone is welcome to attend these public meetings. All of the meeting materials are posted on the internet and anyone may present comments today or at future public meetings, and additionally, anyone may nominate a technology for review by this group.

That's the presentation. We have a handout. There may not be any copies quite yet on the table outside that describes in more detail the program process and where you can get more information. That's it. Thank you.

Joann Elmore: By the way, if you're going to talk, we need people to talk into the microphones. They just asked for my support on that.

Gregory Brown: For the platelet-rich plasma, is that specific for just orthopedic issues or is it all conditions?

Josh Morse: I'm going to ask . . . we'll have an opportunity to talk about that at the end of the meeting. I'll do another round of what's coming up, and if there's questions about the topics at that point, that would be a good time to ask.

Chris Standaert: OK. So, we have a couple of issues to discuss. We have to go through our . . . approve our prior minutes and make final votes on our coverage determination from our prior meeting. So, in terms of our decisions, the first decision to talk about is the lumbar fusion decision. I believe there's a typo in the vote.

Josh Morse: Actually, this is the minutes. So, the typical process here is that you review the minutes from the prior meeting. And then we put it to a vote. There is a typo in the minutes.

Chris Standaert: If we could have clarification on the coverage determination vote for lumbar fusion.

Josh Morse: Yes, and if you look further into your binder, you'll see . . . I just checked this. In the decision itself, you'll see that the, the vote was recorded correctly.

Chris Standaert: In the decision but not in the minutes.

Josh Morse: Correct, in the minutes there is a typographical error. There's at least one, which puts the 10 in the wrong location. So, we can correct that.

- Seth Schwartz: Can you help us find the page, please?
- Chris Standaert: So, on page 2 of 4 of the minutes. So, not in our final vote, but in the minutes, it says HTCC Coverage Vote and Formal Action. You look at the numbers in the vote. Our numbers are in the wrong column. So, the numbers should be under the table titled HTCC Committee Coverage Determination Vote, not covered should be 10, covered under certain conditions should be one, and covered unconditionally should be zero.
- Josh Morse: Thank you.
- Chris Standaert: And now, it says zero, 1, 10. So, it should be the other way.
- Josh Morse: I believe there is a 10 for a 0 or typo under action right below that.
- Chris Standaert: Yeah. It says, "There are no national or local coverage determinations . . . "It should be no national or local coverage determinations to cover the procedure.
- Carson Odegard: I have another correction, too, Chris. I believe I attended that meeting, but I . . . tell me if I'm wrong.
- Chris Standaert: It's not listed?
- Carson Odegard: It's not listed.
- Josh Morse: That's correct. I apologize for that.
- Carson Odegard: Yeah, that's no problem, it's just.
- Chris Standaert: Either that you had a very odd dream one day.
- Carson Odegard: I just wanted to know if I was dreaming.
- Chris Standaert: Yes. I believe you were there. So, if we could add Dr. Odegard to the list of attendees. Any other corrections or concerns with the minutes? Alright, the more eyes the better. OK. So, anybody else have any concerns or things they see? Kevin, do you see something you're concerned about?
- Kevin Walsh: No. I'm good.
- Chris Standaert: Can we have a motion to approve the minutes?
- Seth Schwartz: I move to approve.
- Gregory Brown: Second.
- Chris Standaert: All in favor?

- Group: Aye.
- Chris Standaert: Any opposed? Abstentions?
- Josh Morse: That's ten approved.
- Chris Standaert: Yeah, ten approved. You have to abstain, I think.
- Tony Yen: Yeah. I'll abstain.
- Chris Standaert: Because you can vote now, but you weren't there.
- Tony Yen: Right.
- Chris Standaert: There we go. OK. We'll move on to the decision, and what's on the next set is our decision that's in your guideline, or in your little packet. So, we again, we had voted ten not to cover, one to cover under certain conditions, and there were a number of public concerns about this. We had a number of letters from the public. Does anybody have any comments on the public letters? So, one of the things I saw was a concern about our excluded conditions of things. There is a letter from American Association of Neurologic Surgeons. It says lack of precise definitions and said we excluded from coverage things like the grade 1 spondylolisthesis. They are reading that incorrectly, I believe. Excluded from our decision are things like spondylolisthesis and scoliosis and systemic disease, and they are excuses from our coverage, not exclusions from the fusion. So, our decisions, those are not exclusions from coverage. Those are exclusions from our determination. So, our determination applies to lumbar degenerative disc disease without those entities.
- Gregory Brown: Just a typo, the footer on page one says tympanostomy tubes, as opposed to lumbar fusion.
- Chris Standaert: I didn't look that far down the page. And there were concerns about SCOAP data, but we did inquire of one of the leaders of SCOAP about data, and we were not, we had no published data on SCOAP for us. So, concerns about not using registry data, we don't have the data, as far as I know. So, I'm not . . . when the data becomes available, we can re . . . these get re-reviewed periodically at certain points, and if the data gets published and released and is felt sufficient to cause, again, more scrutiny of this issue, we can certainly do that, at that point.
- Gregory Brown: So, point of clarification. So, we can only review the registry data, if it's published. We can't ask them to generate a report or something based on their registry. Is that correct?
- Chris Standaert: We have a SCOAP that the evidence vendor will perform, and they look for the published literature is what they look for. And if it's not published, there's no

peer review, there is no statistical analysis, there is . . . we don't have all that. So, they . . . Josh may want to answer that also.

Josh Morse: Sure, but there is the opportunity, as well, that anybody, if they recognize or want to submit information prior to the report or during the draft period, the vendor will take that data and review it and consider it for inclusion in the report. In this case, no data were submitted outside of that search function. Nobody submitted information or references pointing to where that data is, suggesting that it was missed or otherwise not included.

Gregory Brown: Yeah, and . . .

Josh Morse: But anybody may submit information regardless of its publication status for consideration in this process.

Chris Standaert: Yeah, so once the draft report is released, there is opportunity for people to submit additional data or studies they think were not included, and then the vendor is required to respond to whether they choose to or not include that in their report. So, there is an opportunity for that.

Gregory Brown: And just for process then, the vendor would then essentially perform the peer review on the data, was it analyzed appropriately or reanalyze it to see if it was appropriate for the report.

Chris Standaert: Most typically, they are given published studies that the people think they might have missed up or did not show up in their search for some reason. I don't know of a case where somebody submitted raw data to them to analyze. People can, and then I suspect it would be up to the vendor to determine the validity of the data the best they could from what they are given and whether it met their criteria for including it in the report, but again, that wasn't, no data was submitted to them here.

Gregory Brown: Right. I guess I'm . . . I'm just looking as we move forward specifically in hip and knee replacement, Medicare now has a mandatory bundled payment program, and part of that is collecting patient reported outcome data.

Chris Standaert: Yes.

Gregory Brown: So, that, so if something came up in the future for hip or knee replacements, they may have valuable data that is not necessarily specifically published on our topic, but they might be very . . . may be excellent sources of data for our questions. So, we can go to them and say, hey, we have this question. Can you submit a report to our evidence review vendor and then . . . do you understand what I'm saying?

Chris Standaert: I understand. I'm just wondering who would actually do that? Medicare will not . . . so Medicare will not submit data, so.

- Gregory Brown: No, Medicare's not capturing the data.
- Chris Standaert: So, someone in the public real world would have to be capturing that data in some way and preparing it in a way that it could be analyzed or assessed.
- Gregory Brown: Correct. Correct.
- Chris Standaert: Yeah, and they have the opportunity to do that.
- Gregory Brown: I presume what Dr. Shonnard said they had however many thousands of data points. And so, if they . . . if spine SCOAP presented . . . or generated a report, they could submit that for review.
- Seth Schwartz: And they did submit an abstract just prior to the meeting that was included in the meeting material that you had at the time, and anybody, a manufacturer, for example, with proprietary data that they don't want public, there is the ability to have a closed session and review that proprietary data. We haven't used that function at any point. Nobody has stepped up and said, we have this data but we can't make it public. There are ways to review that. It doesn't . . . in situations like that it . . . it . . . it, you know, we would probably have the methodologist review the data to be able to provide comment on the validity of that data and how it could be used, but it . . . you could review it in a closed session.
- Gregory Brown: OK. Great. Thank you.
- Christine Masters: We have a new sound system in this room. So, if you could be a little more conscientious about speaking into the microphones. Some people are having trouble hearing, and we've adjusted the volume levels, but it starts wanting to throw feedback.
- Josh Morse: Thank you, Christine.
- Chris Standaert: Are there questions or comments on the findings?
- Carson Odegard: On one of the letters, I forget which one it was, but the respondent was criticizing our verbiage as far as uncomplicated and saying that there's nothing uncomplicated about degenerative disc disease, and I think that's exactly why we used the term uncomplicated, to give the agencies the leeway of approving surgeries that weren't uncomplicated. So, I don't know if anybody caught that, but.
- Chris Standaert: Oh, yeah. I saw that, too. I think I made a statement about that during the meeting, about it being . . . about the uncomplicated low back pain patient. I think what we . . .
- Carson Odegard: Oh, that's what you were talking about, yeah.

- Chris Standaert: I think what we did is, like our statement says, for patients greater than 17 years of age with chronic lumbar pain and uncomplicated degenerative disk disease, then below that it says we discussed, it says we discussed the meaning of this, and it's meant for the population addressed in this decision include people 17 and it excluded, so we did the inverse. So, rather than defining, we defined . . . defined uncomplicated by pointing out the things that would qualify as complicated, and stated that they are not covered. They are not . . . our decision did not address them.
- Carson Odegard: Right.
- Chris Standaert: So, I think . . . I don't . . .
- Carson Odegard: They just didn't catch that.
- Chris Standaert: Yeah, it . . . it's in one of these letters that didn't quite catch that . . . that we're calling them out as if they wanted to be considered complicated, and then they would therefore . . . obviously it would not apply to them. Any other questions or comments? Is there a motion to approve the minute . . . approve our decision?
- Kevin Walsh: I'll make a motion to approve.
- Chris Standaert: Second?
- Gregory Brown: Second.
- Chris Standaert: All in favor.
- Group: Aye.
- Chris Standaert: Any opposed? No?
- Josh Morse: That's ten approved, one abstain.
- Chris Standaert: Abstention?
- Tony Yen: I abstain.
- Chris Standaert: OK. Moving onto the next decision on tympanostomy tubes.
- Josh Morse: So, there is one comment on this decision. It's in your binder.
- Chris Standaert: So, Dr. Hammond of the Department of Corrections suggested a change in our language. It changes our language from, we had said cover if acute otitis media with complications in individuals immunocompromised or otherwise at risk for complications of infection or . . . and he thought we should change the or at inordinate risk, not sure how you qualify inordinate risk versus risk, due to other

- comorbidities and then change one word from of to from at the very end. Any comments on these?
- Seth Schwartz: Can we get some clarification from one of the medical directors about what the difference is between at risk and inordinate risk? I mean, I understand the word inordinate, but I don't know exactly how that defines.
- Chris Standaert: Do any other agency directors have any comment on this? Do they concur with these recommendations? Do they have no opinion on them? If there's going to be . . . would these change implementation in some meaningful way?
- Female: I think he may have just been trying for more specificity to make it not as broadly interpretable, but I don't know exactly to what end. Inordinate is not much more specific than . . . so I'm not sure what his . . . his exact desire was.
- Chris Standaert: People see the need to change the language in the first one?
- Kevin Walsh: I would also ask a question about the comorbidity inclusion. Can you explain that at all?
- Female: Can you please repeat the . . . his statement or request?
- Kevin Walsh: So, number one of the limitations of coverage, Dr. Hammond had proposed to include complications of infection due to other comorbidities. I'd like some clarification on the intent of that state- . . . of that inclusion.
- Chris Standaert: No, he's not here.
- Female: I . . . I don't know if that was referencing the anatomic abnormalities. I . . . I don't know what he was referring to there, but we can . . .
- Kevin Walsh: The way I'm reading this is that it's excluding complications of infection of the ear.
- Chris Standaert: Yeah, infection . . . an infection due to other comorbidities, yeah. So, are there people viewing this change in language favorably?
- Joann Elmore: I think the risk is due to the comorbidities, not the infection.
- Chris Standaert: Yes. Do people see a need to change our original language, or, inordinate risk doesn't seem much different than . . . I don't know how we quantify that any more than risk. It then creates a . . . it's even more subjective than risk, I think.
- David McCulloch: I agree.
- Chris Standaert: And the second correction seems to me as though of is the correct word, not from. The risk isn't from the hearing loss. The risk is of the hearing . . . the risk is the potential to lose hearing.

- Seth Schwartz: Yes.
- Chris Standaert: Oh, I guess I see what he's saying.
- Joann Elmore: He's, yeah.
- Chris Standaert: So, maybe it is from.
- Joann Elmore: It does make sense.
- Chris Standaert: Yeah, risk from hearing loss. OK. I see. I'm reading it the wrong way. I would agree with the second change, myself. Other comments?
- Seth Schwartz: I would agree. I think the second change is OK. I, personally, don't agree with the first change.
- Chris Standaert: So, we are going to keep our initial language for acute otitis media, and then we will change the word of to from under section two of otitis media with effusion.
- Louise Kaplan: Chris, before we do that. I'm not clear that changing the word, so children at disproportionate risk from hearing loss, such as speech delay, that doesn't seem to make grammatical sense if you make that change.
- Chris Standaert: I think it's saying that these are, were we saying the risk is . . . children at disproportionate risk of hearing loss. I mean, they're at risk of losing their hearing. The from implies that the subsequent things are problematic in the setting of hearing loss.
- Seth Schwartz: I think the underlying concern is that children who have those things, who already have hearing loss, already have speech delay, already have underlying issues, are at higher risk and are . . . and should be offered tubes, or should be allowed to get tubes.
- Chris Standaert: So, it should be children at disproportionate risk of adverse, of adverse effects from hearing loss.
- Seth Schwartz: It's from the effects of.
- Chris Standaert: Oh, from? OK.
- Seth Schwartz: But it's . . .
- Chris Standaert: From the effects of hearing loss, OK.
- Seth Schwartz: Because of the subsequent . . .

- Chris Standaert: That's better language. So, it would read children at disproportionate risk of the effects of hearing loss.
- Seth Schwartz: Right. You need to, right.
- Chris Standaert: Children at disproportionate risk from the effects of hearing loss.
- Seth Schwartz: Complications of hearing loss. The effusion . . .
- Chris Standaert: Can you propose language for us?
- Seth Schwartz: . . . puts them at increased risk, because it can affect their hearing further is sort of the, the point and underlying hearing loss is one of the things that puts them at risk.
- Chris Standaert: I understand the concept.
- Seth Schwartz: So, yeah.
- Chris Standaert: Can you help us with the language? Risk of adverse effects from hearing loss?
- Louise Kaplan: So, the section is for at . . . so, we're saying cover, yes.
- Chris Standaert: They're already at-risk children, at-risk children.
- Louise Kaplan: And, so it's cover in number one or covering at-risk children, and I think we're trying to define who are these at-risk children. So, they are children . . .
- Seth Schwartz: Yeah. Essentially what you want to say is children with underlying hearing loss, speech delay, or cognitive source. I'm not really sure how the first statement works.
- Chris Standaert: Because I think we're trying not to call out every potential condition that puts them at increased risk of adverse effects from hearing loss. So, these are examples rather than try to be a definitive list.
- Seth Schwartz: Yeah.
- Chris Standaert: We're trying to use language that allows us to do that.
- Seth Schwartz: I mean, you might say, children at disproportionate risk from hearing loss, as a result of speech delay, underlying sensorineural hearing loss, or cognitive disorders.
- Michelle Simon: But the hearing loss isn't as a result of speech delay. It's . . .
- Chris Standaert: Speech delay is an example of the . . .

Seth Schwartz: No, they're . . . they at increased . . .

Chris Standaert: . . . average child.

Seth Schwartz: . . . risk from hearing loss associated with the fluid.

Michelle Simon: . . . Mm-hmm.

Seth Schwartz: Because they have underlying hearing loss or the other things.

Chris Standaert: Right, so . . .

Seth Schwartz: So . . .

Chris Standaert: . . . though the issue of speech delay . . . the way we word it, speech delay and cognitive disorders are examples of at-risk children within those events.

Seth Schwartz: . . . correct.

Chris Standaert: So, children at, at-risk children who are disproportionate risk, I think we're going to need to say something to the effect of children at disproportionate risk from the effects of hearing loss.

Seth Schwartz: Yes.

Louise Kaplan: Or is it . . .

Seth Schwartz: What we almost should do is . . . is after it says the hearing loss at the beginning, if this is from hearing loss, the rest should be parenthetical, such as . . .

Louise Kaplan: Those with.

Seth Schwartz: . . . as opposed to it being part of the same sentence.

Louise Kaplan: Help out children at disproportionate risk of adverse effects from hearing loss, such as those with.

Chris Standaert: I like that. That works.

Louise Kaplan: OK, good.

Chris Standaert: Did you catch that Christine?

Louise Kaplan: Children at disproportionate risk of adverse effects from hearing loss, such as those with . . .

Chris Standaert: Speech delay.

- Louise Kaplan: . . . speech delay, dah, dah, dah.
- Josh Morse: So, I got that. So, the sentence just to repeat back, this will go between risk and from in the example. Children at disproportionate risk of adverse effects from hearing loss and then continue the sentence. It
- Chris Standaert: Such as those with speech delay.
- Josh Morse: Oh, so there's a those with, such as those with.
- Louise Kaplan: You have to add those with.
- Josh Morse: Those with . . . such as those with speech delay, underlying sensorineural hearing loss or cognitive disorders?
- Chris Standaert: Yes.
- Josh Morse: OK. One, two, three, four, that's six words. OK. Thank you.
- Chris Standaert: Any other corrections or amendments or comments on that? No? Motion to approve as amended, or as corrected?
- Michelle Simon: Moved.
- Seth Schwartz: Second.
- Chris Standaert: All in favor?
- Group: Aye.
- Chris Standaert: Opposed? Abstention? I'm giving you a chance to raise your hand.
- Josh Morse: Ten approved, one abstained. Thank you.
- Chris Standaert: Alright. With that, we can move on. We're actually at the point for public comment if there are, do we have people signed up to comment? We will check to see if anybody has a . . . and then whether they prefer to wait until after the agency representatives. We can switch them and we'll check on the phone and see if there are people on the phone who want to comment. We can let them comment now if they'd prefer also. So, we'll give them the option.
- Josh Morse: Christine will check the list.
- Chris Standaert: Is there anyone who is live in attendance who wants to make a public comment who did not sign up? How do we . . . we don't have a phone. Where's our phone?
- Josh Morse: Christine has the phone controls.

Christine Masters: It's a different magic digital phone.

Chris Standaert: A magic digital phone.

Christine Masters: A magic digital phone.

Chris Standaert: Alright.

Christine Masters: That's why we need to speak into the mikes.

Chris Standaert: OK. So, can we check the phone and then we can give those people the opportunity to speak now or wait until after the agency directors if they choose to wait? Is there anyone on the phone who would like to make a public comment about the topic of Novocure? No? OK. There is no one there. Then, we will move on. So, we have no public comments, and we will move on to the Washington State Agency Utilization and Outcomes. Dr. Lessler will present for us.

Daniel Lessler: Good morning. Is that coming through? Yeah? Great. Well, I wanted to present this morning on a new technology. It certainly was new to me, um, when I, when I learned about it some . . . some number of months ago. I guess the trade name is . . . of the technology is Novocure, and these are known as tumor-treating fields.

Alright. So, we're not, let's see. There we go. OK. So, maybe Christine you could . . . you could just advance for me, yeah. OK.

Christine Masters: I will.

Daniel Lessler: So, this . . . this is a new . . . a new field referred to as bio-electromagnetics, and the idea here is that the application of alternating electric fields can actually kill tumor cells and there is actually quite a bit of literature on how this happens and I'm a primary care general internist by background. So, I sort of distilled this down to . . . that these tumor treating fields actually interrupt cell mitosis and therefore replication of cancer cells in this case. And, in fact, in 2011 the FDA approved the first bio-electromagnetic device for the treatment of recurrent glioblastoma. I would just mention that glioblastoma, a relatively rare disease, I think there'll be more discussion in the upcoming presentation of some of the incidence figures and so forth, but also one for which there really hasn't been much in the way of newer treatments, and certainly the treatments that have, have existed in terms of chemotherapy, radiation, surgery have had very limited impact on life expectancy.

So, Novocure uses a portable battery operated device. I have a picture I'm going to show in a minute where . . . and this allows tumor treating fields to be transmitted to the tumor via surface electrodes, and the actual . . . how those . . . how those tumor treated fields are directed is . . . they're actually mapped to

try and target the tumor itself. In the case of glioblastoma, that would be by using multiple MRI imaging to actually pinpoint where those fields should be directed, and they're continuously applied for at least four weeks. So, the person being treated with these fields actually has to wear this apparatus 24/7 to get the optimal benefit for at least four weeks.

Now, on the next slide, there's an actual picture of what this . . . what the device looks like and how it's actually in this case . . . how the electrodes are made adherent to a person's head. Next slide.

So, the key questions that the agency had were sort of the usual questions that you've seen in terms of the effectiveness of Novocure for the treatment of glioblastoma, the effectiveness for the treatment of other cancers, the harms associated with Novocure, whether the effectiveness of Novocure or adverse effects varied by clinical history or patient characteristics, and what are the cost implications and cost-effectiveness of this technology.

From the agency medical directors' standpoint, we were most concerned about efficacy and cost with respect to this new technology. Next.

So, this is a new and emerging technology, and it's interesting to me, since I've been in this role at the Health Care Authority I think, and I've looked at the work of this committee and the technologies and . . . that have been reviewed. I think they sort of fall into two buckets, one of those that actually . . . and I think we'll have a conversation about one such this afternoon with stents that are really very common, and where there's very high utilization and concern from that perspective. And then on the other hand where there are technologies that are new, emerging, and really haven't disseminated very widely and we're looking for direction from the committee with respect to such technologies. And with respect to Novocure, this is an emerging technology, and there is virtually no utilization. There has been some very little utilization in both PEBB and Medicaid up to this point. So, it really falls into emerging technology. Next slide.

Reviewing and preparing for this presentation actually was quite interesting because the course of preparation, there was a publication that came out in JAMA. I actually would say it was actually the very day that the AMDG was meeting to discuss and sort of grapple with the evidence-based report that reported on a randomized control trial, and I'll talk a bit more about that in a moment, but prior to that, there really was very limited evidence, and as I've looked at this . . . as we've looked at this, I really sort of came to see the evidence, that which existed before December of 2015 and that which was available after 2015. And I think there are really two key articles. I mean, there are, you know, a lot of other evidence here, but of limited quality, but really two key articles that I think have shaped thinking in this field, and the first is this . . . was an RCT of Novocure versus chemotherapy for recurrent glioblastoma, and in this case, it was really used as a salvage treatment and 80% of the patients had failed two or more prior chemotherapies, and the active control group

received additional chemotherapy regimens, and these regimens varied at the discretion of the treating physician. So, these were patients who had had two or more recurrences and the active control was treated with any number of different treatments. The outcome of that was that there was no difference in survival, but fewer adverse effects in the Novocure group. I think it was on the basis of this trial that the FDA approved Novocure, as a new technology, the idea being that it was perhaps equally effective but had fewer side effects. You know, I think from our perspective, you know, there are actually a number of flaws with this RCT, but the one that I think is most problematic for us is just that . . . is that the management of patients with recurrent or progressive high-grade glioma is difficult, and active re-intervention has not been proven to prolong survival. So, the question here is whether or not Novocure was being compared to effectively, in some sense, no treatment at all. We don't really know, because you had patients receiving multiple different types of interventions and patients who were at different degrees of severity in terms of whether they were on their second or third recurrence and so forth.

Kevin Walsh: Are you referring to the Stupp?

Daniel Lessler: Stupp, that's the first, the first Stupp Study, yeah.

Kevin Walsh: OK.

Daniel Lessler: So, and this was sort of the . . . S-T-U-P-P-. I don't know if that's how it's . . .

Joann Elmore: Yeah, 2012 article?

Kevin Walsh: Stupp 2012.

Daniel Lessler: Yeah. So . . . and then . . . and as I say, I really call out this article because this is the one that led to the FDA decision around licensing the technology. There are other studies that demonstrate survival advantages with Novocure, which will be discussed in more detail and as noted in the fuller report, these are poor . . . very poor quality. So, then December of 2015, if you could go to the next slide, there is this publication, the most recent publication in JAMA, in a December issue of JAMA, and this was a randomized control trial of tumor treating fields for treatment of supratentorial glioblastoma in patients with no evidence of progression after standard chemoradiotherapy. So, it was an unblinded RCT. There was no sham treatment. The study was actually stopped early, because of benefit found in the Novocure group, and immediate progression free survival in those treated with tumor treating fields and temozolomide, which is an alkylating agent, was 7.1 months versus 4 months in those treated with temozolomide alone, and then there was also a benefit in terms of median overall survival, and you can see the difference there.

There were complicated sort of stopping rules in terms of the decision to stop the trial. Actually, these were based on "per protocol rules," which was

different from intention to treat, but actually an intention to treat analysis didn't show substantially different outcomes.

Then, with respect to adverse effects, there were no significant increases in adverse systemic affects. There were higher incidence of scalp irritation, anxiety, confusion, headaches from those treated with tumor treating fields. Yeah.

Louise Kaplan: How large was the sample?

Daniel Lessler: It was several hundred, right, yeah. So, this just came out last month, and I think really sort of caused us to reconsider where we were going with our recommendations.

Chris Standaert: Can I answer her question?

Daniel Lessler: Yes.

Chris Standaert: They recruited 695 but obtained 700.

Daniel Lessler: Right.

Chris Standaert: And the interim analysis was on . . .

Daniel Lessler: 400+, I think.

Chris Standaert: 315.

Daniel Lessler: 315.

Chris Standaert: A ratio of 2:1.

Daniel Lessler: Yeah.

Chris Standaert: 2 to Novocure, 1 to no Novocure.

Seth Schwartz: And the vendor will go over . . .

Daniel Lessler: Right. So, there'll be more detail. So, on the next slide, with respect to Novocure and the treatment of other cancers, there is very limited data and really inadequate evidence to evaluate safety and effectiveness of the treatments of cancer other than glioblastoma based on our interpretation of the review.

As far as cost, costs ranged from \$11,000 to over \$20,000 per month, and there is no available data on cost-effectiveness.

These are some of the guidelines and payer policies. Again, these are in the vendor report, and you can see there's no CMS national coverage decision, and you can see the coverage policies of a number of different payers. I would note that this is prior to the December, 2015, publication in JAMA.

So, based on the available evidence, the recommendation that we would have is to cover Novocure at this point for treatment consistent with those treated in the RCT that was recently published. So, that would be those with supratentorial glioblastoma when provided in conjunction with temozolomide in patients with no evidence of progression after standard chemotherapy. We would recommend that Novocure not be covered at this point for recurrent glioblastoma and that it not be covered for cancers other than glioblastoma.

Chris Standaert: Thank you. So, questions?

Michael Souter: I have a question on the cost. So, these are per treatment costs you have here.

Daniel Lessler: So, actually those are monthly costs.

Michael Souter: Monthly costs.

Daniel Lessler: Right.

Michael Souter: OK, but the treatment is ordinarily for about four weeks?

Daniel Lessler: At least four weeks, but it could be longer.

Michael Souter: OK. Can you give a range for the treatment spans that might be utilized?

Daniel Lessler: You know, I mean, I think it's difficult to give a range, except to say that there would be circumstances, I suspect, where just continuing with the treatment would be the recommendation. I believe in the RCT, the most recent RCT, people received four weeks of treatment, and I think there might have been some that were allowed to go longer. So, the basis of the RCT was that four-week continual use, but I think it's possible that there would be, and I would actually have to defer to people more expert that there might be times when it was continued.

Chris Standaert: We can introduce our clinical expert. It may be a good time for that. She's actually one of the authors on the paper.

Michael Souter: Then, you have the concern maybe then that there is . . . you're looking at it in perpetuity for as long as that patient may be . . . so I can understand that. In terms, again, of the cost, what's . . . do we have any experience of the actual experienced cost by the state. I mean, this is per patient, costs you're talking about per month, how many patients are we talking about anticipated within Washington State?

- Daniel Lessler: Well, I mean, glioblastoma is a relatively rare, you know, rare tumor in terms of its incidence, and I'm not recalling it right off hand, again, but the expert probably knows. So, I think you're talking about even across our total population of a relatively small number of people.
- Chris Standaert: Did you all try to pull data on the current number of patients being treated for glioblastoma by . . .
- Daniel Lessler: Sure.
- Chris Standaert: . . . diagnosis code?
- Daniel Lessler: I'm sure we could . . . do we have any . . . did we pull that or?
- Christine Masters: We can't identify the glioblastoma with an ICD-9 or ICD-10. You have to go these O-codes that the cancer board uses, and that's when you can definitely get the . . . you know . . . know that it's a glioblastoma, but we can't just look at the codes on the claims and get that definitively because it's covered under a bunch of stuff, truly.
- Michael Souter: So, and just to . . . I'm not trying to torture you here.
- Daniel Lessler: No. That's fine.
- Michael Souter: The last question on cost, because I think that is obviously a concern, is do you have any sense in what's driving the cost? You know, is it the fact that people are just charging what they can because of the rarity of it being preferred or is it the . . . is the technology particularly expensive, or could we anticipate that were there continued use, that we could see, you know, the cost of the technology coming down, as the process becomes more comparable?
- Daniel Lessler: You know, I really don't know what the underlying cost of the technology of the machine is to produce or to actually utilize. So, I . . .
- Michael Souter: OK.
- Daniel Lessler: . . . I can't say.
- Gregory Brown: I have a question, Dan, as far as costs, I hate to drill this thing but, the . . . do you have some kind of a comparator for this type of disease, as far as treatment costs, what flagged the agency to say this is . . . the concern was high for costs? What are . . . what is a high cost? What would you consider a high cost?
- Daniel Lessler: Well, I mean, there isn't any good cost-effectiveness data. I mean, it would, you know, typically people talk in terms of \$100,000, being less than \$100,000 per life year saved, as being the kinds of interventions that as a society we have . . . that we tend to adopt, but there isn't . . . we don't have that data.

- Chris Standaert: Alright, Kevin?
- Kevin Walsh: Could you comment on why the agencies felt compelled to bring this to us?
- Daniel Lessler: Yeah. So, it is a new and emerging technology. It's actually being evaluated now in a number of other cancers. It had FDA approval, and we actually had seen on the PEBB side, we actually had seen at least one, if not two, appeals, and consideration by an independent review board. That's the way that the appeals process works. So, if . . . because Regence for Uniform Medical does not cover it, says it's noncovered. So, we were concerned because it is expensive, because we were beginning to see some utilization, because we knew it was being evaluated with other cancers. So, I think it's really an attempt to get out in front.
- Kevin Walsh: Thank you.
- Gregory Brown: I would make one comment on the technology. This has been around for decades in bone healing. Bio-electromagnetics have been around decades and after years and years of multiple studies, the answer is, it doesn't work. So, I would . . .
- Chris Standaert: And are you . . . what exactly are you referring to?
- Gregory Brown: For bone healing.
- Chris Standaert: Right.
- Gregory Brown: And I understand that's a different . . .
- Chris Standaert: Right.
- Gregory Brown: . . . application. I guess my concern from a clinical perspective is that if you have a P-value of 0.05 and you throw this at 20 cancers, at least one of them is going to come up significant, or the likelihood is that one of them will come up as a significant clinical effect. If you don't have multiple trials evaluating that technology in a specific cancer, you're going to find a false-positive finding I think.
- Chris Standaert: Right.
- Gregory Brown: And so that's, that's my concern, I guess.
- Chris Standaert: I think it's a good question, as we get to the evidence vendor and the report and the data they found, as opposed to Dr. Lesser, and we have the . . . we did a separate decision years ago on not this particular technology but ultrasound and bone stimulators separately. That topic has been reviewed by our committee in the past.

- Joann Elmore: I have a question, and it might be a good time to introduce the clinical expert. Dan Lessler had mentioned that there is . . . the Novocure is usually a four-week treatment, but in the JAMA article, they say that they continue until disease progression. So, I would assume that there would be, you know, four weeks and a few days off, and then they would continue it. So, there would be continued monthly charges. So, I would appreciate some clarification on that point.
- Daniel Lessler: In terms of whether it's . . .
- Chris Standaert: Used for one month or multiple months.
- Daniel Lessler: I would actually have to go back . . .
- Joann Elmore: The JAMA article . . .
- Chris Standaert: OK, we're going to . . .
- Joann Elmore: . . . says that it's continued until the second radiologic progression. So, it sounds like you just keep going with . . .
- Chris Standaert: . . . OK.
- Joann Elmore: . . . month after month. So, I would like . . .
- Daniel Lessler: Oh, it was. OK.
- Joann Elmore: . . . clarification on that.
- Daniel Lessler: Because that was the first article that was in . . . four weeks, OK.
- Chris Standaert: So, we're going to take a moment and just introduce our clinical expert so we can get some clarity. Our clinical expert is Dr. Lynne Taylor who is a neuro-oncologist at Virginia Mason and a professor . . . an associate professor at Tufts University in Boston here to help us today, and just for clarification from our standpoint, we will call on you periodically, as we need your clinical expertise on some of these issues of application and how things are used. It's a little easier, as you're one of the authors of the paper, and interpretation of the data is simply more something to go through the vendor with. So, we'll have to work around that, but certainly details of what you all did in protocols, we may call on you for, as well, but we very much appreciate your assistance with helping us with this.
- Lynne Taylor: Thank you for having me.
- Chris Standaert: No, it's a pleasure. So, in terms of Dr. Elmore's question, the issue of . . . we talk about one month or a four-month treatment, but in the trial, or the main trial that was just talked about and published in 2015, how long was the Novocure

continued for? It wasn't a one-month trial . . . a one-month treatment. It kept going?

Lynne Taylor: Right. I'm not sure where the four weeks came from. You know, you get your standard radiation therapy and temozolomide chemotherapy at the beginning of your diagnosis, and then the typical Stupp protocol, you have a four-week break before you start the next round of treatment, and maybe that's where it came from, but once patients get the Novocure TTF or Optune device on their head, they use it 80% of every day, and they use it for life.

Chris Standaert: OK. So, it's not even until we have outcomes of disease-free progression and then mortality are different end points here. So, it went for life. It didn't just go until people started progressing again?

Lynne Taylor: It varied from patient to patient, but yes. Some patients for life and some patients until disease progression.

Chris Standaert: Right, because of patient selection here, I assume.

Lynne Taylor: Yeah.

Chris Standaert: Yeah.

Michael Souter: And just for clarity sake, for life, I mean, how long are we talking about the average patient with GBM, just so everybody appreciates that?

Lynne Taylor: Well, if you look at the paper, I think the range was somewhere between four months and five years.

Chris Standaert: Yeah. Median overall survival in that group was 20.5 months in the group with the device. Other questions for Dr. Lessler? Yes.

Tony Yen: So, a quick question. I'm trying to understand the underlying science and efficacy behind this device. In the literature that's presented over here, did you see anything regarding other side effects that would actually be suggestive of a tumor treatment field affecting rapidly dividing cells other than the GBM? I would expect, I would think, and I don't know if simply the tumor treatment field is such that it does not involve say, like, the nasopharynx or the oropharynx but does affect, say, more rapidly dividing cells within the mucosa that we actually see effected with another chemotherapeutic drugs?

Daniel Lessler: Yeah, I'm not an expert on tumor treating fields. So, I mean, the intent would be, you know, obviously it's directed at the malignancy where you've got, you know, presumably more rapidly dividing cells. From what I've read about side effects, there was no mention of mucositis or anything like that, perhaps because they're able to direct the tumor treating fields more narrowly, and I would defer to the expert.

- Chris Standaert: Dr. Taylor, did you want to comment on this question?
- Lynne Taylor: Yeah. So, there's about a 50% incidence of very clear skin reactions in the scalp. Some of them require dermatologic visits. Some of them are difficult to heal, but there is pretty robust changes in the scalp and skull but nowhere else.
- Chris Standaert: Other questions for Dr. Lessler? No? I just want to make sure the public has had an ample opportunity to respond in case somebody now wants to respond after the evidence report. That's when they're supposed to talk. Can you unmute one more time, Christine?
- Christine Masters: Absolutely.
- Chris Standaert: This is . . . they are supposed to be able to ask . . . comment after that presentation. So, is anybody on the phone who would like to make . . . in the public who would like to make a comment for the committee at this time? It does not seem that way. OK. We will move on. Thank you.
- Daniel Lessler: Thanks.
- Chris Standaert: So, our evidence report.
- Natalie Slezak: OK. So, good morning. My name is Natalie Slezak, and I'll be presenting the Health Technology Assessment for Novocure, also referred to as Optune or tumor treating fields. Can you hear me OK in the microphone? Next slide, please.
- So, this slide lists shorthand and abbreviations that I'll be using throughout the presentation for your reference. First, I'll be presenting some clinical background information on the Novocure device and the indications for which its use has been investigated in published clinical trials. I will then give an overview of the scope of the report, the methods used for analysis, and the literature search results. I will then present the findings of the evidence review, relevant practice guidelines, and payer policies, and then wrap up with an overall summary and discussion.
- So, glioblastoma is a fast-growing glioma that develops from glial cells in the brain. It is also known as a Grade-IV astrocytoma. It has an incidence of two to three per 100,000 adults per year and accounts for about 50% of all primary brain tumors. The incidence of glioblastoma has been shown to increase with age, and it is more common in men than in women. Even with optimal treatment, the median survival time is 10 to 14 months from time of initial diagnosis, and the survival time after recurrence is just five to seven months. Longer-term survival has been linked to younger age and better scores on the Karnofsky Performance Status scale, which measures functional impairment.
- The standard care for newly-diagnosed glioblastoma is surgery to remove as much of the tumor as possible followed by combination radiation therapy and

chemotherapy using temozolomide. Virtually, all patients relapse despite best available treatment with a median time return of approximately seven months. Recurrence treatment options are limited. About 20% of patients may undergo repeat surgery, at which time, carmustine polymer wafers may be implanted in the surgical cavity. Chemotherapy is indicated for the majority of patients. Combination treatment with the angiogenesis inhibitor bevacizumab has been approved for recurrent glioblastoma patients. However, many patients are either unresponsive to bevacizumab or experience serious adverse events. Therefore, additional treatment options with reduced toxicity are needed.

So, the Novocure device may help to fulfill this need. Novocure, which recently has been rebranded as Optune is a device that emits alternating electric fields that disrupt the rapid cell division that is exhibited by cancer cells. Novocure requires continuous application in order to be effective. Patients are instructed to wear the device for at least 18 hours per day for each four-week treatment cycle, and patients are allowed two to three days off treatment at the end of each cycle, and treatment is typically continued until disease progression or throughout life. Novocure was approved by the Food and Drug Administration for recurrent glioblastoma in April of 2011 and was recently expanded for use in newly-diagnosed glioblastoma patients in October of 2015, and both of the randomized control trials, which were briefly presented in the prior presentation were based on . . . or included in this assessment.

The Novocure device consists of an electric field generator, which is portable, four insulated transducer rays, which are applied to the shaved scalp or the treatment area, a connector cable, and a power source. Treatment parameters are preset, and there are no electrical adjustments made by the patient or the healthcare provider.

Ongoing clinical trials are currently investigating the use of Novocure in patients with several other conditions. Several studies were found during a search on clinicaltrials.gov investigating various indications for Novocure use. Because the body of literature assessing Novocure was so small, we did not limit our search to just its use in glioblastoma. We did find one published clinical trial investigating the use of Novocure in patients with Stage III and Stage IV non-small cell lung cancer. We also found a case series investigating Novocure in patients with solid tumors stemming from various underlying conditions. This was an early on trial. Just a note that this list is not exhaustive of all the conditions for which current . . . Novocure is currently being investigated.

The PICO statement outlines the scope of this report. The population of interest were adults diagnosed with recurrent glioblastoma or other forms of cancer, including newly-diagnosed glioblastoma. The intervention of interest is Novocure, also referred to as Optune or tumor treating fields. The comparators of interest were chemotherapy, Novocure alone versus Novocure plus adjunctive treatments, placebo, or no comparator, and the health outcomes of interest were overall survival, tumor response and progression, other health outcomes, such as quality of life, adverse events, costs, and cost-effectiveness.

The following key questions helped to guide the development of this report. The first key question, what is the clinical effectiveness of Novocure for treatment of glioblastoma and other cancers? The second key question, what are the harms associated with Novocure? The third key question, does the effectiveness of Novocure vary by clinical history or patient characteristics. The fourth key question, what are the cost implications and cost-effectiveness of Novocure?

The initial literature search for primary studies was conducted in the PubMed and OVID databases on May 28, 2015. Articles were selected for review if they assessed the safety or efficacy of Novocure in patients with cancer and were published in English language journals. Articles were excluded if they contained no quantitative data, conference abstracts, case reports, or a series of case reports. Final update searches were conducted on November 20, 2015. Of course, when the one recent trial was published on December 15th, we included that in our assessment, as well.

This chart gives an overview of the literature search and selection process. Forty-two full-text articles were retrieved, of which ten studies reported and 13 articles were analyzed. Nine studies were found for key questions one and key questions three. There is one unique study found for key question two on safety, and there were zero cost and cost-effectiveness studies found in the literature review.

Like the GRADE working group, Hayes uses the phrase quality of evidence to describe bodies of evidence in the same manner that other groups, such as ours uses the phrase strength of evidence. First, we assessed the quality of the individual studies in order to determine if the study findings are valid. We take into account study design, execution, and analysis using an internal Hayes checklist, and we rate each individual study as good, fair, poor, or very poor. We then assess the overall body of evidence for each outcome of interest to determine how confident we are that the evidence answers each key question. We take into account applicability of the outcomes measures to the PICO statement, the quantity of data available, including the number of studies and sample sizes across studies, and the precision of the data. We also look at the consistency of results across studies and any evidence of publication bias. Bodies of evidence are graded as high, moderate, low, or very low.

This slide provides an overview of what the different overall body of evidence ratings mean. A high quality body of evidence indicates that there is reliable and consistent evidence reflecting the true treatment effect and the findings are unlikely to change with future studies. A moderate quality body of evidence indicates that there is reasonable confidence that the results represent the true direction of the effect; however, the effect estimate might change with future studies. A low quality body of evidence indicates that there is little confidence in the direction of the effect due to poor quality studies, inconsistent results across studies, or paucity of studies, and future studies are likely to change the

effect estimates and possibly the direction of the effect, as well. A very low quality body of evidence indicates that there is no confidence in any result found due to the paucity of the data, and therefore, we cannot make a statement on the findings.

Next, I'll provide an overview of the findings in the order of each of the questions. For additional details on each individual study, you can refer to the summary of findings table or appendix IV in the evidence report.

So, nine studies were selected for detailed analysis for key question number one. Five studies found that Novocure was at least comparable with chemotherapy for treating recurrent glioblastoma, and the overall quality of the body of evidence for this indication was low and consisted of one fair quality randomized control trial, one very poor quality trial with historical controls, one very poor quality cohort study, one poor quality registry study with historical controls, and one poor quality subgroup analysis. Two studies found that Novocure was superior to chemotherapy for treating newly-diagnosed glioblastoma. The overall quality of the body of evidence for this indication was low, excuse me, very low, and this was because it consisted of just one fair quality randomized control trial and one very poor quality cohort study. A single small case series was found evaluating Novocure in non-small cell lung cancer patients, and a single small case series was found evaluating Novocure in patients with solid tumors of various etiologies.

Five studies were selected for detailed analysis for recurrent glioblastoma. The overall quality of the body of evidence was low, due to the few studies of mainly poor quality or very poor quality, and FDA approval for recurrent glioblastoma was based on data from the Stupp 2012 study. Three studies assessed the effect of Novocure on overall survival. Two of these studies included a comparator group of chemotherapy patients and found that overall survival was longer in Novocure patients than in chemotherapy patients. Only one of these studies, Mrugala 2014, assessed statistical significance and found that the between group difference was significant. Two studies found that although median progression-free survival was longer in the Novocure group than the chemotherapy group, this difference was not significant. Two studies found that although percentage of overall survival at six months, one year, and two years was higher in the Novocure group than the chemotherapy groups, the statistical significance was not assessed.

Two studies assessed the percentage of patients with partial or complete radiological response to treatment, Stupp and Vymazal and Wong found that about 14 to 15% of patients exhibited at least a partial response to Novocure treatment compared with 10% in the chemotherapy group in the Stupp study. This difference was not statistically significant. One study compared Novocure plus bevacizumab to a group that received Novocure plus bevacizumab plus a drug regimen consisting of thioguanine, lomustine, capecitabine, and celecoxib, and Wong 2015 found that although overall survival and progression free survival tended to be longer in the group receiving the additional drug regimen,

this difference was not significant. However, it should be noted that there were only three patients in the group that received the additional drug regimen and 34 patients in the Novocure plus bevacizumab only group, and so this study was likely underpowered. Also, it did not include a control group with Novocure only.

Only a single study, Stupp 2012, assessed a measure of quality of life. Stupp assessed quality of life in 63 patients who had remained on treatment for at least three months. No meaningful differences were observed in global health and social function between groups. Cognitive function, role function, and emotional function favor Novocure. However, physical function was worse with Novocure, and there was a worse symptoms scale, including increased pain and fatigue, in the chemotherapy group.

One randomized control trial, Stupp 2015, and one cohort study, Kirson 2009, assessed the use of Novocure in patients with newly-diagnosed glioblastoma. These studies found that median overall survival and progression free survival were significantly longer in the Novocure group than in the chemotherapy groups. An FDA approval of Novocure for newly-diagnosed glioblastoma was based on data from the Stupp 2015 trial.

One small case series assessed the use of Novocure in patients with non-small cell lung cancer and found that 15% of patients exhibited a partial response to treatment; however, because there was no control or comparator group, no conclusions may be made.

One very small case series assessed the use of Novocure in patients with solid tumors stemming from various underlying conditions and found that one patient with breast cancer exhibited a partial response to treatment and all other patients had stable or progressive disease. This was a very small trial. There were only six patients in this trial, and because there was no control or comparator group, no conclusions could be made.

Seven studies reported on safety during Novocure treatment. The most common complication reported was mild to moderate dermatitis under the transducer arrays, which occurred in 16 to 90% of patients across studies. The dermatitis was reported to improve with application of topical corticosteroids, repositioning of the electrodes, or discontinuation of Novocure treatment. In addition, two studies reported that skin ulcers occurred in 1 to 7% of patients.

Several other nonserious complications occurred in Novocure patients, including fatigue, pain, and discomfort, gastrointestinal, and nervous system disorders, and infections. Only one trial assessed statistical significance of adverse events between groups and found that chemotherapy patients had significantly more gastrointestinal hematological and infectious adverse events than Novocure patients. Stupp 2015 noted that mild anxiety, confusion, insomnia, and headaches were more frequent in Novocure plus temozolomide patients, and these complications mainly occurred at the time of treatment initiation.

Several of the studies reported on differential performance of Novocure according to clinical history or patient characteristics. One post-hoc analysis found that patients treated during their first glioblastoma recurrence had significantly longer overall survival compared with patients treated at their second, third, or greater recurrence. Five of the eight studies analyzed for key question one reported the number of previous episodes of glioblastoma experienced prior to initiation of Novocure treatment. Median overall survival and progression-free survival tended to be longer in studies that enrolled a higher number of patients in their first or second episode of glioblastoma.

This table shows the overall function . . . overall survival as a function of number of previous glioblastoma episodes. The two clinical trials enrolled only newly diagnosed glioblastoma patients had longer overall survival at 20.5 months and 39 months compared with only 4.1 months in the Wong 2015 study who enrolled only 18% of patients during their first glioblastoma recurrence. In addition, Mrugala 2014, who enrolled 33% of patients in their first glioblastoma recurrence, observed a greater percentage of patients still alive at one and two years after beginning Novocure treatment compared with Stupp 2012 who enrolled only 9% of patients during their first recurrence.

Similar results were found with progression-free survival. Kirson 2007 who enrolled half the patients in their first glioblastoma recurrence had longer progression-free survival at six months compared with Stupp 2012 who enrolled only 9% of patients in their first glioblastoma recurrence. In addition, Kirson 2009 and Stupp 2015, who enrolled only newly-diagnosed glioblastoma patients, observed a greater median progression-free survival compared with Wong 2015 who enrolled only 18% of patients during their first recurrence.

Several studies conducted post-hoc analysis comparing prognostic factors that may have affected clinic outcome. One study found that patients that required lower daily doses of dexamethasone exhibited longer overall survival. Two studies found that patients that exhibited more favorable Karnofsky Performance Status scores had significantly longer overall survival. These two studies also found that patients that were not exposed to bevacizumab prior to starting Novocure treatment were more likely to respond to treatment, and one study found that patients that had a secondary glioblastoma upgraded from a lower grade gliomas were more likely to respond to treatment, as were patients that had smaller tumor sizes.

Compliance with Novocure treatment was an important factor related to treatment outcome. Two studies found that median overall survival was significantly longer in Novocure patients with a monthly compliance rate of at least 75%, which translates to using the device at least 18 hours per day, and in patients that had a compliance rate of less than 75%. A third study found that response to treatment was significantly and positively correlated with compliance. Furthermore, patients with partial or complete treatment response had an average compliance rate of 92%. Those with stable disease had an

average compliance rate of 85%, and those with progressive disease had an average compliance rate of 79%.

There were no published studies evaluating the cost of Novocure per unit of clinical benefit found during the literature search. In addition, none of the reviewed studies provided cost information for the Novocure device. Therefore, we resorted to an internet search, and we found two articles that gave estimates of the Novocure device to be between approximately \$11,000 and \$21,500 per month, and these values were converted to 2015 values.

There was no CMS national coverage determination identified. Several payer coverage databases were searched for mention of Novocure or tumor treating fields. AETNA's coverage policy states that tumor treating fields are medically necessary for persons with recurrent glioblastoma after receiving chemotherapy; however, Novocure is considered to be experimental and investigational for all other indications. Group Health and Regence Group consider tumor treating fields to be experimental or lack sufficient evidence supporting their use.

Six guidelines were found for treatment of glioblastoma. For treatment of newly-diagnosed glioblastoma, surgery is the first recommended treatment followed by radiotherapy with concurrent temozolomide followed by temozolomide. Three guidelines also state that carmustine polymer wafers implanted into the surgical cavity may help to prolong survival. When glioblastoma recurs, treatment options include repeat surgery, irradiation, chemotherapy, or bevacizumab, and two guidelines state that patients with progressive glioblastoma should be enrolled in an appropriate clinical trial. Four guidelines mentioned the use of Novocure for treatment of recurrent glioblastoma. One guideline states that Novocure should only be administered in the context of clinical trials. Another guideline states that Novocure may be considered a comparable treatment option to chemotherapy in treating recurrent glioblastoma patients. A third guideline from 2013 states that Novocure failed to prolong survival in patients compared with chemotherapy. That was from the Stupp 2012 trial, and the most recent guideline found from 2015 states that Novocure is an option in the treatment algorithm for recurrent glioblastoma.

In general, the evidence for Novocure for treating recurrent glioblastoma is positive and suggests that Novocure is at least comparable with chemotherapy in increasing overall survival and progression free survival; however, the body of evidence is of low quality due to a small quantity of data and lack of concurrent control or comparator groups in most studies. Two studies investigating the use of Novocure in patients with newly-diagnosed glioblastoma found that Novocure increases overall survival and progression free compared with chemotherapy, and the body of evidence for this indication is of very low quality due to the very small quantity available for this indication.

A single small case series available investigating the use of Novocure in patients with non-small cell lung cancer found that 15% of patients exhibited a partial response to Novocure treatment, and this body of evidence is of very low quality due to the small quantity of data and lack of comparator group. A single, small case series was available, investigating the use of Novocure in patients with solid tumors of various etiologies, and they found that 17% of patients or a single patient, exhibited a partial response to Novocure treatment. All other patients had stable or progressive disease. Finally, the body of evidence for Novocure for all other indications is insufficient due to the lack of studies.

Current evidence suggests that Novocure does not pose major safety concerns. The most prevalent complication that occurred during the trials was dermatitis under the transducer arrays, and this was reversible; however, the body of evidence for safety is of low quality. Several studies provided data suggesting that compliance with Novocure treatment was an important factor related to treatment outcome. The device manufacturer recommends that the device be used almost continuously throughout the treatment period, and there is at present very little direct evidence on the quality of life or functional states during Novocure treatment. One randomized control trial suggested that although cognitive and emotional function favor Novocure, physical function was worse with Novocure, which may have been due to wearing the Novocure device for at least 18 hours per day. The symptom scale was worse in the chemotherapy group and was likely related to the direct effects of chemotherapy treatment.

Further research, especially randomized controlled trials and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of Novocure in patients with recurrent or newly-diagnosed glioblastoma, non-small cell lung cancer, or other cancers; however, it may be difficult to conduct large-scale studies due to the low prevalence of glioblastoma and certain other cancers. Additional studies designed to systematically investigate differential effectiveness and safety according to patient characteristics and previous treatment history are needed, as are studies investigating the impact of Novocure on quality of life and functional status, and at this time, there are no economic evaluations on the cost-effectiveness of Novocure. So, thank you, very much. Any questions?

Chris Standaert: Thank you for the presentation. I'm sure you're going to have a few questions. I'm willing to bet. I'll let people digest for a second.

Natalie Slezak: OK. I'll go back to my seat so I can have . . .

Chris Standaert: You have your data and things over there? OK. People ponder for a second. I'm certain there are questions out there. Anybody like to get a little additional information?

Gregory Brown: I'll start.

- Chris Standaert: Thank you.
- Gregory Brown: Is there a way to measure compliance of use, and that might be a question for our expert?
- Chris Standaert: Well, we'll start with our vendor for one sec.
- Gregory Brown: OK.
- Natalie Slezak: So, from what I read on it, there is actually . . .
- Josh Morse: Could you please use the microphone?
- Chris Standaert: Use the microphone.
- Natalie Slezak: Can you hear me OK? Is it on? OK. So, from what I've read, there is actually, within the device, there . . . it's built in to actually track compliance. So, it's an objective . . .
- Chris Standaert: OK.
- Natalie Slezak: . . . measure. Is that your . . .
- Chris Standaert: OK.
- Natalie Slezak: . . . understanding, as well, Dr. Taylor?
- Lynne Taylor: Yes. Both during the clinical trial and when we use it in the FDA approved indication for recurrent glioblastoma, we get weekly and monthly updates of the compliance of the patient.
- Chris Standaert: Dr. Taylor, I had forgotten to clarify before, conflicts of interest. You had given us a written declaration, but . . .
- Lynne Taylor: Yes, thank you. I have no conflicts of interest to disclose, unfortunately, and just so you know, just a brief comment about the Optune NovaTTF device, I've been at Virginia Mason as a neuro-oncologist for over 20 years and declined to open this study as a principle investigator at Virginia Mason, because I thought the science was not clear, and then I left Virginia Mason and went to Tufts Medical Center in 2011. The trial was already open, and I became the principle investigator on the trial, and I'm the seventh author on this not because I have any personal investment in this but because it was already open, and we had a large number of patients that accrued to the trial. So, that's my involvement, but no . . .
- Chris Standaert: OK.
- Lynne Taylor: . . . I have nothing to disclose.

- Chris Standaert: Thank you for clarifying.
- Gregory Brown: So, what . . . in these trials, what percentage, you know, of patients met the 75 or 80% compliance rate? Is it 50% of the patients meet it, 90%?
- Lynne Taylor: No, it was well over 95%. These are very . . .
- Gregory Brown: OK.
- Lynne Taylor: . . . motivated patients. They have a terminal illness and they were very motivated.
- Gregory Brown: OK. Thank you.
- Chris Standaert: Again, we need to direct . . . all questions on the evidence go towards the evidence vendor initially. So, thank you. Do we have another microphone, Christine, so they don't have to bounce back and forth?
- Christine Masters: I will get one.
- Chris Standaert: Thank you. Yes, Louise.
- Natalie Slezak: So . . .
- Chris Standaert: Are you . . . did you want to have additional . . . answer a question?
- Natalie Slezak: . . . what would you like, so . . . meeting compliance, in the Stupp 2012 trial was 86% and would you like the very poor quality trials?
- Joann Elmore: Actually, on the compliance, can you verify how that was measured? Is that by patient self-report at the monthly visits or is it by the machine?
- Natalie Slezak: By the machine.
- Joann Elmore: Thank you.
- Gregory Brown: And on the machine, technically, is that a patient turns on a switch and it measures when it's on or does it measure impedances through the, you know, software to know that the patient's actually wearing the transducers and everything else?
- Natalie Slezak: The evidence didn't go that far in reporting that.
- Gregory Brown: Yeah.
- Natalie Slezak: Do you know the answer to that?

- Lynne Taylor: It's measured in the battery and it has to be turned on, and on the patient in order to measure compliance. So, it's on and on the patient.
- Joann Elmore: So, it's 24 (inaudible).
- Lynne Taylor: Yeah. It measures during that 24-hour period how long . . . how many hours it's on the patient and turned on.
- Chris Standaert: Louise, you had a question?
- Louise Kaplan: In your report, you gave us a slide that said quality of the evidence, which is . . .
- Chris Standaert: Use a mike, yeah.
- Louise Kaplan: . . . I'm sorry. So, in the report, you gave us a slide that listed the quality of the evidence that you used, high, moderate, low, very low, correct? And then in some of the slides, you gave quality as fair or very poor. So, is there a difference with that one slide? Is that overall evidence and then you did a different measure for the quality for the individual studies?
- Natalie Slezak: Yes. So, we assessed each individual study individually, and then we do an overall rating of the quality of evidence.
- Louise Kaplan: So, could you tell me in the new Stupp 2015, what the factors were that lead you to decide it was fair quality?
- Natalie Slezak: Mm-hmm. So, we did start out . . . so we did start out with . . . we downgraded it from a good quality trial because randomized control trials added the faulty start at good quality, because they're the best design available, but then we downgraded it based on there was about 20% attrition in the chemotherapy group. So, that was the main factor for that one.
- Louise Kaplan: Thank you.
- Chris Standaert: Just one note on the compliance issue. So, I don't believe these studies were . . . you weren't assigned to . . . you were at . . . 75% of the day you were at 90% of the day. They weren't randomizing that? I did have one patient who had one of these, and as a physiatrist, these are not easy to live with. You have to be plugged into a wall or have a fairly large heavy battery pack with you, and it was difficult for him to move in the exam room when he was relatively well. As he declined, it was very difficult for him to move with the device, and I could see that if you stay well and are highly functional, you could probably deal with that better, but I wonder if there isn't some self-selection the other way that patients who decline decide I can't even walk around my house anymore, because I can't . . . they abandon it more because they can't function with it. I don't know if that was investigated, but that would certainly seem a plausible alternative explanation to the fact that lots of device use associated with good outcome, maybe it's a good outcome that's associated . . . the other way

around, the good outcome leads to be people being compliant, as opposed to, you know what I mean? So, people who decline just choose not to use it more because it's too hard to function with it. I did note physical function is worse with the device on, and again, I suspect that's in part because it's very hard . . . they're cumbersome.

Michael Souter: Surely, if you're comparing that with the chemotherapy groups, and (inaudible) studies that kind of, you know, differential would actually come to the fore, and I think we have to look at the basis of the evidence.

Chris Standaert: Oh, no. I am looking at the evidence. I'm just, what we're getting is she's stating there's a . . . the association is . . . the implication of the association is a higher compliance is associated with a better outcome, but that's not a cause and effect issue, right? So, we don't know that higher compliance causes the better outcome. It could certainly be that people have a natural history that is more favorable . . .

Michael Souter: We're . . . we're saying . . .

Chris Standaert: (inaudible)

Michael Souter: . . . compared to groups where there was no device used. I don't understand the validity of your comparison, I'm sorry.

Chris Standaert: I'm not sure . . . I don't understand your . . . so . . .

Seth Schwartz: I think what Chris is getting at is, amongst the users . . .

Chris Standaert: Yeah.

Seth Schwartz: . . . we're seeing a high . . . they are showing high . . . longer survival in the patients who had a greater than 75% usage rate versus less than 75% or whatever the percent cutoff was. So, those groups both were wearing the device but saying in the patients that were wearing it more were doing better. Chris is saying, maybe they're not . . .

Michael Souter: No, I . . . I understand the kind of the chicken and the egg nature of that. I'm just not certain that I understand that when compared to . . . when you're looking at studies using the device compared to people who haven't had exposure to the device at all.

David McCulloch: Can I make a comment?

Chris Standaert: Yeah.

David McCulloch: These are terribly sick people and it . . . it's really hard being in randomized control trials. I get all that, but in truth, they haven't done an appropriate randomized control trial. The control group, cruel as this may sound, ought to

be wearing a sham thing 18 hours a day with a big battery, the whole deal, but it's going to be buzzing once every . . . doing something. I mean, you really would need . . . because I'm . . . it's unclear whether the survival or any change in outcome was associated with sitting there 18 hours a day with, I mean, who knows what that does to your psyche and meditation or whatever. It's just true. We don't have any studies that truly . . . I mean, that would be . . . in an idealized world, that's what you would do as your control group.

Joann Elmore: I want to follow up on that comment, because in the discussion of the 2015 paper, they discussed the placebo affect and how they did not have a placebo arm. It was a control arm that didn't get anything, and they went on about how well . . . you know, you can't really have a hat that's heated, etc., but I had the same feeling that you did, in that many studies have been published in the peer review literature showing the impact of a placebo effect. They have shown an impact when patients are adherent to placebo pills, and studies have shown an impact when a placebo is invasive you get much more of an impact, and as a clinician, I know the importance of hope in patients' outcome, and I was also bothered by this.

Chris Standaert: Yes?

Gregory Brown: Yeah. I want to switch studies here to the Kirson study of 2009. I was just a little confused about how, on methodology, you have ten newly-diagnosed GBM patients and then it's . . . you borrow data from a previous study of recurrent GBM data and how mixing those two would skew the outcomes reported? Do you have a comment on that?

Natalie Slezak: We did end up rating that study as very poor because of that. It was a very poor study design.

Gregory Brown: Why? I mean, what, was it a . . . it wasn't a compliance problem. It was a recruitment problem. Did they get . . . I mean the numbers are so low that . . .

Natalie Slezak: Well, they had a very small sample size.

Gregory Brown: Mm-hmm.

Natalie Slezak: Of course. They did not report the origin of the historical control data, and the methods for recruiting and collecting data in the concurrent group was not reported.

Gregory Brown: OK.

Natalie Slezak: So, there were several limitations in that study.

Gregory Brown: Yeah. OK. Thanks.

Chris Standaert: So, let's go back a second and be clear. I'm understanding Mike's questions and what . . . that I am clear. So, if you go to your slide 31, you talk about the compliance issues, and you say there's a correlation between compliance and outcome, but correlation isn't cause and effect, and my only comment is that cause and effect can go two ways.

Natalie Slezak: Mm-hmm.

Chris Standaert: That either the (inaudible) can cause a better outcome, or the worse outcome . . . better compliance causes a better outcome, or a worse outcome causes less compliance. They both show a correlation and association. Does the data distinguished between those two possibilities?

Natalie Slezak: No.

Chris Standaert: No. OK. That's my only point, yeah. Does that make sense, Mike?

Seth Schwartz: And along those same lines, there was some talk, and I can't recall which article or maybe it was several, but about the Karnofsky scores, which is that . . . we're saying that patients with better Karnofsky scores showed better responses, and I had the same thought, which is that what . . . you're dealing with healthier patients, might they just be having more (inaudible) because of that. Was there any way to differentiate that? Was there any subgroup analysis based on Karnofsky scores?

Natalie Slezak: No. The only thing was that the one study did break down . . . the Mrugala Study did break down whether they responded to treatment or not and then reported how compliant that group was, but there wasn't any further analysis.

Chris Standaert: The average Karnofsky score in the latest Stupp study was 90, as I believe, right? So, these are very highly functional people on the spectrum of disease here.

Natalie Slezak: Yes, and most of the studies had, as entering criteria, at least a score of 70. So, they're still mobile, able to move around. They may not be able to work.

Chris Standaert: Right. Other question?

Gregory Brown: I had one other clarification, just so I think I understand. So, all the recommendations that you reviewed from other societies or clinical practice guidelines, all those were published prior to this December, 2015, article publication, correct? So, they were unable to include that evidence in their recommendations? OK.

Natalie Slezak: Yes.

Chris Standaert: I would like one other clarification, just on the disease and perhaps this is for our clinical expert also. We have studies of recurrent versus primary glioblastoma, and the main study we have from Stupp, the intervention went

from essentially initiation of treatment to death, which I assume moves through recurrence. These are never actually tiered. So, recurrent means people decline. Recurrent is probably the wrong term, I would . . . because you don't really get rid of it, and it comes back. There are defaults. They are minimized. They are otherwise reduced, and people are clinically stable. So, does recurrence refer to the point at which they start to decline again after initial treatment, decline clinically, or get growth of tumor on imaging? How are people . . .

Natalie Slezak: On imaging.

Chris Standaert: . . . a growth of tumor on imaging is defined as recurrence for most of these studies or clinically, because again the study you have goes the entire spectrum of life. So, it's clearly moving from . . . it's treating patients all the way through recurrence and through whatever else they're doing. So, recurrence is defined . . . again, if people in the studies define it as growth of tumor, decline in function after a period of stability, how do you define a recurrent?

Natalie Slezak: So, it was based on MRI. So, during . . . when the MRI . . . so, recurrence based on McDonald criteria.

Chris Standaert: So, regrowth? Further growth? Progression of the tumor.

Lynne Taylor: It was defined based on MRI with extension variability. Even though it was blinded they couldn't agree, and you had to bring in a third person to sort of decide do you really think there's progression or not, in 17% of the cases. So, there was . . . this was a challenging subjective evaluation, but it was blinded.

Seth Schwartz: I'm going to ask a totally separate comment. We're flipping through this and recognizing that Novocure sponsored several of these trials. Do you have any comments about whether there was differential effectiveness based on whether or not Novocure was the sponsor for the trials?

Lynne Taylor: So, Novocure was the sponsor of all the trials presented in this evidence assessment.

Chris Standaert: Not much differential there. Do we have other questions? More will probably come up as we discuss this. So, I'd appreciate it if . . .

Joann Elmore: I'd like to . . .

Chris Standaert: (inaudible).

Joann Elmore: . . . ask our clinical expert to comment on the placebo effect in the fact that there wasn't a . . . in the control arm, for understandable reasons, they did not have a sham headgear.

- Lynne Taylor: Yeah, I hear your concerns about the placebo effect, but this really was a true tumor effect, as far as I could see, and what I would say is, those of us that were involved in the clinical trial noticed something, and that is, these are not actually very sick patients. What was notable about the patients in this clinical trial was I had a pilot that was bungee jumping and had three young kids and was very functional. So, as the trial went on, what was most interesting to me is, these are people that were highly-functioning individuals. They wore it in a backpack. They were up and about. Most of them were working, and most of them had no tumor visible on their MRI scans. So, this technology works best for very high functioning people with very small tumors, and typically the tumors were gone. There was no tumor present on the MRI scan. So, what made it very dramatic for those of us in the clinical trial is that we were very clear before the trial ended that it was going to be a positive trial, because in the rest of the world of glioblastoma, you just don't see tumor that goes away. So, I don't think the placebo effect actually is a meaningful concern here, because it was just very dramatic and the problem with recurrence in the world of neuro-oncology is there is pseudo-progression. So, you could actually get MRI changes where the tumor looks larger when it's actually responding to treatment. So, every patient in this trial that was said to have progressive or recurrent disease, it was not just based on MRI scan. The neuro-oncologist had to weigh in on every single patient and typically, it's greater than a 25% increase in the size of the tumor on MRI scan or new tumor where there was not tumor before, and very significant clinical decline. So, it was not just based on MRI scan. So, I don't think the placebo effect really is operable here.
- Gregory Brown: But I do hear a concern about selection bias.
- Lynne Taylor: Oh, yeah. Absolutely. I think that's a real concern.
- Chris Standaert: And for the vendor, so what . . . there was no subgroup analysis by tumor size, by Karnofsky scale, by . . . again, the average Karnofsky scale was very high, so again high functioning people, but they didn't do . . . none of these studies did a stratification other than the compliance issues, but stratification by tumor size or similar objective features of some sort.
- Natalie Slezak: So, Vymazal and Wong 2014 did find that patients with a small tumor size were more likely to respond to treatment. So, there . . .
- Chris Standaert: That was an RCT, or what was that study?
- Natalie Slezak: . . . no. That was . . .
- Chris Standaert: The compare . . . was there a comparator or was that just a cohort study?
- Natalie Slezak: It was a subgroup analysis of select patients from Stupp 2012 and Kirson 2007, so, patients with recurring glioblastoma.

Michael Souter: Just to pursue this question, because it seems to be circling. Was there an attenuation of compliance over the treatment time of these patients when they were on the trials that we're aware of other than their selection because they died, you know, but over the course of their treatments and . . . basically, I'm trying to see whether or not there's a difference, you know, whether there truly is an association of cause and effect and whether we can discern that.

Natalie Slezak: So, to clarify, you're asking if there was any evidence reflecting a decrease in compliance over time for individual patients?

Michael Souter: Yes, that, you know, that mirrored their progression of their disease.

Natalie Slezak: There was no evidence, but I mean, that is very interesting. That would be useful information to have, but the articles did not give that information.

Gregory Brown: So, just to clarify, none of the studies reported that or?

Natalie Slezak: None of the studies reported a decline in compliance over time.

Gregory Brown: So, maybe the other way to ask that then is, when they reported compliance, were they reporting it for the first six months of the study, were they reporting it for the entire duration of the study?

Chris Standaert: So, it wasn't, like, a survival curve. It was these blocks of . . . over time. That's what you're saying . . . asking?

Gregory Brown: Right.

Chris Standaert: Yeah?

Natalie Slezak: They didn't say.

Gregory Brown: They didn't . . . so they could be reporting the first month, so . . .

Carson Odegard: Yeah. I think that's what they did. I don't think they went beyond that.

Chris Standaert: They reported compliance over the first month and not for six or eight or nine or ten or twelve or fourteen months out?

Carson Odegard: No. There's 22% noncompliance over four weeks.

Chris Standaert: Over four weeks.

Carson Odegard: And that was it.

Chris Standaert: So, if you could . . .

- Carson Odegard: Whereas, the chemotherapy group went the whole distance of their life . . . of their life.
- Chris Standaert: So, if you could just clarify that question while we're at break, the question that is sort of how long . . . the period of time for which they monitored compliance and how they reported that, and is compliance in the first month different than compliance in the six month, and is there any relationship with severity of disease with that, but that's what people are asking.
- Carson Odegard: Mm-hmm.
- Chris Standaert: And if they didn't report it, they didn't report it, but the window of reporting is just for four weeks, or the window of reporting is for the entire . . . some of these people live for five years.
- Natalie Slezak: Let me, I can look at the Stupp. One of the Stupp trials might answer that.
- Chris Standaert: OK.
- Louise Kaplan: Is this the answer to the question? Three-quarters of the patients receiving treatment with tumor treating fields were adherent to therapy wearing the device 18 hours per day on average during the first three treatment months. So, it's . . .
- Chris Standaert: So, for three months?
- Louise Kaplan: . . . it says first three treatments.
- Chris Standaert: Right. So, you're tracking a three-month window, in which . . .
- Louise Kaplan: And that's . . .
- Chris Standaert: . . . they tracked them.
- Louise Kaplan: . . . that's the Stupp study, the 2015 one.
- Carson Odegard: Well, the appendix doesn't say that. The appendix says . . .
- Louise Kaplan: Pardon?
- Carson Odegard: I don't see three months followup in the appendix. The appendix says it . . .
- Louise Kaplan: Well, I'm just in the body of the article under treatment delivery. That's what it defines.
- Carson Odegard: Oh, OK.

Natalie Slezak: So, the 2012 trial did state that mean compliance was measured from month to month, and then they reported a median compliance throughout the study, and median compliance throughout the study was 86% of the time in each treatment month.

Chris Standaert: OK.

Natalie Slezak: But they don't get more detailed into breakdown of month by month.

Chris Standaert: Right. Any other questions, or do we take a break and then come back. We have more opportunity to ask the questions as we discuss. Go ahead, Tony.

Tony Yen: Sure, just one question for our clinical expert over here. Would we expect any other side effects on this treatment other than the maybe, the dermatologic findings and how do you attribute the dermatologic findings. Do you think that's maybe more contact dermatitis or maybe something else?

Lynne Taylor: So, it's definitely not a contact dermatitis. The patients actually feel a lot of heat on the top of their head, and they get some ulcerations. So, I think it's actually tissue destruction from the device itself. As for quality of life measures, actually what we found in the patients that we saw is that quality of life was actually improved, and I think it had to do with incorporating family members into helping put the device on. Several people had adolescent kids, 15 or 16 years of age, shave their scalp and apply the device, we actually felt that this hands-on sort of controlling the equipment actually gave people an improved quality of life because they felt they had more control, and there were no other side effects apart from the burden of, as you point out, carrying the heavy battery around, which is like a five-pound bag of sugar in a backpack.

Chris Standaert: Right.

Lynne Taylor: But no other systemic symptoms and in our 19 patients, actually an improved quality of life.

Chris Standaert: I think some might say that would go back to the issue of placebo effect and the lack of a true sham with the same types of familial intervention.

Lynne Taylor: Right.

Chris Standaert: Alright. Why don't we take our . . . we are miraculously almost on time. So, why don't we take a break until 10:15, and we will start back with our discussion.

OK. So, the next step is our own internal committee discussion. We still have access to the evidence vendor and to our clinical expert. We probably have several layers in which to think about this if we would like, depending upon technology in general, specific issues with it. We looked at studies of different populations of different types of tumors and recurrent versus primary. So, at

some level, we'll have to decide how we approach those. People are clearly wondering about various aspects of this in the literature that we have. Initial comments?

Gregory Brown: So, I have a question, I guess a procedure. So, I'm not sure I heard a specific concern about selection . . . I'm sorry. I'm not sure I heard a specific selection bias issue from our evidence vendor.

Chris Standaert: Mm-hmm.

Gregory Brown: But I did from our expert.

Chris Standaert: Mm-hmm.

Gregory Brown: And so how do we weigh that?

Chris Standaert: That's a perfectly fair question to rescind back to the evidence vendor to ask about potential for selection bias in the literature.

Gregory Brown: OK.

Chris Standaert: Again, you can continue the same line of questioning you had before. If you have a question to ask, we have to get to the best answer we can get to. Any initial comments, perspectives for the group to start?

David McCulloch: I mean, I don't want to discourage discussion, but I have to tell you, if I step back and be as objective as I possibly can, with all due respect to the expert, seeing this can possibly be a placebo effect, we saw these magical marvelous disappearing tumors in patients wearing this amazing hat and the battery pack and it's incredible. That is why you really need to have a properly controlled randomized trial with a sham device, and until that happens, I would say we have no evidence of any valid good caliber to suggest that this Novocure treatment does anything beneficial in patients with glioblastoma.

Gregory Brown: Actually, I didn't think I heard that. I thought what I heard from our expert was that the patients that did well have very small or no tumor, were already doing very well, and that it wasn't the device. That they knew ahead of time that they were going to have a positive outcome. So, I guess my question is to our evidence vendor. Is there . . . because we all know that what's reported in the actual article and one of the co-authors knows about how it actually really happened may not be the same thing, especially if it's an industry-funded trial. So, I'm trying to understand how could they, was there a selection bias evident in the way it was reported, or was it somehow masked, or?

Lynne Taylor: So, in the Stupp 2012 trial and some evidence selection bias was that there was a 22% loss to followup in the Novocure group, and in the 2015 trial, there was a 20% . . . about a 20% loss to followup in the other group, in the chemotherapy only group. So, that gives . . .

- Gregory Brown: But I . . .
- Lynne Taylor: . . . some evidence of selection bias.
- Gregory Brown: . . . I guess what I'm hearing would be more in the inclusion or exclusion criteria. Did they structure it such that they only included patients with small or minimal tumor, residual tumor, so that's how they ended up with this very functional subset of patients they were trialing it on.
- Lynne Taylor: So, they had a minimum Karnofsky Performance Status score of at least 70. So, that was an inclusion criteria, but as to . . . they just had to have established glioblastoma. That was the inclusion criteria.
- Chris Standaert: So, David, you gave some concerns about the study design and the lack of a sham, and our evidence level overall was low is what I believe you . . . for primary glioblastoma, for all . . . for both the primary and recurrent was low.
- Natalie Slezak: For recurrent was low, and for newly-diagnosed was very low.
- Chris Standaert: Was very low.
- Natalie Slezak: Mm-hmm.
- Chris Standaert: On the basis of the one study. The other concerns were our literature basis. We have only industry-funded studies. We have . . . are other people concerned about things in there?
- David McCulloch: What, I mean, just to clarify in the . . . I thought it was a nice report by Hayes, and then I liked that in slides 15 and 16 on page eight where you remind the committee and the general public about exactly how you go about the evidence. That's very helpful. If you read what the little boxes of low and very low, how could you possibly make a decision approving something if you're left with studies that give you little confidence or no confidence of any result found. I mean, that . . . I can't get past that, Chris, and no amount . . . to me, no amount of diving into the details of who was included and didn't, and did they keep it on for three weeks or three months, it isn't . . . there isn't . . . a study hasn't been designed that can even answer the question. Therefore, I just find it very hard that we would start approving the use of these expensive devices that look to me as if they decrease the quality of life. So, anyway.
- Chris Standaert: Right.
- Carson Odegard: Yeah, I still have a question about the costs, because I don't think we can really make a decision on cost, because we don't have any data to support being cost effective from the studies, but just from what we received, I mean, the potential costs could possibly \$250,000 a year, you know, over two years a half a million dollars. So, you're talking about the survival or at least progression free

survival, no. Overall survival of two years, 24 months, being a cost of perhaps half a million dollars compared to the chemotherapy group at 24 months, which is only 1.5% difference of the two groups. So, it's expensive.

Chris Standaert: Yeah. Lack of cost data is not helpful.

Carson Odegard: Yeah, right.

Chris Standaert: But the extrapolation of the cost is rather high.

Carson Odegard: Right.

Chris Standaert: Yeah. Do we have other thoughts on the data? What do you think we know or don't know?

Seth Schwartz: Well, I don't know if we know or don't know anything, but I'm struck by . . . ultimately, the effect sizes are relatively small, but we're looking at small numbers of patients and an impact of a matter of months, and I . . . so I'm struggling with worsening effects of, you know, in the 5 to 10% range differences in small studies with some questions about selection bias in some of these papers, and more historical controls, and in randomized trials we're not really seeing significant differences in effects. So . . . and yet I recognize that this is a challenging situation with patients who are at their end of life and you don't have a lot of good options. I'm just struggling to see any real benefit from this based on the numbers that we're seeing, and I also struggle with the same issue of cost that Carson brings up, which is, you know, are we talking about spending hundreds of thousands of dollars to prolong life expectancy in one out of ten patients for two months or three months. I struggle with that. Then, I'm also curious, sort of, about the number needed to treat in this, because it looks like the effect is not occurring in everybody. It's occurring in a small percentage of patients. So, if we're talking about \$20,000 a month for the direction of life for a potential effect of a couple of months in one patient, that . . . I'm struggling with those numbers, and please somebody tell me if I'm wrong in interpreting the data that way, but that's sort of what I'm seeing is that if we're . . . for the number . . . the number needed to treat is pretty high for a fairly small effect size.

Chris Standaert: We don't even actually have the data extrapolated. We don't have those statistics. They haven't done the work to give us those numbers. Kevin, do you have a thought?

Kevin Walsh: I agree. It's hard to be objective when you put yourself in the patient of, you know, kind of thinking about this disease and its natural history, but when I can be a little bit objective and look at what these studies are telling me, I'm not impressed that there is real benefit or that the benefit is a meaningful, clinically-important difference.

Chris Standaert: Right. Any other thoughts? Anybody sort of more . . .

- Seth Schwartz: I guess the only other followup comment that I would make is, I don't understand this technology, yet I'm very curious about it, and I feel like we need more data, and, you know, I think that for something that is this uncertain, it seems like the best environment for use is in a trial setting. So, I don't have problems with this being used in a trial setting. It's more a question of the broad applicability of it, and we've had this come up before where we have had things that we think we want to know more about and should be studied, but we don't, we don't know what the current data really means. So, I think that's . . . that's where I am on this one, which is, I would love to see, you know, I have no problems with this being used in a trial setting, but for general use, I . . . the data is pretty unconvincing, so far.
- Chris Standaert: The report does note a number of ongoing trials, and I even saw, I think, two that aren't funded by Novocure, or didn't reportedly say they were funded by Novocure. So, there is ongoing research still.
- Louise Kaplan: Well, a couple of these articles did not reveal that they were funded by Novocure, even though our evidence reviewer said they were all funded by Novocure.
- Natalie Slezak: I'll look again, but I'm pretty sure they were all funded by Novocure.
- Chris Standaert: Funded by Novocure.
- Natalie Slezak: But I can look again.
- Chris Standaert: And we've been talking broadly about the device in general and tumors. Is there reason to be looking at different things differently? So, the non-glioblastoma tumors elsewhere in the body versus glioblastoma, or there's . . .
- Kevin Walsh: I am strongly of the opinion that as little evidence as there is about glioblastoma, there's almost none about anything else.
- Natalie Slezak: So, there was one very poor quality registry study that did not report their source of funding.
- Chris Standaert: Oh, OK. They didn't say they weren't funded. They just didn't report it.
- Natalie Slezak: Mm-hmm.
- Chris Standaert: OK.
- David McCulloch: I would be very interested in this committee re-reviewing this topic at some point in the future when there is more moderate to high quality evidence available.

- Michael Souter: I think one of the things I'm looking for here, but I'm not really finding, is some structured appraisal of the quality of life of these patients, because in this disease, you know, I think we sometimes get obsessed about the data that we can measure and hold, which is the . . . an objective one, which is survival, because survival is a fairly stark metric. You're either dead or you're alive, you know? There's no two ways about it. However, I think that for these patients who are facing, as the data shows us, an inevitable conclusion at a somewhat more accelerated rate than the rest of us enjoy, the quality of life and the symptom control that one can look for is really, really important, and we shouldn't lose sight of that. It is a really unpleasant way to die, and I think that that's something I would hope for, that we try to capture somewhere. I'm just not seeing that in the kind of reported data, nor in the key questions there, because the effectiveness does seem to be very much built upon survival.
- Chris Standaert: And your point is the difference between just sheer survival and the quality of that life during survival, and you're seeing a lack of particularly the latter being reflected in everything we have.
- Michael Souter: Because one may make a very cogent argument that there is . . . if you have somebody who has four months of survival versus seven months of survival, but those four months are spent in a kind of, you know, drug confused haze, as opposed to somebody who may actually get, you know, five of those seven months with actually relatively clear function before they suffer an abrupt demise, I mean, I think that's . . . one might argue that that's an important metric of clinical outcome, because we're bringing some care to those patients, but you know, that . . . that's the kind of rigor, I think, or kind of metric data that I'd be looking for when considering this type of population, and that's what I'm troubled in the absence of.
- David McCulloch: I agree with you, Mike. I mean, I think . . . and one of the set of compelling emotional arguments is, you know, wouldn't this hat and giving hope is maybe improving the quality of life over just being poisoned with drugs. This study was in addition to poisoning with drugs. I would say that we can describe . . . we could write very good study design for an appropriate study, because I would say wearing a head warmer with a backpack playing 18 hours of Mozart might improve quality of life and survival, as much or better than this. I mean, that's at least a testable hypothesis.
- Chris Standaert: Right.
- Gregory Brown: So, I want to make sure I'm looking at the correct article from Wong in Cancer Medicine 2015. That's one of the ones just published and supposed to be so important.
- Chris Standaert: Mm-hmm.
- Gregory Brown: I guess I'm . . . so methods, a retrospective chart review was conducted. So, it's not a randomized control trial.

Chris Standaert: What disease process are we talking about, just so everybody's clear?

Gregory Brown: Glioblastoma.

Chris Standaert: Recurrent or primary?

Gregory Brown: Recurrent.

Chris Standaert: OK. Thank you.

Gregory Brown: Clinical benefit in recurrent glioblastoma. OK, it's . . . so it's not even an RCT. It's a chart review.

Chris Standaert: Mm-hmm.

Gregory Brown: And this benefit was in a group with three patients?

Chris Standaert: Small.

Gregory Brown: But, I mean, at 3 versus 34 in the other group. So, you can't make any statistical inferences.

Chris Standaert: No.

Gregory Brown: So, I guess I'm confused, as to . . . I thought I heard from Daniel that it was kind of a game changer from your perspective as to thinking about qualifying.

Seth Schwartz: It was the Stupp article.

Carson Odegard: And it was considered very low, very poor.

Gregory Brown: Right. OK.

Michelle Simon: But even, even with that Wong article, they're talking about, if you look at slide, what are we on here, on page 14 anyway. The overall survival of the Novocure group, they're reporting at 4-point months with the recurrence, and we heard natural history of this disease is the recurrent survival is generally five to seven months. So, actually, they are reporting less than what we know to be the natural history.

Gregory Brown: Mm-hmm.

Chris Standaert: Yeah, so there's . . .

Louise Kaplan: So, I don't know if I'm going down a totally wrong path by asking this question, but I would appreciate some help, perhaps from our clinical expert or those of you who likely have much more expertise than me, but one of the thoughts that

I keep having about this treatment is that there has been a lot of controversy about exposure to electromagnetic fields and childhood cancers and other types of cancers. So, I'm trying to really get at the biologic plausibility of this treatment doing what it says it does when there has also been a lot of controversy about electrical magnetic exposure actually being the cause of cancer as opposed to here we're saying it's really a cure. So, that's . . . I mean, I would just really appreciate either our clinical expert or any of you commenting on that. Am I just totally in the wrong realm?

Chris Standaert: It also sounds like there's an overgrowth of skin issues and other things that are an active effect of the thing.

Michael Souter: But just to be, and I may be being sordidly simplistic in this, but look at radiation. Radiation is both a cause of cancer and a cure.

Chris Standaert: Mm-hmm.

Michael Souter: That's how I view it.

Gregory Brown: And certainly all chemotherapy, or a lot of chemotherapy, you get secondary tumors down the road. So, I understand your question. I'm not sure it effects this.

Chris Standaert: Yeah. We certainly don't have longer-term data on what happens here.

Gregory Brown: If you've got a glioblastoma, you would hope you die from a secondary tumor ten or twenty years down the road.

Louise Kaplan: Mm-hmm.

Chris Standaert: So, Tony, what do you think? What's going through your head?

Tony Yen: So, the bottom line is, I question the basic science behind this. In other words, is this really relevant science that's really being applicable within the human being rather than just within, you know, cultured samples? So, that's my concern is that, is are we seeing something else, or are we seeing a true, true, clinical effect that we can actually backtrack and actually make sense of within the human being. I do have my doubts about the validity of these studies, I think, with all the points that have been raised here in this group, so far, but I think the basis is that I'm trying to make sense of why does this technology even work. This is basically just slightly before, below radiofrequency waves. So, why would that help me out, or why would that help any patient out. Maybe it's because of the energy that's involved. You can see that the specified energies for this treatment, but it still doesn't really make, I guess, rational sense to me, you know? Why does this even work beyond . . . I think a lot of other issues have already been discussed here.

Louise Kaplan: And that's what I'm trying to understand is the plausibility of it.

Gregory Brown: Right.

Chris Standaert: I hear concerns on a number of levels. I hear the basic plausibility concern. I hear concerns about this being essentially invasive technology with a very shallow depth of literature and very little analysis of that for things that have really allowed any potential population where there's a more prominent effect or a clear effect. There is concern with study design and concern with bias and concern with industry sponsored studies and similar issues.

Gregory Brown: I have a question for Dr. Taylor. Are you aware of the Vetner Studies done with this frequency on animals, because I know there has been a lot of work done? I don't know if it's the same frequency or not. It's very, very low frequency on tumors in animals and they are reporting positive results. So, I don't know if you have any awareness of that.

Lynne Taylor: So, I don't know specifically about the animal study, but I had those same questions that all of you had about this technology, and my understanding is that it's low intensity intermediate frequency, and there were a couple of biomedical engineers at Tufts and queried them about this, too. When it . . . it really can get through the skull. It really can get down into the brain. I was reassured by their basic science and Dr. Wong in Boston had done a lot of work on this, as well. He was an electrical engineer before he became a neuro-oncologist, and when it disrupts the myotatic signal formation it really acts the same way as taxanes do in breast cancer, the same method, but I don't know about the (inaudible).

Gregory Brown: OK. Thank you.

Chris Standaert: No other comments? We can move on to our decision tool unless we have something else to talk about?

Gregory Brown: Actually, could I make one other comment and . . .

Chris Standaert: Mm-hmm. Sure.

Gregory Brown: . . . I have a Ph.D. in engineering, so I'm speaking from that perspective, but one of the professors I worked with in grad school actually wrote a book on electro, you know, electromagnetic physiology, essentially, and he actually argued that, you know, the relaxation (inaudible) everything that charges in the frequencies, that they wouldn't have an effect. So, my perspective, as an engineer, is basic science is level five research. So, it may be plausible, I won't argue that, but it's really irrelevant, because, I mean, I can do . . . I don't need a randomized control trial to prove that Newton's law and forces applies to biomechanics, but I do need to know that the application of Newton's Law to fractured healing is appropriate. So, it's not the basic science, whether it's plausible or not, but is there the true evidence to show that it actually works and that's where I want to focus my decision on.

- Chris Standaert: Fair enough. Let me jump to our decision tool for a second.
- Louise Kaplan: Could I just ask one other question?
- Chris Standaert: Yeah.
- Louise Kaplan: So, we don't know exactly how many state covered beneficiaries there are who are receiving this therapy, because we didn't get that data, right Dr. (inaudible).
- Chris Standaert: Well, at the moment, the state wouldn't know how many received this therapy because it's only purely an experimental study. So, the state, I assume, is not paying for this at the moment, because it's all in studies.
- Michelle Simon: The occurrence of the disease is one to two per hundred thousand. So, if we know how many people are in the state database, then we would know how many people potentially would be candidates for that.
- Louise Kaplan: Well, I'm just saying about how many people is the state actually paying for or has not paid for, any at all? I just want to be 100% clear.
- Daniel Lessler: So, the incidence is rare. If you take two in a hundred thousand, there are about, there are about 2.1 million or 2.2 million people covered under PEBB . . . PEBB and Medicaid. Now, that includes both Uniform Medical Plan and then the fully insured Group Health and Medicaid. So, where . . . and as you saw, Regence does not, and that's UMP and Group Health, does not cover. Where this comes up is when somebody appeals a Regence decision, it goes up through, or as David knows, a Group Health decision goes up through the appeals process within the organization, but then a person has a right to an independent appeal to IRO . . . to independent review organizations. So, we have seen in a couple of cases independent review organizations making decisions that are different than the recommendation or than the policy at Regence, in particular. So, that's where it's come up. So, it's not many, but it has come up.
- Louise Kaplan: Mm-hmm. And so then, if . . . since Regence has a policy to not cover, if we decide not to cover, then it does not affect Regence, but since Medicaid and L&I don't have a policy, then it . . .
- Daniel Lessler: No, excuse me. So, in fact, if you make a decision not to cover, it does affect the Uniform Medical Plan and Regence is a third party administrator. So, we depend importantly on their clinical policies, but the decisions of this committee are the decisions that UMP and Regence, as our third party administrator, must follow, and likewise on the Medicaid side with our Medicaid managed care organizations, in contract, we require them to follow the recommendations of this committee.

- Louise Kaplan: So, then if we said not to cover, and Regence decided to cover, then UMP would stay not covered, correct?
- Daniel Lessler: That's correct. Right.
- Louise Kaplan: OK. And then, um, if we adopt a do not cover policy, how does that affect the IRO about which I only recently learned? So, does the IRO have to then . . .
- Daniel Lessler: My understanding is that what that means . . . if you . . . when you adopt a non-coverage policy, what that means is that it is not . . . it is not a covered benefit, and so in that case, it sort of falls outside the prevue of a decision that an IRO can make, because it's understood up front that this is not a covered benefit.
- Louise Kaplan: OK. Thank you. That's helpful.
- Chris Standaert: Just one quick question back to the vendor, so back to Dr. Souter's question. So, in the study . . . the latest Stupp study that's . . . they don't talk about quality of life. They have survival, progression free survival, and survival, and that's it. They don't talk about quality of life or physical impairment or any of these things that are worse and different. We actually don't know if their quality of life is better or worse. We don't know, correct, because they didn't list those as outcomes.
- Natalie Slezak: Right. So, not in this publication. So, there might be another publication pending in the cervical, in this . . . in the article. There is nothing in this article.
- Chris Standaert: Yes. You can speak.
- Lynne Taylor: I just want to make sure people understand that neurologic progression-free survival of 4 months versus 7.1 months is the quality of life metric, because what we mean by neurologic progression-free survival is if you're destined to live for a year, and this treatment gives you an additional 3.8 months of neurologic progression-free survival, that means you're not developing any paresis, you're not having seizures. So, the quality of life is measured in that neurologic progression-free survival.
- Chris Standaert: But it's not measured by any type of patient reported outcome, as to their actual quality of life during that time period.
- Natalie Slezak: Right. So, in the Stupp 2012 trial, they actually had a questionnaire based for quality of life, but not in the 2015.
- Lynne Taylor: For quality of life, right, in that trial, right.
- Chris Standaert: But that was not used in the 2015 study, or not reported in the 2015 study, curious. Barring other perspectives, why don't we go to our coverage tool and see if we can work through this. Other perspectives? OK. So, we go to coverage tool, which is in the back, right before the cardiac stents tab in your

binder. So, first I want to make sure at least we are thinking through everything that's relevant about this that we should be thinking through. Comments totally understood regarding the stated literature in which you think, but we still have to make sure we think through the . . . go through the things we were supposed to consider. We haven't talked much about safety.

Louise Kaplan: We need to add in here, anxiety, headaches, insomnia, and confusion because they were noted to be increased in those that were randomized to the Novocure.

Gregory Brown: Is that under nervous . . . nervous system disorders? Would that, or?

Chris Standaert: They were specifically called out. So, do we have safety concerns about . . . so, this is essentially being viewed in the last study as an adjunctive thing. So, it's on top of other things. So, it's not in place of something else. So, on some of the studies, maybe it was in place of chemotherapy. This is now in the primary glioblastoma study it's on top of existing treatments. So, I don't see concerns about mortality issues with it, but some of the things you brought up may effect quality of life potentially?

Louise Kaplan: Yes, that's why I brought them up, and they were significantly increased in the Novocure arm.

Chris Standaert: Which just goes to that question of the idea that you report disease free survival and assume that means they're living better, but you don't actually know that because other things happen that we're not capturing in that metric.

Michelle Simon: I think those might show up under efficacy. We have quality of life under that category instead of the safety concern, really.

Chris Standaert: Yeah. Sort of the inverse of quality of life, yeah. So, we have sort of, sort of life effecting, or quality of life impacting level of safety, as opposed to medical concerns in terms of safety, and we'd like to know more about the impact of those if we could, but we don't know it. OK. Any issues in efficacy effectiveness that we should be thinking about? We have survival and progression-free survival in this latest study. Quality of life vaguely.

Gregory Brown: Well, I think David's comment hits it on the head, 'cuz we don't have a true placebo-controlled randomized trial. So, we have no idea of the efficacy or effectiveness.

Chris Standaert: Outcome . . . and so other measures of it that we should . . . that we would like to see that we should thinking about. We talked about physical performance, too. There is one other outcome metric, which actually was worse in people with the device. Were the . . . the efficacy . . . the outcomes of (inaudible) are relative, effectiveness, just metrics we should be looking at. OK? In different populations? Again, we can consider this as a bulk therapy, which is a sense I'm getting is where people want to be going. So, as one thing, I guess, you know,

as opposed to dividing up by separate conditions or separate cancers, which we've done for other things. We've divided them up based on the tumor type or the location or these other issues, but my own sense from you all is that I'm not getting the sense that people are thinking that way. So, under special populations . . .

Seth Schwartz: So, Chris, I would separate that a little bit. I think that the evidence is different for glioblastoma versus other conditions where we have effectively zero, and I think it makes sense to differentiate, I mean, we may have the same answer for both, but I think also going forward it would be . . . it would make sense to have those handled separately.

Gregory Brown: Actually, do we want glioblastoma or initial presentation versus recurrent glioblastoma? I . . . to me, the evidence is there. So, I would suggest three subgroups, initial presentation glioblastoma, recurrent glioblastoma as defined by whatever recurrent is there, and then others, so those three groups.

David McCulloch: I would agree with that, because even if we don't have data now, I suspect this committee may at some future year, this topic will come back. So, having it in those categories makes sense, because we can debate how good or bad the quality of the evidence is, but we'll have some evidence on primary glioblastoma, recurrent glioblastoma, and other tumors. So, that makes sense to me to have it in those three.

Chris Standaert: How about we vote about it?

Carson Odegard: I agree, because it follows the study separations.

Chris Standaert: OK. So, within our special populations then, we're sort of special populations within those categories, as opposed to considering those categories as special populations.

Gregory Brown: Right.

Chris Standaert: Again, we're after sort of comments on the metrics themselves or measuring other things. Are there issues in here that make you worry? Do we know anything about age, sex, ethnicity, race? Do we know anything to differentiate these for us from what you all saw?

Group: No.

Chris Standaert: I'm getting a bunch of no's.

David McCulloch: Yeah.

Chris Standaert: Quiet no's, but a bunch of no's, and cost. I heard some certain concerns about cost. We don't have cost-effectiveness data, because we don't have that kind of study, and we have very vague cost data, because the state really hasn't paid for

this. Even within that, people express concerns about the extent of the costs and the potential extent of the costs, in particular. OK. So, can I get a general . . . so, the way we do this for Tony, in particular, is that we first vote not on whether we cover or don't cover. We vote on our relative thoughts of safety, efficacy, effectiveness, and costs, and whether we think this is essentially better, equivalent, or undetermined in terms of its relative value or relative benefit in those fields. So, my sense from you all voting is that you'd like to divide this up by three different categories, as opposed to considering it as an isolated intervention. So, we'll talk about that. So, were there other thoughts on that, because otherwise, we're going to vote essentially three times for each one of these is what we're going to do, unless there are other thoughts that people think we . . . there's no need for that, and we lump it all into one. Just throwing it out there for you, make sure you got the chance.

David McCulloch: I, personally, don't think with the current evidence we've seen, there is a need to vote three times. What I meant was, in writing this up and . . . as a public document . . .

Chris Standaert: Right.

David McCulloch: . . . there is . . . data has been . . . information has been given to us in these three categories, and at some future date might come back. It would make it easier just for re-review to say, OK, we're bringing it back because of this. Ten new studies have looked . . .

Chris Standaert: On glioblastoma.

David McCulloch: . . . at this and . . .

Chris Standaert: On primary glioblastoma.

David McCulloch: . . . right, or . . .

Chris Standaert: For example.

David McCulloch: . . . there's a new set of studies on, you know, pancreatic cancer, but I don't think we need to go through the dance of doing the cards three times.

Chris Standaert: So, if we don't do that, we have a very hard time distinguishing them unless people want to say . . . unless we . . . so, my statement about special populations was either we divide up into three categories and our issues of again, ethnicity, gender, are for each of those, or whether we consider the different tumors as special populations, essentially, since they fall under the same rubric at that point. So, at least we can make a comment about them if you want to make a comment about them, but if you want to bring out that difference and the difference in concern in the discussion, we really have to talk about them individually and probably vote three times, I would think. I'm not sure that's a major headache for people, but . . .

- Seth Schwartz: Just a point of clarification for me. The three categories, is that primary glioblastoma, recurrent glioblastoma, and other?
- David McCulloch: Other cancers.
- Chris Standaert: Other . . . other tumors, yeah. That would be it, so. So, other thoughts or we're going to go through those three categories. So, we can bring out the distinctions, even though I recognize where you're going.
- David McCulloch: Yep.
- Chris Standaert: OK. So, we're going to start with primary glioblastoma. You want to do the quicker ones? We can go in reverse?
- Joann Elmore: It gets us going.
- Chris Standaert: Get us going. It gets them . . . it warms people up, right, get the . . . I don't want anybody to, like, throw out their (inaudible) going too fast here. Alright. Alright. So, we will start talking about other tumors, so non-glioblastoma. So, in terms of safety, we are comparing sort of the safety of this device to other treatments, essentially. So, under any circumstances, do you think that this is essentially, hmm? Yeah. Whether it is, yes. We're starting with safety. We go one at a time, right? Oh, we start with effective. We can go with either of them. We'll go with safety. We'll go easy. So, people think it is safe under any or all circumstances? More safe than the alternative treatment.
- Josh Morse: OK, eleven unproven.
- Chris Standaert: So, again, we're talking about non-glioblastoma tumors, so effectiveness . . . efficacy.
- Josh Morse: Eleven unproven.
- Chris Standaert: And cost issues.
- Josh Morse: We have, it looks like, ten unproven, one more.
- Chris Standaert: OK.
- Joann Elmore: Now, recurrent.
- Chris Standaert: Go back up the scale. So, recurrent glioblastoma. So, we'll flip our order and go the order the form says we should go, which is efficacy first.
- David McCulloch: We have to keep Josh on his toes.

Josh Morse: So, right now, I need to clarify. So, did you . . . what was the previous order, safety?

Chris Standaert: I went safety, 'cuz I went in the order not of our form, but of our thing, so.

Josh Morse: OK.

Chris Standaert: We're good. So, we're going to . . . we're going to follow the form. We're going to follow the form.

Gregory Brown: So, we did one or two, two or three votes there?

Chris Standaert: Yeah, we vote on three different issues for each subcategory, essentially, so we can draw these up. So, again, so now we're on recurrent glioblastoma, and again, our first issue will be effective. So, in any circumstances, essentially, is it effective, more effective, or unproven compared to alternative treatments?

Joann Elmore: And this is recurrent?

Josh Morse: OK. I see one vote for more effective and ten votes for unproven.

Chris Standaert: So, the same tumor category, recurrent glioblastoma, for safety, and same choices.

Josh Morse: Ten unproven and one equivalent.

Chris Standaert: I'm waiting for Josh.

Josh Morse: Thank you.

Chris Standaert: And finally, for cost-effectiveness. So, Kevin, you're saying improved cost-effectiveness or that it is more costly?

Kevin Walsh: Oh, cost-effectiveness.

Chris Standaert: Cost . . . not cost, cost-effectiveness.

Josh Morse: One less, ten unproven.

Chris Standaert: OK. And we'll go to primary glioblastoma. The same issues, so effective, and the language is . . . this is under, let's see, any circumstance, correct? The language isn't on here.

Josh Morse: Pardon me. What is the question you're asking?

Chris Standaert: The exact language of our question. It's under any circumstance.

David McCulloch: Is there sufficient evidence under some or all circumstance.

Chris Standaert: That's it, under some or all circumstance.

David McCulloch: (inaudible) the technology is.

Chris Standaert: Effective.

Josh Morse: One more, ten unproven?

Chris Standaert: Two more.

Josh Morse: Two more, I'm sorry. We have two. I didn't see the other one. OK.

Chris Standaert: Same question for safety. So, again, compared to alternatives.

Josh Morse: Ten unproven and one more.

Chris Standaert: And same question for cost-effectiveness, so cost-effectiveness as opposed to cost.

Kevin Walsh: Oh, sorry, less.

Chris Standaert: I'm not trying to influence your votes and make sure we understand the direction.

Josh Morse: One less, ten unproven.

Chris Standaert: Alright. So, next we move on to voting, and we're going to follow those same three categories to vote, just so it can be clear what we're thinking and give the agencies some direction. At this point, we are talking about do we cover these unconditionally would be one choice, not covering them at all, or do we draw lines and say we're going to cover them for certain conditions or populations? So, before we vote, otitis media with effusion thoughts from someone about where we might go here? We'll start . . .

Kevin Walsh: I would suggest we vote.

Chris Standaert: Suggest we just vote, no more discussion. The point of discussion is to make sure that we are documenting our rationale for what we're saying, as we go to vote. That helps people say . . . so, it is helpful in some level to document. So, if we look at non-glioblastoma tumors, and my sense is we were unimpressed by the literature, but I comment about that so we can make sure our thinking is clear.

Louise Kaplan: I think what you're also asking is, is there a rationale for conditions? And I . . .

Chris Standaert: Mm-hmm.

Louise Kaplan: . . . I think what we're saying is, there does not appear to be any rationale for segmenting a decision for a special population or a circumstance.

Chris Standaert: So, under no . . . then, we have no circumstances, no data.

Gregory Brown: We have no evidence to support a rationale for any condition in non-glioblastomas.

Chris Standaert: Thank you.

Gregory Brown: Would be my summary of the . . .

Josh Morse: But if your vote came out with conditions, you would then flush those out.

Chris Standaert: Yes, I would.

Josh Morse: Thank you.

Chris Standaert: So, people still have the option to vote any way they want, and if you feel there are conditions we should talk about more that you've not brought up, you can vote for with conditions, and if the majority say that, we will discuss that. Otherwise, we are going to vote on coverage . . .

Josh Morse: For other tumors?

Chris Standaert: . . . for non-glioblastoma tumors, is that the language?

Josh Morse: Yes.

Chris Standaert: Non-glioblastoma, tumors that are not glioblastomas.

Josh Morse: Eleven no cover.

Chris Standaert: If we go to recurrent glioblastoma, we have a little more data. We need some way, again, for our people to know that we're thinking about what we should be thinking about these issues of safety and cost. We don't have a lot of inclusive data.

David McCulloch: No, we have . . . we have studies of low or very low quality.

Chris Standaert: Sort of in all realms.

David McCulloch: In all realms.

Chris Standaert: In all realms. So, nothing compare, yeah. OK. Then, we will vote. So, now we're talking about for treatment of recurrent glioblastoma, guarding this technology, and again, your same choices, cover, no cover, cover with conditions.

- Josh Morse: I see two cover with conditions and nine no cover.
- Chris Standaert: So, the majority are no cover. So, therefore, we won't have conditions. Now, we are to primary glioblastoma, for which we have a recently-published RCT, and its influence on people's thinking. That, of note, was halted early because they thought their findings warranted that, and they unblinded the trial at that point.
- Joann Elmore: I guess if you're looking for us to summarize comments, it's a single RCT. It was funded by industry. They did not have the placebo arm. It was published in a very prestigious journal, a high impact journal. It is a terrible disease that we really care about these patients. We wish we could do more. We . . . many of us articulated a desire to see a positive impact on quality of life. The outcomes that were looked at were months of sort of longer duration, and it was also discussed that the Novocure, it might give patients something to do, give them hope, give their family hope and that many of us wish that there was further studies beyond just this single RCT.
- Michelle Simon: I think one of the other things we talked about is a concern for selection bias and wondering if already higher Karnofsky Scale patients are included in that study and they're going to have better outcomes regardless.
- Gregory Brown: So, the balance on the allowing patients to retain hope needs to be balanced by not giving them false hope.
- Chris Standaert: And the issue of more depth to the literature would have helped this issue . . . draw out this issue of potential selection bias versus actually selective treatment response somewhere, but we just don't have it. The way the studies were designed don't give us that and the one out there is no . . . it's not a true sham, and the lack of a true blinded control are concerning. So, people are thinking maybe conditions and somebody who might be thinking of voting for conditions, I suspect now would be your chance to say something if you'd like to, if you're thinking that way. Otherwise, I get a sense that we would talk about conditions after the vote if that's what the vote turns out, just from what people are saying. So, barring other perspectives, we'll vote on this then.
- So, I'm voting on a treatment of primary glioblastoma with the Novocure device. Again, it is their . . . we have three choices. We have cover, not cover, or cover with conditions. We can vote.
- Josh Morse: I see one cover with conditions, two, excuse me, cover with conditions, nine no cover.
- Chris Standaert: So, now we have to make sure that we are consistent with our guidelines and Medicare issues. There is no Medicare decision on this. Again, it is my sense the overlying majority of guidelines where they were suggesting this is still investigational although admittedly they were published before this last study

came out, but we were consistent with the existing guidelines to the best of my impression, personally. I don't think we have any concerns there. I think . . .

Josh Morse: So, if you could flip to . . .

Chris Standaert: . . . the guidelines?

Josh Morse: Yes.

Chris Standaert: So, page 5 of your coverage tool. So, again, this is a review of our guidelines. So, in the treatment of glioblastoma, again, Novocure should be administered in the context of clinical trials. There is one guideline from the European Association of Neuro-Oncology. Recurrent glioblastoma may be considered a comparable treatment option to chemotherapy for the American Association of Nurses. That is just making nurses aware. That is not a treatment recommendation of any sort, as I read it. European Study of Medical Oncology, failed to prolong survival with chemotherapy. NCCN, National Conference of Care Network, says it's an option in the treatment algorithm for recurrent glioblastoma, but they are not . . . they are inconsistent with . . . not necessarily. It seems as though our committee found the evidence not compelling in terms of making this an advised treatment and are more aligned with the view that this is still experimental treatment that warrants further study and to be used in that context.

David McCulloch: Solidly.

Josh Morse: Thank you.

Chris Standaert: Alright. So, we are half an hour early.

Female: May I ask one (inaudible) question?

Chris Standaert: Sure.

Female: So, I just want to understand how this fits into the context of cost overall for Washington State for my patients. So, if this isn't available for my patients, the only other option that they have is bevacizumab, which is about \$90,000 more per year and far more toxic. So, is there ever a place where the decision that this committee are looked at in sort of a broader picture of the cost for Washington State, and what do I take back to my patients?

Chris Standaert: So, our charge is to look at the available data on cost and cost-effectiveness. We don't . . . there were no studies on cost-effectiveness was our problem, and the state . . .

Female: (inaudible) technology, it also wouldn't be . . . you would all vote against it. So, I'm just saying, what does a practicing clinician do when we've got bevacizumab

approved and payers who pay for it, and yet the evidence for bevacizumab is no better than this (inaudible).

Joann Elmore: That's another committee that votes on pharmacy.

Chris Standaert: Yeah, pharmacy is covered in another space, and I mean, as you just heard, we are charged with using evidence to make a decision regarding the application of these technologies and use of them within the state healthcare systems, and the committee felt fairly uniformly that we didn't have any adequate data on costing. We don't really know what this costs. We don't know. We have no idea, and we don't have any comparative studies, and even the most recent study was . . . it was an adjunctive treatment. It wasn't . . . in the recurrent it's used as an alternative. It's used as an adjunctive treatment in its most recent study, but we don't have cost data. So, we have no data from which to make the decision. We weren't presented with data on the cost of bevacizumab, nor are we given sort of real cost-effectiveness studies within the treatment of that, and trying to relate the connection between cost and outcome and safety is sort of our charge here, and that's what we're missing, that leg, essentially. I hear your point, but we don't have the data from which to answer that question.

Gregory Brown: Maybe a clinician's pragmatic response would be that if you think that this is an important treatment, that your site be involved in a clinical trial that can offer this as a clinical trial treatment, but that's the only way I would know that you could offer it pragmatically.

Chris Standaert: Alright, where is our schedule? I lost my schedule. So, this afternoon, we have cardiac stents. We are a good 45 minutes ahead of time. So, we can probably get some things done before lunch to make our afternoon a little more manageable, because this afternoon is rather complicated, actually, I thought.

Joann Elmore: That would be good. That's what I was hoping, but they're not here, so.

Chris Standaert: So, we're going to have issues with public comment, but we can still call for public comment, and then we can just open back up at 12:50 to make sure we capture people who came in late, and the agency's directors reports are available online. So, if people are afraid they weren't going to get them, they certainly can reference them there if they want to make comment.

Seth Schwartz: Chris, can I make one suggestion?

Chris Standaert: Yeah.

Seth Schwartz: We usually do at the end of it, do some of the, just the committee work, kind of looking at key questions and that kind of stuff. Do we want to do that right now first, because that way we're done with that stuff, and then we can move on?

Chris Standaert: How much of that do we have?

- Josh Morse: We have very little and really what we have is a preview of what's to come.
- Chris Standaert: OK.
- Josh Morse: An expansion of what I went over this morning about the topics of the next . . .
- Seth Schwartz: I mean, if it's only going to take a couple minutes, why don't we just bang it out before we start the afternoon's work and then we . . .
- Josh Morse: I'm sure we can do that.
- Chris Standaert: We can do that.
- Josh Morse: So, in the back of your binder, you have a slide presentation all the way in the back pocket, and I will just quickly go over what is coming up. Again, this is an expansion of what I told you this morning. So, in this first slide here . . . so, the spinal injections re-review, the draft report was out for public comment, and that, I believe, closed yesterday or closes today. You will have that topic on the 18th. It will be in the afternoon, and in the morning on that day is extracorporeal membrane oxygenation, a new topic, and very similar, the draft comment period closed yesterday, I believe, on that topic, and the final reports for those will be available in a couple weeks here. In May, the two topics are bronchial thermoplasty and autologous blood or platelet rich plasma injections. A draft report is due to us in February on each of those. So, if there is information that an outside body or registry wants included, it may not be available in the published literature or has any comment at all. That comment period will occur sometime after the middle of February. There will be a 30-day comment period, and that would be a good time for people to submit additional data that they want to be considered in that review. We have not yet scheduled topics for the November meeting.
- So, moving on to the spinal injection. So, the context for spinal injections, again, is that there is new literature that has been published, since the original review was done and completed in 2011. I think that review was completed, and there have been some other related publications, I think, related to safety concerns around that. That's what triggered that review. So, as I already said, the evidence report, you can see the schedule on slide number three here, around that topic, and what will happen and the next step is that we will be publishing the final report to our website. About the 12th of February, that report should be online.
- The ECMO topic, this is slide number four. So, this is a critical care treatment, and in adult populations, this was identified for concerns related to the evidence on its safety, effectiveness, and cost-effectiveness, and you can see the schedule of events for that topic on slide five. Very similar to the spinal injections topic, we anticipate publishing the final report for this in February followed by a meeting on the 18th. So, any questions or any things that I should take back on those two topics?

Carson Odegard: Not on those two, but on the November meeting, are there some potential subjects out in the wings of thought, as far as what could be coming up in November. I know it's not scheduled, but . . .

Josh Morse: It's not scheduled, but there is a list of outstanding selected topics, yes.

Carson Odegard: But they haven't been selected yet?

Josh Morse: No, they have been selected, but they haven't . . . I have not assigned and populated that agenda yet, but the existing topics to go from memory here that are out there are a review of pharmacogenetics.

Carson Odegard: Mm-hmm.

Josh Morse: Yeah, see, I knew I wasn't going to be able to go down.

Carson Odegard: I think we had that at the last meeting, the list of potential . . .

Josh Morse: Yeah.

Carson Odegard: . . . yeah.

Josh Morse: There's a list of existing topics that have yet to be reviewed, but were selected, so.

Carson Odegard: OK.

Josh Morse: Yeah, there is stuff to do. So, the target there, just to explain that a little further, the outside limit is usually eight months . . . by eight months before, I will have a project plan in place for topics, so, it's just kind of coming up right up on that edge, we'll have . . .

Carson Odegard: Yeah.

Josh Morse: . . . something in there in a couple weeks. So, for the May meeting on slide six here, the bronchial thermoplasty for asthma. This is a procedure that's used to treat asthma that's not well controlled. So, smooth muscle in the lungs is altered by placement of an RF catheter that heats the muscle tissue and thereby reducing the bronchial constriction during an asthma reaction. So, this . . . there was a device that was approved in 2010 for this procedure. There were high concerns related to the safety and effectiveness of his procedure, medium concerns for cost-effectiveness.

Again, on slide seven, you'll see the schedule. So, the meeting in May is May 20th. The final report is due out to be published on the 15th. A draft report has not yet been published. We anticipate publishing a draft around the same time that we're going to publish the next two final reports, which is around the 14th

of February. So, there'll be four reports published in that week of February, two drafts and two final.

Finally, the other scheduled topic for this year is autologous blood, or platelet-rich plasma injections. This was proposed . . . this is a treatment that's used for a variety of conditions. There are concerns related to its safety, effectiveness, and cost-effectiveness. It has a similar schedule to the bronchial thermoplasty. The final report should be out in mid-April for the meeting on May 20th. We don't have any drafts out now to bring to you, draft key questions, though we continue to try to synchronize, and when we do schedule for the November meeting, we will be conscious of those draft key questions and try to sync it with your meeting in March. And that is all we have.

Michelle Simon: Josh, I had a question about that. So, for the PRP, it says healing applications. Does that mean after trauma? Does that mean chronic? What is healing applications?

Josh Morse: The scope of the report is for musculoskeletal and joint conditions.

Michelle Simon: Of all kinds.

Josh Morse: Chronic . . . I think it's chronic and acute. Yeah, all kinds.

Michelle Simon: OK.

Josh Morse: And the final key questions on that are available on the web now. You can see the entire scope, like the document.

Michelle Simon: Oh, those are done? OK.

Josh Morse: Yeah, but the key . . . the final key questions are out for that subject.

Chris Standaert: Other questions or comments? It would be nice to get Dr. Fotinos a chance to make her presentation before lunch so we can make some headway.

Louise Kaplan: Could I just make, ask a quick question, just a process question? So, what is the focus of the July meeting?

Josh Morse: Good question. So, two years ago, I think. Last year was the first year we had modified the schedule of this committee so that a series of meetings occurred and ended by the middle of the year to give the agencies more consistent abilities to implement by the first of the following year, because when you . . . so, the end result was, you will make decisions in this year through May, draft decisions, and the July meeting, which is 45 minutes to an hour and a half schedule, is to finalize your work in May. By concluding in May, that gives the opportunity for, in July, the agencies can have that decision, and they have many months to prepare for implementation prior to the first of the following

year. So, the agenda for the July meeting is strictly to deal with previous meeting business.

Chris Standaert: And we switched the retreat from January to September. So, we have a meeting in May. We don't meet again to vote until November. So, the one they have in the summer. It's very short, just basically to approve the minutes and the decisions from the May meeting in July so that things can move forward, and then we have our retreat and go, and we don't have to come back until six months later.

Louise Kaplan: And so that is in-person or . . .

Chris Standaert: It's on the phone.

Louise Kaplan: . . . by phone?

Joann Elmore: Telephone.

Chris Standaert: It's on the phone.

Josh Morse: We schedule it as a teleconference. We haven't been using or needed web technology for that.

Chris Standaert: It was pretty quick last summer. Hopefully, we can say that again. Did you have a comment?

David McCulloch: No. I just have a procedural question for you guys. While I . . . I love the idea that Christina can give her talk now before lunch and we might get done a little quicker, but is that allowed? I mean . . .

Chris Standaert: Uh-huh.

David McCulloch: . . . are there people . . . public people who may be wait . . . expecting that to happen at 12:30, whether it be on the phone or in person until then. I'm just curious.

Chris Standaert: We've done it before.

David McCulloch: That's fine.

Chris Standaert: And the important part, I think, is to keep the . . . we need to pay attention to the window that is for public comment. So, wherever we happen to be at 12:50, we have to take a pause and open that up, so people . . .

David McCulloch: Yeah.

Chris Standaert: . . . can comment.

David McCulloch: I'm fine with that then.

Chris Standaert: Yes. It's . . . there is no . . . there is no problem with that. If you look at the agenda, there is notice given that the times are approximate and are subject to change at the chair's discretion, and this does happen on a fairly regular basis that the . . . you move more quickly or it takes longer through certain agenda items.

David McCulloch: No, yep. I'm fine with that, great.

Chris Standaert: And again, my concern is the first topic was more contained than the second, and if we can give ourselves an extra half hour. So we might or might not need it, but it would be nice to have it.

David McCulloch: Great idea.

Chris Standaert: OK. So, Dr. Fotinos.

Charissa Fotinos: Alright. Excellent. So, this is the agency medical directors' presentation on the re-review for cardiac stents. This re-review examines whether and when stents are appropriate in the setting of stable asymptomatic coronary artery disease and whether or not in the settings of stable, unstable, or acute coronary syndromes, if there are differences in outcomes based on the type of stent chosen, either bare metal or drug-eluting stents, and just to point out, that first piece was not included in the original review, whether or not the use of stents is better than medical therapy in stable asymptomatic coronary artery disease.

Looking at other cardiac-related decisions the committee has reviewed, the stenting subject was first reviewed in May of 2009. Calcium scoring was looked at in November. The same year, CT Angiography in May of 2010, and then 2013 was cardiac nuclear imaging.

These were the previous key questions from 2009, specifically what was the evidence of efficacy and effectiveness of drug-eluting stents versus bare metal, and were there any differences in terms of effects on subpopulations either before or after an MI or by vessel or lesion type? What were the evidence . . . what was the evidence related to the safety profile of drug-eluting stent versus bare metal stent, both in patients with and without continuation of antiplatelet therapy, and then what was the evidence of cost-effectiveness and cost implications between the two types of stents, including the effects of pharmacologic therapy and re-interventions?

At the last determination, the committee voted to cover with conditions. Bare metal stents were covered without conditions. Drug-eluting stents were covered for stent diameter of 3 mm or less. The length of stent longer than 15 mm in a single vessel in patients who had diabetes. Stents were also recommended to treat restenosis from a prior procedure and for the treatment of left main coronary disease.

In terms of our current stage agency policies, Medicaid follows the HTCC decision for drug-eluting stents. There is no prior-authorization requirement for bare metal stents. PEBB follows the HTCC decision, as does Labor and Industries, and the Department of Corrections requires PA on all of their stents.

So, again, just to point out the expanded scope of this particular review, focusing on patients with stable coronary disease. Does the addition of stent placement to optimal medical therapy add benefit compared to medical therapy alone, in terms of effectiveness, safety. Are there subgroups that are more benefited or harmed by the addition of stent placement, and what about the cost-effectiveness? In terms of the re-review, the questions remain the same.

Outcomes of interest include all-cause mortality, cardiac mortality, myocardial infarction, reported quality of life, both target lesions revascularization, as well as target vessel revascularization, so what difference there. Then, in terms of safety, stent thrombosis, peri-procedural complications that occur within 30 days.

I'm going to use this slide to sort of deviate a tiny bit in that the evidence report you will hear is extraordinarily thorough and detailed. So, a chunk of the rest of my discussion related to the agency medical directors' presentations is sort of some background considerations to keep in mind, as we hear about the evidence that do, in fact, relate to the evidence report.

So, there are many guidelines that do, in fact, relate to the evidence report. So, there are many guidelines published out there that recommend the use of percutaneous interventions, specifically stents versus CABG across a wide variety of patient and clinical variables. There has been a large registry-based study that looks at patient characteristics and the clinical characteristics under which up-to-date bare metal and drug-eluting stents have been placed and essentially shows that there is wide variation, and then studies also suggest, given this wide variation, that there is the potential for savings if more bare metal stents rather than drug-eluting stents were placed in situations where it made sense, specifically as we look at the evidence and situations where there was a low risk of restenosis.

Again, guidelines exist. The American College of Cardiology, along with a number of other societies, have developed the appropriate use criteria for stable coronary artery disease, and again, that's just focusing on that piece for medical therapy plus stenting or medical therapy alone. Then, the Society for Cardiovascular Angiography and Interventions (SCAI) has also developed appropriateness criteria for the procedure. These are well published. There are apps. I downloaded a couple on my phone. They're pretty cool. So, you can put in all these patient characteristics and get your risk of complications. So, they are available, and they are out there in a number of forms.

This is just a glimpse for patients who have low-risk findings on noninvasive testing or who are asymptomatic with coronary artery disease. When it's appropriate to consider the use of a stent or not, and A is an acceptable condition, U is uncertain, and the red I's mean don't do it. There's more harm related than benefit, and across the left, it talks about sort of the class of anginal symptoms from one to four. Canadian classification, which you'll hear detailed in the evidence report, but essentially, class 4 is unstable angina. Class 1 is you're not limited. You can walk pretty well and do your daily activities. You may need a nitro occasionally. Two is you're a little bit limited, maybe one or two blocks, and three is you're fairly limited by symptoms. So, you can see that there are fairly circumscribed circumstances and across the bottom is the type of vessel involvement and number of vessels involved, as to whether or not a stent is appropriate or interventions appropriate in the case of asymptomatic disease, and there will be a test on that.

So, the other piece to sort of keep in mind is this is . . . when I see Choosing Wisely recommendations, that's where it advised me that there is a discussion to be had, and Choosing Wisely does have a recommendation from the Society of Cardiovascular Angiography and Intervention. It was released in March of 2014 that essentially says avoid PCI in asymptomatic patients with stable ischemic heart disease without the demonstration of ischemia on adequate stress testing or with the FFR testing, and that specific piece of FFR testing was not part of the review, and I show this to sort of point out that it's not a slam dunk, that clearly there is some discussion to be had. The American College of Cardiology did also endorse this, but I believe a little over a year ago, they removed their endorsement, as they felt that new evidence . . . they could not be as clear cut in their offerings.

There are decision aids. These are from the Mayo Clinic and they're not the easiest to see, but this in the Canadian Class I and II angina, which again is fairly able to do activities of daily living, perhaps with some limitation, relieved by nitroglycerine. What you can see is that in terms of the benefits . . . give me just a minute. So, in terms of the prevention of heart attack or death in stable coronary disease, in the top left you can see that there's no difference whether or not you had stenting or maximal medical management. Then, if you look in terms of symptom control at one month, you're going to see 47 people, symptoms improved just with maximal medical management, and you're going to add an additional ten in terms of improvement for folks who had stents. At six months, more folks are going to have benefited from medical management, and another nine more from stents, but about a year, only one more person who has had a stent placed will have better symptom improvement at that time. So, initially quicker improvement, but over time, the benefit is about the same at a year. In terms of risk, the good news is, risk are low. For every one hundred people who have a stent placed, two will have bleeding or damage to the vessel, and then one will have a complication, such as a heart attack or death. That's during the procedure, and then within the first year, it's three people will have some sort of bleeding event from the additional blood thinner

that is needed for the stent or two will develop a clot in the stent requiring revascularization or develop into an MI.

This is just sort of reflecting what I mentioned earlier in terms of the wide variation and use of drug-eluting stents. This was a study that looked at, I believe, 665,000 procedures between 2006 and 2011 and included the number of drug-eluting stents placed in providers who placed more than 75 stents per year. So, these are folks who did the procedure reasonably often, and you can see that there is wide variation. Some providers may use drug-eluting stents 20% of the time, some use them all the time.

In terms of the restenosis risk, and I highlight that because as you will hear in the evidence report, one of the main benefits that could be called out from the literature from reasonably moderately quality studies is that drug-eluting stents do benefit in terms of a risk of reducing restenosis. So, on the left side shows who, which patients are at risk of restenosis, folks who are older, male, patients with diabetes, hypertension, have specific lesion related risks, and then there are procedure related risks that relate to the risk of restenosis. This does not include things that we're learning about genetic predisposition or other subtle variables, but those are the main ones on the left. On the right, this was a registry study that looked at 1.5 million stent placements and sort of said, well how do we know . . . what factors are associated with the choice to use drug-eluting stents? Again, risk for restenosis on the left, and what cases did folks use drug-eluting stents more, on the right. So, women received drug-eluting stents at higher rates than men, folks with private or HMO insurance. Folks with elective admission. Then, hospitals that perform large volumes of interventions, place more drug-eluting stents. Then, in what circumstances were drug-eluting stents used less than bare metal stents? That was in the case of acute MI or shock, folks who self-paid, folks who were sicker in terms of comorbidities, and then when it occurred on the weekends. And at first, this struck me as that doesn't make sense, but actually it does in the sense that if you're in an urgent situation, and you don't know that patient, one of the main considerations in whether or not you can place a drug-eluting stent is, is that person able to take dual antiplatelet therapy for 12 months, and if you're in a setting where you don't know that, the better part of valor may be just to use the non drug-eluting stent, but at any rate, they don't necessarily all match up.

This is . . . I don't expect you to be able to see this, but this is a tool, and I believe this was done not out of Harvard, out of another Boston area hospital, but this is a risk calculator tool that allows you to estimate the risk of restenosis based on client characteristics, whether or not they've had previous intervention, what type of comorbid conditions they have, type of angina, and then what sort of types of vessel and lesion, and I just plugged into this one someone who is less than 50. They have hypertension. They have not had a prior percutaneous intervention. They have Class II angina. It's stable. It's an elective procedure, and they have two vessels involved. This person's risk of revascularization with a bare metal stent is about 13%. Taking those exact same characteristics using a drug-eluting stent, that risk is halved to 7%. So, it's an

impressive difference, but it's 13% to 7%. So, again, just showing that there are ways in which you can determine the risks.

David McCulloch: Sorry, Charissa, I'm . . . what do you mean revascularize? The risk of . . .

Charissa Fotinos: Needing to either go back and . . .

David McCulloch: . . . Oh, I . . . that it fails . . .

Charissa Fotinos: . . . yes.

David McCulloch: . . . and you have to go back and do it again? Got it.

Charissa Fotinos: Yes. Go back and do it again. Yes, thank you for clarifying that. This slide it just kind of goes back to the one that I showed the large variation in terms of some providers use not so many drug-eluting stents, and some use pretty much exclusively. Thinking about that last slide in terms of the risk of restenosis, the white bars show over the different timeframe how many drug-eluting stents were placed in folks with below risk of restenosis versus high. You can see that folks with higher rates of restenosis risk are receiving drug-eluting stents at higher rates, but still, there is not a whole lot of difference regardless of the restenosis. So, in light of the evidence, that's just a point to call out.

In terms of our utilization as an agency, this is PEBB/Uniform Medical Plan utilization from 2011 to 2014, and I really just highlighted the year 2014. The blue highlighted . . . it's actually opposite, interesting. The orange highlighted on your slides, or bare metal, and right below that are the drug-eluting, and you can see that it's about 6:1, 6 drug-eluting stents placed for every one bare metal. They are more expensive, in terms of cost both submitted and allowed, and in terms of paid amount and about \$8000 additional is paid for drug-eluting stent placement per procedure, as opposed to the bare metal. So, again, about a 6:1 difference.

Looking at the Medicare population, 2011 to 2014, pretty similar. Again, looking at the bottom two rows, it's about . . . not quite a 6, maybe a 4 to 5:1 bare metal versus drug-eluting stent, and I'll point out that the reimbursement rate is actually less for a drug-eluting stent. So, despite the fact that there is not a money difference, there is still clearly a preference for the use of drug-eluting stents, and this is all causes, all conditions, all types of presentations.

This is Medicaid Fee for Service stent utilization. It looks like if you look from 2011 to 2014, primary care providers are getting folks healthy. That's just the transition time in which everyone went to managed care. So, those lower numbers don't reflect a healthier population. Unfortunately, they reflect people being covered by different carriers. In this instance of Medicaid, it's not quite a 2:1 difference in terms of bare metal to drug-eluting stent, and the reimbursement rate is about \$5000 different. So, still more drug-eluting stents

than bare metal, but not quite in the ratio as with other payers, and we don't have managed care.

So, I took a look at the top ten diagnoses across the different payers and pulled out the top four, and these are the same top four reasons for which stents were placed in each of the payer groups, acute MI anterior wall initial, and AMI inferior wall initial, then subendocardial MI, and then on the far right, coronary artery disease of a native vessel and really focusing on that far right, the stable coronary disease. It was not an emergent indication. By far, more drug-eluting stents were placed than bare metal in folks who were covered by Medicare.

Looking at PEBB as the primary payer, similarly for coronary artery disease, stenting of the native vessel, quite a bit more drug-eluting stents than not, and then again, drug-eluting stents favored across all conditions but not necessarily to the same degree.

Then, if you look at Medicaid Fee for Service, interestingly, still drug-eluting stents placed more often than bare metal, although the difference was higher among folks who had an initial subendocardial MI receiving drug-eluting stents, and they're about the same actual ratio.

So, pretty consistent patterns across payer, but again, highlighting the point that in folks with stable coronary disease, a lot of drug-eluting stents are used compared to bare metal.

This is the average distribution looking at that same thing another way, again with drug-eluting stents across the different payers making up 70 to 87% of stents used, and these include all diagnoses.

So, what does all this mean? Again, I did not detail any of the studies, because the presentation you're going to get is extraordinarily thorough and detailed, but sort of thinking about that first question, percutaneous interventions plus optical medical management versus medical management alone and what are the benefits. You'll hear that the mortality, both all cause and cardiac, are similar from about a year to ten years out. Nonfatal MI, stenting may be better at 120 months, but the studies are mixed. Revascularization favors the placement of stent at a little less than five years and for every ten people who use stent, you may prevent one person needing revascularization. That deserves an asterisk, because the larger studies suggest that, but a number of smaller studies . . . their quality varies. The groups differ, and there was not any necessarily more . . . we can ask the expert in terms of subgrouping, as to how that played out necessarily. Yes?

David McCulloch: Question. If the comparison is medical treatment versus stent, then, I mean, medical treatment is not revascularization. You're meaning if you follow these people out, more people who just medical therapy require . . .

Charissa Fotinos: Yes.

David McCulloch: You know, so that wouldn't be revascularization. In their case, it wouldn't be revascularization, it would be they needed to be vascularized.

Charissa Fotinos: Well, it would be . . . if you've got a, I see what you're saying. So, if you've got a lesion and you need to stent it, and you can either choose to stent it and take medicine or just use medicine.

David McCulloch: Right.

Charissa Fotinos: For every ten patients . . . I see what you're saying. For every ten patients who you stent, one fewer would need a stent who didn't get it before. So, that's a confusing sentence, but essentially the point . . .

Gregory Brown: Additional intervention as opposed to . . .

Charissa Fotinos: . . . yeah. If you . . . you may, exactly. You may reduce your risk of needing an additional intervention, but the evidence is mixed.

David McCulloch: Right.

Charissa Fotinos: I was trying to come out with something that benefits . . .

David McCulloch: Yeah, it's . . . it's tricky.

Charissa Fotinos: . . . it is tricky. There does seem to be some benefit in patients with diabetes in terms of reducing the risk of needing revascularization when stents are used, but again, in the meta-analysis, really high heterogeneity. So, you need to wonder if this study should have been combined in the first place.

In terms of safety, higher risk of peri-procedural MI in patients who are stented, compared to not. Whether or not they have diabetes and the number needed to harm is 35 to 50.

Cost-effectiveness analyses, really no cost advantage to the placement of stents, and in some of the studies, the cost of platelet therapy was not necessarily considered, and bleeding risk. So, that's just something else to keep in mind, in addition to other costs.

So, what do we make of all this? Our recommendations are that the professional guidelines for performance should be followed in patients with stable angina, class I to III and then in asymptomatic patients found to have lesions on angiography, and this is pretty in line with the recommendations.

In terms of the summary in terms of drug-eluting stents versus bare metal, again, you will hear a great deal of detail around this, but in terms of mortality, really no difference between the two, either in cardiac or overall mortality between the drug-eluting and bare metal, and the results, as far as the future

risk of MI are mixed. In terms of total lesion and vessel revascularization, there is moderate evidence that drug-eluting stents are better, in terms of the need for that at 12 months for about every 20 patients, but as you go further out, it appears that those numbers equalize, but that is lower level evidence.

So, safety, lower rates of restenosis in patients with diabetes and drug-eluting stents. Cost-effectiveness analyses, there is no difference at four years out, and again, the benefit of the drug-eluting stents from this information seems to be in the, in the risk of revascularization, or the risk of restenosis is probably a better way to say that and figuring out the underlying risk.

So, in terms of reviewing, again, the determinations from the last review, bare metal stents covered without conditions, and then drug-eluting stents covered with these very specific conditions, the size of the stent diameter, length of the lesions, comorbid conditions, and then the treatment of left main disease. There are a number of different guidelines and coverage decisions, which you'll hear from the evidence vendor. I will say . . . yeah. I'll stop at that.

So, what do we recommend? For patients with stable coronary artery disease, again, stable coronary artery disease, we recommend coverage with conditions, and these essentially follow the guidelines of the ACC/SCAI, and the patients who are asymptomatic and noninvasive testing, if those tests suggest high risk and they are not on maximal medical therapy, they have either one or two vessel disease with proximal LAD involvement or three-vessel disease without left main, stenting is appropriate. Patients who are asymptomatic and noninvasive testing suggests they're at high risk and who are on maximal medical therapy and have other lesions, they would be appropriate candidates, and then patients with Class I to II angina who continue to experience significant symptoms, despite maximal medical therapy and have either of those types of lesions. So, again, elective catheterization. You can see the anatomy. These are folks with stable angina who have lesions, and then these are the indications under which stenting would be preferred or covered over just maximal medical therapy.

In terms of recommendations for drug-eluting stents in patients with stable coronary artery disease, we would say they would be covered with conditions and that is in whom medical treatment has failed, and they should be considered for use when the risk of restenosis is high. It depends on which body of evidence you look at, whether high is greater than a 20% or 10%. I don't have a great sense of that, but there are ways to determine risk of restenosis that have been validated and perhaps that's a way to consider coverage.

In terms of drug-eluting stent use in patients with unstable angina or acute coronary syndrome, this is also nuanced that we felt that it would not be reasonable to try and project a coverage decision at the time patients are experiencing an acute event, and that would really be left best to the discretion of the provider.

Chris Standaert: Thank you, very much.

Charissa Fotinos: Any questions?

Chris Standaert: Do you people have questions? Yes, Tony?

Tony Yen: So, your coverage decisions, are they basically reflective in your slide number 11, that March table right there?

Charissa Fotinos: Oh, yeah, the complicated colored one?

Tony Yen: Yes.

Charissa Fotinos: Yes, for the, yes, for asymptomatic patients, correct.

Tony Yen: So, your coverage recommendations mirrors this table?

Charissa Fotinos: Follow those guidelines, correct.

Tony Yen: OK, thank you.

Charissa Fotinos: Yeah. And I will say that there is some . . . there has been some question and refutation as to whether or not these are truly evidence based guidelines, and whether they should be followed, and I think our point in presenting these is just, this is a very nuanced topic and subject, and there are so many variables that at a minimum, there is a wide variation in the use of drug-eluting stents sort of in terms of when they should be used and not and in terms of stable angina versus not. There seems to be pretty good evidence that medical management for a good chunk of folks is . . . yes.

David McCulloch: Yeah, just for clarification, they . . . in slide 29, which is your recommendations, that's whether you get . . . whether you get a stent, either bare metal or drug-eluting . . . whether . . .

Charissa Fotinos: Yeah.

David McCulloch: . . . some form of stent would be covered or not, and then slide 30 is under which circumstances will the more expensive drug-eluting stent be covered, right?

Charissa Fotinos: Correct. Yeah, and I know that these are very detailed, but I know that in the past sometimes when we've sort of given you vague stuff, you're like, you could have helped us a little bit. So, maybe this is too much help, but it's there.

David McCulloch: No.

Chris Standaert: They're detailed. Yes. Yeah.

- David McCulloch: This is what we're . . .
- Charissa Fotinos: It's an easier starting point to talk about.
- David McCulloch: Right. And compared with a lot of things, we have to make decisions, but there's a lot of data.
- Chris Standaert: There's a lot of data. We're not lacking for data this time.
- David McCulloch: No, I'm all for, yeah, getting very specific with conditions I think is a good thing.
- Chris Standaert: Yeah.
- David McCulloch: So, great. Yeah, nice presentation.
- Charissa Fotinos: Any other . . .
- Chris Standaert: Greg?
- Gregory Brown: Clarification on 29 again. The third point . . . bullet point, patients with Class I to II angina who continue to experience significant symptoms. I thought the definition of classes I and II was asymptomatic or minor symptoms, so.
- Charissa Fotinos: Right. And I suppose that's going to be a sort of an eye of the beholder thing. I mean, if you're . . . I guess that would be somewhat subjective in terms of how much are you bothered by any symptoms and which, you know, do you want to be able to walk more than two blocks without stopping. If so, and you need to do that to have a good quality of life, then maybe that's an appropriate indication. So, that's not as clean as you would like it, obviously, and that sort of makes that question there. I think, you know, part of . . . as we looked at our utilization and sort of sorted out the evidence, it became clear that there really does not seem to be a lot of deliberate distinction between when to use what and again, there are circumstances where that may not be appropriate, but in circumstances where it is, it seems like that might be an appropriate decision to make, so.
- Chris Standaert: Louise?
- Louise Kaplan: In the utilization data, you gave us data from 2011 forward, and the decision was made in 2009. So, I'm just curious how utilization compared before our decision and after our decision and after our decision, just an overview.
- Charissa Fotinos: Yeah, do you know, Kris?
- Kris Urv-Wong: You know, I'd have to go back and look. I've probably got that data.

- Charissa Fotinos: We could bring that back if the committee would be interested. We didn't really look at the change in utilization from prior to the 2009 up to 2011, but if you'd be interested, we could get that at a future meeting.
- Chris Standaert: It'd be interesting for us to see at some point.
- Charissa Fotinos: OK.
- Chris Standaert: Things like that are always of interest to us, see what impact.
- Charissa Fotinos: OK.
- Chris Standaert: If there was, we can note of it.
- Louise Kaplan: Well, and it makes a difference. If the utilization didn't really change . . .
- Gregory Brown: Yeah.
- Louise Kaplan: . . . then however complicated or simple we make it, then it doesn't necessarily make a difference, but if it changed significantly, then this does make a difference. So, it's that.
- Charissa Fotinos: Yes, all things being equal, although one of the things that I can say as an agency, at least in terms of the Medicaid lives that we're responsible for, because so many clients are now covered by managed care plans, our sort of business needs have changed. We don't need to do all the prior authorization and utilization review that we needed to. So, now we're going to be in a better position to really figure out, how can we, in fact, better follow when we have a decision like that. Let's put it out there and better track it as opposed to, oh, it's time for re-review. Let's go back and look. So, the point is we are trying to be a more proactive agency in terms of looking at these decisions and saying, OK. We've got these in our contracts. Are they being followed? So, yes and there still may be some utility.
- Louise Kaplan: So, if they're in your contract, they're not necessarily followed unless you go back and review it again?
- Charissa Fotinos: We would have to review every single one, yeah, which right now we don't have the ability to do. I would hope they're followed, but you're all clinicians. I don't always follow guidelines. I mean, if I'm told to or I'm going to get fired, I will, and if I know it's harmful, but I mean, you can provide, there's a distance between a contract that a managed care organization has and what the provider does at bedside, and as you all know, it's . . . there are so many variables, it's impossible to.
- Chris Standaert: Thank you.

Charissa Fotinos: So, what I'd like to be able to tell you, absolutely. They follow it 100% all the time. It may be. I don't know.

Gregory Brown: I think maybe a better way to state that is, as a clinician, I have no idea what all the contracts my healthcare system has that I'm supposed to be following.

Charissa Fotinos: Yeah. So, there's a big gap.

Chris Standaert: It makes it complicated. It definitely gets challenging.

Michelle Simon: And so, the effect of what we do is what?

Chris Standaert: That's a good question for about two hours now, I've wondered.

Charissa Fotinos: Well, I will say, in terms of this subject that the one study that shows a variation in terms of drug-eluting stent use, there was the national registry that was looked at and showed this huge number of drug-eluting stents, and stents in general placed, and they sort of put the word out and said, gosh, we're using a lot of stents. Here, really the indications we should be using them for, and they did find a pretty good drop in utilization for stents over the next two to three years after those guidelines were put out, and then they kind of, like everything, you get better for a while and then you creep back up again, any quality measure. So, it's just a matter of, I think, continual reminders and refreshing.

Chris Standaert: Any more immediate questions? Otherwise, we can take a break for half an hour and get something to eat. Are you going to be here this afternoon?

Charissa Fotinos: Yes, I will.

Chris Standaert: So, if there are more questions, she'll be available. OK. Why don't we take a break and go eat. It's already 12:30.

Just a couple comments on this one, from my perspective. I was here the first time we did this back in 2009, as were several other people who were on the committee. It was challenging. That was a challenging decision of the ones we've done. None are easy, and that one certainly was not at all. This is a re-review, but we've had a couple of other re-reviews. I found this one . . . because this is not just a re-review. This also expanded the scope of what we did. So, the . . . so part of the whole literature search and the key questions had nothing to do with our prior decision. And with a re-review, the ones we've done, we've had this issue of, does the data . . . is there . . . data has come out since we made our decision that's compelling enough that we think we should change what we decided, right? And that would be normally a re-review, and we have that issue for the drug-eluting versus bare metal stent, but in this one, we have totally uncharted territory for us on the other half of our topic. So, although this is a re-review, I wouldn't consider it quite strictly that. So, as we get to the drug-eluting stents, we can bring up the issues of our prior decision and how does it relate and how does . . . new evidence . . . is there new

evidence that changes how we think about it? And for the other portion of that, it is what it is. It's a new topic for us. We're still missing Mike.

So, we're also going to be a little out of order here. So, Andrea, at 12:50 is supposed to be public comment before you speak, but we sort of jumped ahead and had the agency present already. So, when it hits 12:50, we're going to have to let . . . open up the phone line briefly and make sure there's nobody who popped into the phone wanting to speak.

Andrea Skelly: So, did you want me to start, or?

Chris Standaert: Yeah, we should, we had, we were going to ask if anybody in the public came. So, if we can take public comment initially from people here and then at 12:50, we'll just stop briefly and pop open the phone and make sure nobody on the phone has just come in, and make sure nobody walked in here at 12:45 hoping to speak at 12:50, because we want to give people the chance to speak if they want to speak in the window we gave them.

So, we have somebody prescheduled, who is here?

Josh Morse: Yes.

Chris Standaert: And we have no other, nobody else in the audience signed up to come in?

Christine Masters: Not at this time.

Chris Standaert: OK. So, our presenter? Step up to the podium. And then if you could introduce yourself and tell us your disclosures or conflicts of interest or your relationship to this, or if anybody funded you to be here. That is always very helpful for us. Get a little close . . . pull the mike a little closer. Yeah. There you go.

Gary Weiss: [Difficult to hear as speaker is not at a microphone.]

I'm Dr. Gary Weiss. I'm an international cardiologist. I'm with the University of Washington (inaudible) here in Seattle, and I am representing the Society for Cardiovascular Angiography and Intervention, uh, I have no conflicts of interest. I have no stock ownerships or other conflicts of interest and am not being paid to make this presentation.

So, the Society of Cardiovascular Angiography and Intervention is a 4500 member group, and they represent invasive and interventional cardiologists in the United States and in 70 countries across the world. The mission of the SCAI is to promote excellent in invasive and interventional cardiology, and they do that through physician education and advancement of evolving standards to improve the quality of care. You have all been very versed in the appropriate use criteria. I thought I should address this from the SCAI perspective.

The agency had been developed by SCAI and American College of Cardiology to determine when a particular approach here is reasonable in certain medical situations. The agency for coronary revascularization are intended to provide general guidelines in the rational use of coronary revascularization that would further the delivery of a high quality of care. The goals of clinical guidelines is to improve physician decision making and also patient education about the expected benefits of coronary revascularization. As you are aware, the guidelines summarized evidence based cardiovascular (inaudible). When that evidence is lacking, the guidelines provided expert consensus opinion, which is approved by both SCAI and American College of Cardiology, in addition to the American Heart Association. So, the guidelines are intended to define practices that meet the needs of most patients in most clinical situations. The ultimate decisions about the care of a particular patient needs to be made by that patient and their healthcare provider in the setting of shared decision making. As a result, situations are going to arise in which deviations from the guidelines are appropriate, because all clinical situations cannot clearly be defined in a single clinical scenario (inaudible) guidelines. So, these should be used, the agency should be used as a tool to provide feedback to the individual practitioner and the institutions to see how their standards of care vary from those with national standards. The goal of the agency, of course, should be improvement in the quality of care. The agency were not developed to be coverage policy, they were not developed to be used for individual coverage decision making or reimbursement decisions, and we do feel that if the agency are used to determine individual specific coverage decisions, there will potentially be a disservice to patients, and it certainly will be a disincentive to the professional societies who are creating all these here guidelines. You probably are aware that the agency terminology has changed recently. New guidelines requiring revascularization are expected to be published this summer. The new guidelines will have categories of appropriate, maybe appropriate, and rarely appropriate. You probably are aware that the appropriate designation applies to clinical situations in which there is high quality of evidence-based (inaudible). There may be appropriate data that applies to those situations in which the clinical complexities are too great, or in which pertinent literature is not available, or there may actually be discrepancies in the literature that remain unresolved.

So, the practice of medicine is filled with a lot of uncertainties, and I think it is important that thoughtful clinicians use their best decision making process in light of the individual circumstances of the patient. Therefore, we think that it may be appropriate where an uncertain category will arise in which appropriate decisions are made to proceed with revascularization. We are concerned that the agency recommendations on slide 29 suggest that only appropriate indications would be covered. This coverage recommendation will potentially exclude many patients from receiving coronary revascularization, which is the best approach based upon their individual circumstances. The blanket restrictions for PCI, as recommended for chronic occlusion and left main stenosis, will potentially exclude a lot of patients from receiving therapy that will improve their quality of life (inaudible) status. Therefore, we strongly

recommend that revascularization should not be restricted solely by clinical scenarios deemed to be appropriate by the AAC. The SCAI has made significant educational programs to improve the quality of care. You've seen their Choosing Wisely campaign in your slides. Our goals are to advance high quality cost effective high value care. We agree with the slides that were presented under slide 26 that professional guidelines for PCI performers should be followed in patients with stable anginal pectoris Class I to III and in asymptomatic patients found to have (inaudible).

So, we look forward to working with the Healthcare Authority throughout a collaborative approach to providing high quality, high value care ensuring that all patients have access to coronary revascularization based upon their individual circumstances. We think that evidence based practice should guide these decisions, but we also feel that the (inaudible) Commission should also have a role to play in (inaudible) revascularization. Thank you, very much, for your time.

Chris Standaert: Thank you. We appreciate the comments. OK. Alright. I was going to open up the phone line, because there's no point in Andrea talking for three minutes. So, again, so . . .

Christine Masters: So, there's no . . . nobody has signed up since we last reported, so.

Chris Standaert: . . . OK. We got about three minutes before we have to open up the phones. So, we're going to talk . . . we'll introduce our clinical expert, Dr. Michael Ring. Dr. Ring was kind enough to do this several years ago and still return. It's a remarkable feat. He is an interventional cardiologist in Spokane, and if you could help us a bit just with clarifying conflicts of interest and similar issues, that would be appreciated.

Michael Ring: [Microphone keeps cutting out.]

Good afternoon. Can you hear me OK? I'm Mike Ring. I'm an interventional cardiologist at Providence Sacred Heart Medical Center in Spokane. I have been in practice for approximately 25 years as an interventional cardiologist. I have served as the immediate past governor for the American College of Cardiology. I have also (inaudible) for Sacred Heart and served some administrative roles there, as well (inaudible). I, like Dr. Weiss, am also a member of the Society of Cardiovascular and Angiography and Invasive cardiology. I have . . . in terms of conflicts of interest on a commercial level, I have served as a medical advisor for (inaudible). I have worked at (inaudible) for (inaudible) on their transcatheter aortic valve placement system, which means that I will go to other sites and help proctor them to the procedure. Those are really my main relevant conflicts.

Chris Standaert: OK. Thank you. Just to clarify, so the role of the clinical expert is to help the committee and committee members with technical questions about the procedure and the technology and the clinical applications, data analysis,

literature interpretation, we go to our evidence vendor more typically, OK? Thank you. So, can we check the phones? So, is there anyone on the phone? This is the Washington State Health Technology Clinical Committee meeting. We are talking about coronary stenting, cardiac stenting. Is there someone on the phone who wanted to make a public comment? No. OK. Are we good or should we check again? We'll check again in what? OK. We will just check back with the phone lines at the end of the vendor presentation. If you get some indication somebody is on the phone wanting something beforehand, let us know, OK? Thank you. Alright. So, we will start with our presentation. Dr. Skelly of . . .

Andrea Skelly: Do you want me to stay here or go up there?

Chris Standaert: . . . it's better if you're up there. I think then we can see you and talk to you more specifically. So, Spectrum Research.

Andrea Skelly: So, thank you for the opportunity to present this report, and I would like to take this opportunity to thank my colleagues at Spectrum Research for their contributions to this report. Since all of you have had the report to look through, I'm going to go through some of the slides fairly quickly, so we can focus on the primary aspects of the results. As you know from Dr. Standaert, this was an update to 2009 Health Technology Assessment that focused on comparison, drug-eluting versus bare metal stents. Those were primarily first generation stents and as you mentioned, the scope was expanded to include a look at stenting versus medical therapy.

By way of background, you already know that coronary artery disease has a very high cost to it in terms of healthcare dollars, a very high public health burden. It's a chronic disease that spans decades and is the result of atherosclerotic plaque buildup on artery walls, which may become disrupted and cause problems in terms of further obstruction and inability of the blood flow and nutrients to get to the heart. Chest pain is usually the most common symptom of obstructive coronary artery disease and can be further defined in terms of its typical characteristics, atypical or noncardiac characteristics, and patient history is partly used to categorize patients as having stable or unstable angina. By way of definition, stable angina in general terms is comprised of chest discomfort that presents with a predictable pattern that may be brought on by mental or physical stress and generally subsides with rest or anginal medications. It is associated with stenosis but without plaque disruption or plaque associated thrombus.

The Canadian Cardiovascular Society provides this classification based on the physical limitations that one might experience with angina from Class I being the least severe to Class IV being more limiting. Generally, the studies that were included in this Health Technology Assessment, individuals with Class I through Class III were not part of the inclusion criteria or patients who had Class IV angina that were medically treated and were considered to be stable.

In terms of terms, again, it is important to know some of the terminology. Acute coronary syndrome represents a spectrum of conditions that includes unstable angina, as well as different types of myocardial infarction that are characterized by EKG. The unstable angina definition is fairly broad and includes new onset within two months of at least CCS III angina. It may increase with frequency and intensity or duration or occur at rest and is usually prolonged. It is further subdivided based on the evaluation of the EKG and whether or not there is sufficient myocardial damage to have myocardial biomarkers values increased. So, short-term risk individuals with unstable angina are considered those that have normal or unchanged EKGs and normal cardiac biomarkers and those people in the ACC guidelines are considered comparable to those with stable angina and is frequently associated with plaque disruption. Non-ST elevation MI and ST-elevation MI are both part of acute coronary syndrome, as well.

Diagnosis for those patients that are at high risk of myocardial infarction and death are generally going to go on to invasive coronary angiography. Those who are at intermediate risk are more likely to get noninvasive testing, including stress testing, either nuclear perfusion imaging, cardiac echo, a variety of things. It is not within our scope to really talk about those, and treatment is divided into two general categories. However, it is noted that medical therapy or what is termed optimal medical therapy in most of the literature that you have seen or the newer term guideline directed medical therapy, is given to all patients with coronary artery disease. Revascularization may be appropriate for some individuals, as you've heard about the guidelines, in addition to guideline directed medical therapy, and PCI is sometimes used very generally. For the purposes of our talk today, it will mean stenting with angiography and then CABG is not included. Coronary artery bypass grafting as a revascularization technique is not part of our report.

Stents are basically metal scaffolds that are designed to help expand the area of blood flow and address the narrowing of area of blood flow in the coronary vessels that is caused by plaque. A catheter is inserted either through the femoral access or radial access and goes across the lesion. A balloon is then used to expand the stent and compress the plaque against the wall, after which the balloon is retracted, and the stent remains in place to keep the lumen open and allow blood flow. New endothelial tissue eventually forms over the stent.

We're not going to go over the history, but back in 1977, the first descriptions of balloon angioplasty were described, and there was a lot of restenosis. Bare metal stents were used to then maybe address the opportunity to keep the vessel open, but they had problems with restenosis, as well. Dual-antiplatelet therapy assisted with decreasing that risk, and restenosis is a potentially important problem because of serious morbidity and mortality.

Drug-eluting stents have a polymer coating that allows for anti-proliferative drugs to be eluted into the local area to keep the vessel from re-stenosing. Dual-antiplatelet therapy is used with both bare metal and drug-eluting stents.

This is a list of the newer drug-eluting stents, the second generation stents. One that is now under the biodegradable classification was approved in October of 2015, and you can see that the newer drugs are listed there. Your report has a whole list of the different stents and their indications and contraindications.

You are already familiar with the objectives and the focus of the report. We have systematically reviewed the literature and focused on the available literature with the least potential of bias for this report.

You're familiar with the key questions. They have to do with evaluating the efficacy, safety, and differential benefit or harm and cost-effectiveness. For key question one, that is in stable patients with stable coronary artery disease, and the comparator is looking at PCI. Again, it is understood that medical therapy is part of that versus medical therapy alone.

For key question two, as you know, we're looking at any presentation, whether stable or unstable in comparing drug-eluting versus bare metal stents.

The PICO table is, again, detailed in the report on page 16. So, I'm going to go over it here in detail.

By way of outcomes, the same outcomes that were considered primary for the 2009 report are again considered primary here and focusing on hard clinical outcomes, safety, and economic outcomes.

Out of over 3400, or almost 4000 citations, there are 39 citations were used to evaluate key question one and 21 to evaluate key question two.

As you know, all studies that were included undergo a critical appraisal process that is detailed in the appendices and in your report, after which across studies we look at specific outcomes and look at the data, the information across studies using the grade process in order to come up with a summary of the quality of the evidence or the strength of the evidence, which reflects basically our confidence that the effect estimate that we're seeing in the literature is consistent with the true effect, and I think most of you are familiar with that.

For key question one, again, we're looking at patients with stable coronary artery disease. It's important to note that patients who had acute coronary syndrome, patients with STEMI were excluded. Also, it is important to note, because one of the public commenters to the draft made a comment about some older studies not having patients who had stents. We excluded any studies that did not have at least 70% of patients receiving stents, so no coronary angioplasty by itself.

In terms of the evidence base, there were 39 citations for key question one. One was considered moderately low risk of bias, but the other three were considered at moderately high risk of bias. There was a substantial crossover

from medical therapy to PCI, and that is something that needs to be considered in considering these results.

If we take a look at the first set of results, we had to actually . . . let me go back, because I think it's worth talking about. We, the four primary RCTs, there were two trials that were in general populations. One is the Courage trial, and one was the MASS-II Trial. There was one trial in diabetic patients and one small trial in males only. So, in the general patient population, all-cause mortality, looking at all timeframes, there were no statistical differences between the treatment groups at any time point with regard to all-cause mortality. If we look at all-cause mortality in special populations for the subgroup, or for the population of males only in the Hambrecht study, there was no statistical difference. However, the study was likely underpowered to detect a difference. Mortality was similar in the patients with type 2 diabetes. There was moderate evidence in that group and low evidence in the patients who were only males.

In terms of cardiac death, again, there were no statistical differences between treatment groups at any time point, as you see here. The quality of evidence ranged from low to moderate, and with regarding to special populations, again, for cardiac deaths, there were no statistical differences between groups, but again, the Hambrecht study was likely underpowered to detect a difference.

If we look at myocardial infarction, in the general population, again, there were no statistical differences at most timeframes, but in the MASS-II Trial through 120 months, nonfatal myocardial infarction was less common in the PCI group versus the medical group, and it would be important to note that there were some substantial differences between the study populations in the Courage trial and the MASS-II Trial, which may or may not explain the difference in the results at this point, but just noting that there were differences. The MASS-II Trial had individuals who had more . . . there were more individuals who had multivessel disease and their baseline characteristics were not completely on par at baseline. They did adjust some analyses for those discrepancies, but again, there were differences in patient population, and in your report, there are the inclusion criteria and also a demographics table that may help you take a look at some of those differences, as well.

In terms of special populations, again looking at nonfatal MI, there were no statistical differences between groups. Again, Hambrecht likely did not have sufficient power to detect a difference.

In looking at freedom from anginal relief, and this was not well defined in the studies that were included, but significantly more patients with PCI than those in the medical therapy group were angina free at 12 months and 36 months. That did not persist until 60 months, but at 60 months, the evidence was considered insufficient because only 51% of the patients contributed data. So, we have a large loss to followup. If we look at the MASS-II Trial, at 12, 60, and 120 months, at all three time points, more patients with PCI versus medical therapy patients were anginal free at all these times. Looking at special

populations, they have a little bit different way of defining it. They looked at worsening anginal frequency, worsening severity, or change from no angina to any angina or unstable angina, and fewer patients in the PCI group versus the medical therapy group through 12 months experienced any of those categories of anginal worsening. There were no statistical differences after the 12-month period.

In terms of other patient reported outcomes, the Courage trial looked at the Seattle Angina Questionnaire. There was some inconsistency across the domains. For anginal frequency, the clinically significant improvement was seen in more PCI patients at six months and at twelve months. The strength of evidence was low for those time periods. Then, at 36 months, it became insufficient again due to dropout. Other domains, there was, again, some inconsistency in terms of anginal stability. There were no differences between groups at any timeframe, but the strength of evidence was low. If you look at the quality of life and physical limitation domains, again, more PCI patients at six months had clinically significant improvement, but that was not true at 12 months or at 36 months. In terms of satisfaction, this was one was kind of interesting, because there was statistically significant more satisfaction among the PCI patients at 12 months but not at any other timeframe.

If we go on . . . in terms of other patient-reported outcomes, the RAND 36 was used, as well. A ten-point difference was considered clinically significant and for the physical functioning domain, the role limitation physical domain at six months, again, more PCI patients had clinically meaningful improvement, but there was no difference at 12 months, and there were no difference in any other domains at any other timeframe. The modified RAND, there were no differences in the diabetic population, and the SF-36 scores for the MASS-II Trial, again, the physical functioning domain vitality at 12 months showed patients with PCI expressing better quality of life, but there were no statistical differences at the other domains, and in the BARI2-D Trial, patients with diabetes, there were no differences between groups at 48 months, but the strength of evidence was considered low.

If we look at revascularization, and here revascularization refers to the need for repeat revascularization following PCI or the need for primary revascularization in the medical therapy group. Taking a look at these results, revascularization was more common in the PCI group looking that MASS-II Trial, but the statistical significance was not there. So, even though there was, percentage wise, a higher number of patients requiring revascularization and PCI, again, it was not statistically significant. If we look at Courage, statistically fewer patients in the PCI group had revascularization, and again, there were some substantial differences between the Courage and the MASS-II Trial. Courage had more male patients. There were more single-vessel disease patients in the Courage trial versus MASS-II Trial, and the Courage trial incorporated patients who had more prior CABG or PCI. Now, the extent to which that may influence these results, I'm not sure. Again, baseline differences in the Courage trial were seen with regard to some important things in terms of prior myocardial infarction,

diabetes, and more of the patients in the PCI group had a positive treadmill test in the MASS-II Trial. In terms of special population, looking at, again, the study among men only, significantly more PCI patients had revascularization. By contrast, in the BARI2-D trial among diabetic patients, significantly fewer patients in the PCI group had revascularization.

Looking at safety, because medical therapy generally does not require hospitalization, we're looking at the results related to PCI from the MASS-II Trial and safety in terms of hospital adverse events was generally low. You can see the percentages here. A 30-day mortality also was very small in PCI. Among those patients who had crossed over for medical therapy to PCI looking at medical therapy versus PCI, significantly more patients in the PCI group had peri-procedural MI. There was true in the Courage trial, as well as the BARI2-D trial among diabetic patients.

Peri-procedural stroke was similar among groups at all time frames. A difference was not detected again in Hambrecht, likely because of poor power. If we take a look, then, at differential safety and efficacy, the bottom line is that patient characteristics such as age or symptoms such as angina or coronary artery disease characteristics, such as the number of diseased vessels or angiographic risk do not appear to modify any of the primary clinical outcomes. The other two that are listed there are for completeness sake. It is very difficult to assign a meaningful interpretation to the results.

In terms of cost-effectiveness, two cost-effectiveness studies in the general population suggested that PCI was not more cost-effective than medical therapy. One was a high quality . . . moderate quality study. The other was a poor quality study. In terms of special populations, the average cost to improve one CCS category for angina was greater with PCI and was considered not cost-effective. For type 2 diabetes, PCI plus medical therapy for stable coronary artery disease was not more cost-effective than the initial strategy of medical therapy alone. Again, that one was a moderate, the other one was a poor quality cost-effectiveness study.

We will move on to key question number two, which is the comparison of drug-eluting versus bare metal stents, and again, the patient population is a presentation of either stable or unstable coronary artery disease in patients presenting with de novo lesions for stenting. The keys questions, again, have to do with efficacy, safety, differential safety or efficacy, and cost-effectiveness. The thing to note here is that we focused on newer generation drug-eluting stents. If we take a look at the evidence base and compare it to the 2009 report, the evidence base for the 2009 report was substantially greater. There were many more publications available to look, and with the update you can see that we have a smaller evidence base.

There were 21 publications representing seven primary randomized control trials. There were four trials in the everolimus stent. There were two that looked at zotarolimus stenting, and then one combined both types of stent.

Interestingly, only two of these trials were in patient populations that we call general populations. In other words, populations that either presented with stable or unstable coronary artery disease and did not have a specific type of patient population that they were looking at. One study was in octogenarians. There were two trials in patients with ST-elevation MI. The Basket-Prove was among patients who needed stenting in larger vessels. The Zeus trial was in patients who were considered possibly uncertain candidates for stenting because of risks for bleeding with dual-antiplatelet therapy. Five of them were considered at moderately low risk of bias, and two were considered low risk of bias.

We have some pooled data for you with regard . . .

Male: Can I interrupt us for a second? For some reason, nobody can hear anything (inaudible).

Chris Standaert: Can the people on the phones hear?

Male: They can't hear. The people who are watching on the PC right now can't hear a thing.

Chris Standaert: Yes, her mic's on. So, is our phone . . . our phone line is open? Can you ask for people on the line to say something to see if they can hear you? So, if you're on the phone and you're listening to the meeting, there is a question that you cannot actually hear what we're saying. If you can hear us, please reply so we understand that you can. Do you know if there are people on the line? Does it tell you that?

Christine Masters: The last time I checked, there wasn't anybody on the line. Originally, there were five, but then they could be trying to (inaudible). So, I can . . .

Chris Standaert: How do we have a test their reception with our new system?

Christine Masters: (inaudible) people on the line (inaudible).

Chris Standaert: They can hear us, I assume, but we don't know if they can hear us. If you're on the line, hang on. We're trying to solve this problem. We may have to hang up and have you recall in, but we'll see.

Josh Morse: Hi, can you hear me? We're working on the phone issues. This is Josh from the Health Technology Clinical Committee meeting. So, we have the line open. We're going to close the line and redial the line in about two minutes, OK? Thank you. There are four people on the call.

Chris Standaert: So, have them hang up and then redial?

Josh Morse: I think we need to hang up and redial, so.

Chris Standaert: So, if you're on the phone, we're going to close the line and then reopen the line. So, give us about two or three minutes and recall in, and we will restart in about three or four minutes. So, we're going to hang up now.

So, if you're on the phone, unmute yourself for one second and tell us if you can hear us so we know that you can hear us and we can hear you. I heard a laugh. You can hear us, OK. OK. We're going to go back on mute, and we will resume our meeting. We're good? Alright. OK. We'll keep going.

Andrea Skelly: OK. So, we're here at the first outcome for key question two, which is the comparison of drug-eluting versus bare metal stents, and the slide that is up is slide, what, 37 I believe, and it looks at all-cause mortality at 12 months. The bottom line is that there is no statistical difference between new drug-eluting stents and bare metal stents. The strength of evidence was considered high. The fourth plot looks at risk differences. The vertical line represents zero, meaning that there is no difference between treatments. If it were to favor drug-eluting stents, it would be on the left side of the zero. If it favors bare metal stents, it would be on the right side of the zero. Again, these are risk differences. If we take a look greater than 12 months, we have three different things to look at, as pointed out by the arrows.

At the 12 month . . . or excuse me, the 24 month, again, there was no statistical difference between the drug-eluting and bare metal stents with regards to all-cause mortality. If we look at the time period after that, which was 48 months, at 48 months there was no difference in one study, and if you look at the total for any time period after 12 months, there was no statistical difference between drug-eluting and bare metal stents. At 60 months, in one trial, there was moderate evidence of no difference, and in an individual patient data meta-analysis among women only at 36 months, there was no difference, but the strength of evidence was considered low.

If we take a look, then, at cardiac mortality on the next slide, again we see that there were no differences between newer drug-eluting stents and bare metal stents and the strength of evidence was high across the trials that you see here.

If we take, again, a look at over 24 months, the two trials that contributed data to this outcome, again, there were no statistical differences in the pooled estimates, and the strength of evidence was considered moderate. Again, one trial looked at data up to 60 months, and the strength of evidence was moderate that there was no difference at that time frame, as well.

If we look at cumulative myocardial infarction to 12 months, we have some heterogeneity going on here. The top set of bars relates to the everolimus drug-eluting stents and the bottom arrow points to zotarolimus. You can see that the zotarolimus stent did appear to be a stent that decreased MI cumulative to 12 months. So, drug-eluting stents was favored in that instance, but when you pooled things together, the pooled estimate was within the limits of chance. The strength of evidence was low, however, because of the heterogeneity and

the lack of precision noted. Two trials reported fewer MI's with drug-eluting stents, but again, the populations did differ.

Again, the Examination trial looked at patients with STEMI. The XIMA trial looked at patients that were octogenarians, and the Zeus trial was among patients who had uncertain candidacy for drug-eluting stent placement. So, there is a lot of heterogeneity here.

If we take a look at other classifications of myocardial infarction reported in the included studies, there were no significant differences between drug-eluting stents and bare metal stents for any of the time frames listed or the classifications of MI listed on the slide here.

If we look at target lesion revascularization, statistically significantly fewer patients receiving the newer drug-eluting stents versus bare metal stents had to have a target lesion revascularization. The strength of evidence was considered moderate. If we take a look at 24 months in the plot, we can see that there is some heterogeneity again. The Prodigy trial included both everolimus and zotarolimus drug-eluting stents. The confidence intervals vary widely, and that may contribute to the fact that we are not seeing any difference between the drug-eluting stents and bare metal stents with regard to this particular outcome. It was less common at 36 months among women, and the hazard ratio was shown below, and the evidence quality was considered low.

In terms of safety, one of the important safety features, safety considerations is definite stent thrombosis and the timeframe has been variably reported in the studies that were included. There were only two studies that looked at less than 30 days. That's where the first arrow was pointing. There were no statistical differences between treatment groups in either of the trials, and the other thing to note is that it is likely that trials were underpowered to detect a difference in rare outcomes, such as definite stent thrombosis and to harken back to the 2009 report, we had 17 RCTs. We had over 34,000 patients that were included, and some estimates were . . . some individuals indicated that at that time, even with that power, it may still have been insufficient to detect rare outcomes like definite stent thrombosis.

There were two registry studies, again, that showed similar risk in stent thrombosis. Both were in STEMI patients. Looking at definite stent thrombosis from a cumulative perspective versus early versus later stent thrombosis, cumulative to 12 months. Again, there were no differences between trials. You can see that each trial straddles different areas of the line of zero. One favors drug-eluting stents. One favors bare metal stents, but again, neither is statistically significant. It is within the limits of chance individually and collectively, and we considered this to be insufficient evidence.

If we take a look at other safety results, peri-procedural results, there was no differences in all-cause mortality within the 30 day procedural period . . . peri-procedural period, or in cardiac mortality. If we take a look at myocardial

infarction within 30 days, again, there were no differences in one trial, and one registry study also reported no difference in patients with STEMI. In terms of bleeding at any time, major bleeding at any time, which again was not well defined across trials, again pooled estimates suggested they were similar between newer drug-eluting stents and bare metal stents, and the strength of evidence was moderate.

In terms of other complications, the study of octogenarians reported stroke at all timeframes, and the preprocedural and cumulative stroke at six and twelve months was similar between groups, and if you excluded those who had stroke at less than 30 days, more drug-eluting stents patients experienced stroke at six months. In terms of other RCTs, one RCT suggested that there was no difference between groups, and there was moderate strength of evidence at 48 months. Ischemic stroke was similar between groups in one RCT at six months and two RCTs at twelve months. Target lesions revascularization on the peri-procedural period was less common in patients with drug-eluting stents in one RCT. The drug-eluting stent fracture and sten deformity were only available . . . information was only from case series, and because they were included in the initial report, we included the information here. Part of the concern, to my understanding, is that these may contribute to in-stent thrombosis and problems. So, they are included for completeness.

In terms of differential efficacy and safety and the primary outcomes of interest for this report, one trial did look at patients who had STEMI and whether or not age seemed to modify treatment effect. It did not for the outcomes of all-cause mortality, cardiac mortality, or bleeding, and there were no other trials that evaluated modification of treatment effect for the primary outcomes. There was one moderate quality cost-effectiveness study, which said that there were no significant differences in survival or quality adjusted life years at four years for the newer drug-eluting stents, but they only used the zotarolimus stent versus bare metal stents. So, incremental cost-effectiveness ratio, or ICER, was not calculated.

That's the evidence portion of the report. The centers for Medicaid and Medicare national coverage determination indicates that CMS will cover what they call PTA with or without stenting when it's used in accordance with FDA approved protocols for the treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary artery bypass grafting and who exhibit the following characteristics. They have to have refractory angina, objective evidence of myocardial ischemia, and lesions amenable to angioplasty. The considered coverage for all others at the discretion of the local CMS contractors. We did not find any specific information from the regional coverage for a determination.

The clinical practice guidelines are voluminous and they are very complex. We, in your report, I think beginning, I can tell you what page they're beginning on, but I think it's, like, page 60, the primary one for stable coronary artery disease is the Fihn 2012, and there was a 2014 update. The Amsterdam 2014 looks at

management of patients with non-ST elevation MI and acute coronary syndrome. The Levine 2011 looks at PCI and management of patients with STEMI, and there was an update in 2015, which was also included. Also, in your binder, you have the appropriate use criteria that were described previously by Dr. Weeks, as well as a consensus statement by SCAI.

So, in summary, if we look at the first key question, which evaluates whether or not PCI with stenting and medical therapy versus medical therapy alone. In terms of the outcomes for efficacy for all-cause mortality, there was moderate evidence that mortality was similar, up to 55 months in the Courage trial and no significant differences in the MASS-II Trial, but the strength of evidence was considered low. In the special populations, in diabetic patients, again, mortality was similar, and the strength of evidence was moderate. For the patient's population of men only, there were no differences, but again, low statistical power may contribute to that and strength of evidence is low. Again, for cardiac death, strength of evidence was low to moderate, but there were no statistical differences between groups in the general population and the same is true for the special populations. If we look at myocardial infarction, there was moderate evidence that the risk of myocardial infarction was similar at a median of 55 months in the Courage trial, and that there were no differences at 12 or 60 months in the MASS-II Trial. However, it was less common in patients who received PCI at 120 months. In the special populations, there were no differences between treatment groups at any time. Looking at symptom improvement, the general population, again, the strength of evidence was considered low. That is statistically significantly more patients who received PCI versus medical treatment patients were angina free at 12 months. It was low if we looked at it persisting up to 120 months and insufficient in the Courage trial because of dropout at 60 months. In the special populations group, fewer patients with PCI versus medical patients at 12 months had worse angina or change to unstable angina, but it was similar after 12 months up to 60 months.

Again, patient reported outcomes are a little bit difficult to parse out. There was low quality evidence to suggest that from the Seattle Angina Questionnaire that more PCI patients had clinically meaningful improvement and frequency of angina at six and twelve months, and the quality of life, physical limitation at six months, and more were satisfied at twelve months, but no difference at other times. There was no difference in anginal stability at any time. In terms of the RAND, again, there are several domains where patients who received PCI had better scores, but most domains, there were no statistical differences between groups. In terms of special populations, there were no differences in the patients with type 2 diabetes in the modified RAND questionnaire.

In terms of safety, again, adverse events were low, 30-day mortality was low among PCI patients. Again, peri-procedural MI was significantly more common with PCI in two RCTs, one in the general population, one in the diabetic population. Stroke, again, was similar among the two general population studies, and there was moderate to low evidence for that. Stroke in special populations, again, was considered low to moderate for a similar risk, no

difference between groups. In terms of differential safety and efficacy, patient baseline factors do not appear to modify treatment effect for any of the primary outcomes that were considered, and PCI versus medical therapy alone did not appear to be more cost-effective than an initial strategy of medical therapy alone.

So, shifting gears now to key question two and a summary of results of evidence for comparing newer drug-eluting stents for bare metal stents. All-cause mortality, comparing newer drug-eluting stents and bare metal stents at all timeframes was similar. Evidence quality was considered high at 12 months across four RCTs and 24 months and two RCTs and 48 months at one RCT. Moderate, but there was no difference at 60 months in one RCT and low in an individual patient data meta-analysis at 36 months. Cardiac death was similar between the two treatments at all timeframes and across the RCTs. Myocardial infarction, as previously noted, there were some inconsistencies in the findings, some heterogeneity, and there were various definitions of MI. There was low evidence that any MI up to 12 months that the pooled estimate was within the limits of chance, but again, significantly fewer people had MI with drug-eluting stents. If you looked at some of the individual studies, and population differences, again, are noted in the different RCTs. The strength of evidence was considered high for the risk of any MI at 24 months for different categorizations of MI at any timeframe, and the same thing with nonfatal myocardial infarction and for the individual patient data meta-analysis of 36 months, only unadjusted estimates and percentages were evaluated, but it did indicate that fewer MI's occurred with the newer drug-eluting stents, but again, that's an unadjusted estimate, and there were substantial baseline differences in patients who received bare metal stents and drug-eluting stents. There were no reports of symptom changes or patient reported outcomes related to health-related quality of life.

Target lesion revascularization and as you read in your report, target vessel revascularization was significantly less using newer drug-eluting stents compared with bare metal stents. Strength of evidence was moderate, up to 12 months, but considered low after that time period. Safety, again, definite stent thrombosis. The studies were likely underpowered and the pooled estimates were likely underpowered to detect a difference. There were no differences at any timeframe. All-cause mortality related to peri-procedural time period or major bleeding at any time suggested similar risks occur for drug-eluting stents and bare metal stents, and as far as stroke is concerned, again, studies may have been underpowered, but again, it appears that the risk is similar between treatment groups. There is no evidence that age modifies the treatment effect comparatively between drug-eluting stents and bare metal stents, but again, studies were likely underpowered to detect that, and there was no evidence to suggest that newer drug-eluting stents were more cost-effective than bare metal stents over a four-year time horizon.

There are a couple of gaps in the evidence, more than a couple, and there are some remaining questions. I would like to offer a few observations. The first

one is, is that the statistical power to detect clinical outcomes, particularly for the drug-eluting versus bare metal stents, may have been low, and there is a lot of heterogeneity across the studies, in terms of the patient populations that they enrolled, as well as variability in definitions that they used for various outcomes and measures, and of course, the methods did vary across studies. With regard to PCI with medical therapy versus medical therapy alone, it is important to note that the included randomized control trials likely do not reflect the current guideline directed medical therapy or the new drug-eluting stents. A trial that is scheduled for completion at 2019 holds a lot of promise to help answer some of these questions, the ischemia trial, I'm sure, will be very eagerly awaited. We also had a very small evidence base compared to the evidence base we had for the 2009 report.

Patient reported outcomes, this is not a Seahawks comment. The PROs were not, you know, we're not pros. Patient reported outcomes were not reported for the drug-eluting stents versus bare metal stents, and for the key question one, it is important to note in that study patients were not blinded. They could not be blinded for PCI versus medical therapy. So, there is always the possibility of some subjectivity and bias regarding those outcomes. Across the studies, the thresholds for revascularization were not clearly defined. Some indicated that they used clinically driven criteria for revascularization. Others had indicated that they had some protocol-driven revascularization, but again, the thresholds for when to revascularize were not clearly delineated. Based on the evidence that is available, it is not clear which patients may be the best candidates for PCI, and then there are some more existential questions, if you will, of how should the relative outcomes . . . how should the various outcomes be relatively valued and weighed over the short term and the long term, and I know that with the 2009 report, there was a lot of discussion about target vessel and target lesion revascularization, but it appears that there is still some question, based on the evidence that we have included, about whether or not revascularization correlated with a decrease in death or cardiac death or MI over the short-term and how that might be or might not be the case. So, with that, I will see if anyone is still awake.

Chris Standaert: Oh, I think you got everybody's attention. That's not a problem. Thank you, very much. That was very well done. That was a lot of data to go through. I appreciate the structure you followed. Anybody have immediate questions? I may take a second to form a question, as they shift their brains into a different gear. Yeah, Tony?

Tony Yen: So, in your review of the literature for drug-eluting stents versus bare metal stents, were you able to stratify the patients by stable and unstable coronary disease?

Andrea Skelly: There were not data in the trials to do that.

Tony Yen: OK. Thank you.

- Gregory Brown: Did you find any professional society recommendations on bare metal stents versus drug-eluting stents?
- Andrea Skelly: I did not. I don't know if . . . Dr. Ring, you may be more familiar with some of that than I am.
- Michael Ring: Yes, in general, the practice is to avoid drug-eluting stents in patients who are not good candidates for prolonged dual-antiplatelet therapy. So, patients who (inaudible), concerns about bleeding typically would not receive the drug-eluting stents.
- Chris Standaert: So, just a clinical question. Can you explain the differences in the use of antiplatelet therapy in drug-eluting stents versus bare metal stents? Are they . . . they are different or are they the same?
- Michael Ring: They are . . . the general practice is that in both patients receiving either drug-eluting stents or bare metal stents the practice would be to try to give them some course of dual-antiplatelet therapy, assuming that they don't have an allergy or contraindication to aspirin or clopidogrel. Occasionally . . . or maybe there might be a situation where a patient is also on . . . has a need for Warfarin. So, there's a need to try to avoid what's called triple drug therapy where you give dual-antiplatelet therapy and Warfarin and other anticoagulants, since the risk of bleeding is very high in that situation. So, the goal is to try to keep patients on dual-antiplatelet therapy for at least the first four weeks, and if they are not candidates beyond that period of time, typically they would be, they would receive a bare metal stent.
- Chris Standaert: So, is there a difference in the use of antiplatelet between the bare metal stents and drug-eluting stents? So, do you keep them on longer (inaudible) or do you . . .
- Michael Ring: It mostly has to do with the duration of the therapy.
- Chris Standaert: Yeah, that's . . . that's my question. So, can you just tell me what the difference in duration is?
- Michael Ring: It's a complicated question, in that what we've learned is that many patients actually benefit from being on dual-antiplatelet therapy after stenting assuming they don't have any bleeding complications. So, what's happened is that even patients who receive bare metal stents, if they're doing well, they may be maintained on dual-antiplatelet therapy for a year if not longer.
- Chris Standaert: And it's more mandatory with a drug-eluting stent? I guess that's what I'm getting at?
- Michael Ring: Yes, it would be more mandatory that patients go on dual-antiplatelet therapy for probably a minimum of three months after drug-eluting stents.

- Chris Standaert: Longer than for bare metal stents?
- Michael Ring: For bare metal stents, you can probably get by with as little as four weeks.
- Chris Standaert: OK. Thank you.
- Gregory Brown: So, maybe I can ask the question differently, now that we've had that explanation. So, is there any evidence or professional guideline explaining in what patients' drug-eluting stents are better than bare metal stents?
- Michael Ring: Well, I think to a large extent we've covered that in 2009 in the Health Technology Assessment review, and I don't know off the top of my head if there is actually a kind of guideline that . . . for AUC, but they don't break it down in terms of (inaudible) specifications that we (inaudible) to the AUC. Does that make sense?
- Chris Standaert: I guess the question is, are there no societies who are advocating specific boundaries, but you said drug-eluting stents versus bare metal stents?
- Michael Ring: Not . . . not beyond certain general terms that have been discussed.
- Chris Standaert: OK. Thank you.
- Michael Souter: Just going out to the all-cause mortality, and I'm looking at the all-cause mortality and trying, you know . . . going out to 48 months and there's no discernable difference there implied between drug-eluting stents and bare metal stents. Then, thinking about that in comparison to the risks of major bleeding. The major bleeding is only given out to one year, and of course, the . . . if somebody has remained on dual-antiplatelet therapy for that first period of time, then you're going to be more sensitive to picking up . . . or rather the window of time at which you look for major bleedings, of course, is going to be relevant. So, I'm just wondering is there any information that you're aware of on the literature that you did to try and pick out what are the other events for all-cause mortality that might be operating beyond in that kind of year to 48 months window. In other words, can you be sure that there's no differences in bleeding that have occurred after a year.
- Andrea Skelly: Mm-hmm, a couple of responses. First, the types of bleeding events were not well described in the studies that were included. The timeframes were variable. I am not aware of any of the studies that looked at separately the components of all-cause mortality and the timing of them. I would have to go back and look at our data extraction, but I, off the top of my head, I am not aware of any of them that broke down all-cause mortality by type or . . . other than the timeframes shown, but your point is well taken.
- Seth Schwartz: So, looking at this data, in terms of mortality and MI events, I'm really not seeing any significant difference between stents and medical therapy alone other than there is some in terms of the functional status. So, I guess I'm trying

to understand what's the advantage of bare metal stents? I'm not sure if this is the question for our vendor. I guess the first question for our vendor would be, am I interpreting the data right? That we're seeing, in the pooled data, no significant difference between stents of any kind and medical therapy at really any time point, and then the second . . . in the outcomes of mortality or MI. Then, the second question being related to, in the functional status questions, is that the only area that we do see a difference?

Andrea Skelly: Overall, that, yes. Your statement is true. Now, with the MI, the one study, the MASS-II Trial did show a difference between drug-eluting stents and bare metal stents at 120 months, and I can tell you what slide that is. That's for the comparison of PCI versus medical therapy, but that is the only . . . that was the only one in terms of the hard clinical outcomes.

Chris Standaert: But that was PCI versus medical therapy not bare metal stents versus drug-eluting stents. We have to . . .

Andrea Skelly: So, your question . . .

Chris Standaert: . . . there are two separate things we have to talk. We have . . .

Andrea Skelly: Yeah.

Chris Standaert: . . . stable coronary artery disease with medical therapy versus stenting and then we have the bare metal versus metal stenting in all circumstances, essentially.

Andrea Skelly: Right.

Chris Standaert: So, the study that's referred to is in the first group in the PCI versus medical therapy.

Andrea Skelly: Correct. Yeah. That was what I was talking about. And you said . . . you said it was slide 24?

Seth Schwartz: So, then my next question would be for our clinical expert. I just am trying to understand how this, how this goes clinically. If there's . . . if we're not seeing any meaningful difference between these, why are we seeing so many people getting stents?

Michael Ring: Sure. Can you . . . everybody hear me OK now? I understand there was a problem with my microphone earlier. So, we're referring to the specific issue now of . . . because you had . . . there were two components to your questions and one is the question about stenting in stable coronary disease and why you would do a stent. So, the most common reason that that would be done would be for the patient who is having significant symptoms that are not controlled adequately with medical therapy. So, if they're continuing to have, say, Class III or IV symptoms or depending on the individual. It might even be Class II if they

were young and healthy. So, the reason for stents would be to alleviate their symptoms. It would not be to decrease the likelihood of death or myocardial infarction where, you know, the reason being that myocardial infarction is generally due to plaque rupture that can occur in any part of the coronary tree and not necessarily the smaller area that's being treated by the stent. So, there is really not an expectation that stenting in patients with stable coronary artery disease is likely to reduce the occurrence of MI or death. If I can expand just a little bit further in that, and this is what Dr. Skelly was talking about with the ischemia trial, was that there is some belief that the chance of death can be predicted by the severity of abnormality seen on stress testing. So, if somebody has a high-risk test, we do know that those patients have a worse prognosis and that there is the hypothesis being tested that intervening in that type of patient might decrease the probability of subsequent MI or death, but that's the trial of the ischemia study. That's the goal of it, and we don't know the answer to that yet.

Seth Schwartz: So, then, just to be clear, to a degree, all of the stuff about mortality and MI's are irrelevant, and really the one slide that matters is the slide 25 about angina treatment, is?

Michael Ring: I think that's fair to say.

Seth Schwartz: I had a question. On our initial decision, just as we get into . . . we talk about differences. We had, several years ago, I believe the Health Technology Assessment that had been done, there were all these concerns about lesion diameter and lesion length and all these sorts of things that we harangued over for months that seemed to have either never panned out or never been of significance to the authors of the studies you wrote, or you pulled. So, I don't see them reflect that sort of . . . parameter reflected at all in the data you've presented. So, is it no longer an issue of concern amongst the authors and people who did these studies? Is that the interpretation?

Andrea Skelly: I think that . . . well there was one trial that looked at large vessel stenting. I think that the initial Health Technology Assessment, the medical directors wanted to look at to what extent the indications and contraindications related to stenting, which had to do with diameter and length of lesion, etc., and that was really sort of the driving factor, in my recollection, from that. In the studies that met our criteria for inclusion, there was only the one study that looked at the large vessel stenting.

Chris Standaert: OK. Are there other questions for Dr. Skelly?

Gregory Brown: I don't know if this is appropriate. Is there . . . when I asked my earlier question you referred me to the 2009 review about bare metal stents versus drug-eluting stents.

Chris Standaert: Which question?

- Gregory Brown: The first question I asked, you know? And so, I didn't see a summary of those recommendations, I guess. So, that's why I'm confused.
- Josh Morse: There is a copy in your packet. There should be anyway. If you go after the slides that Dr. Skelly just presented, you will next see the current findings and decisions, which was generated in 2009.
- Gregory Brown: OK.
- Josh Morse: With the criteria.
- Andrea Skelly: The other thing that I would point out is, in the executive summary, there is a table side-by-side comparison of the key findings from the 2009 report, and this updated report, if that's of help to you.
- Gregory Brown: Thank you.
- Chris Standaert: It's also slide five of the agency director report has them. Other questions for Dr. Skelly, and she'll be available.
- Michael Souter: Just one more, just . . .
- Chris Standaert: Yeah.
- Michael Souter: . . . because we've asked this in prior situations, and I just think it would be good to be thorough. In terms of the, you know, the trials that we really looked at in depth, the zotarolimus, the examination for example. How many of all of those that we've looked at are the primary RCTs that you've identified? How many of them were industry funded versus funded from alternate sources?
- Andrea Skelly: I would have to look that up. We extracted that and I'd have to look that up.
- Michael Souter: OK. I think that would be helpful to know again.
- Chris Standaert: Yeah, Tony?
- Andrea Skelly: I'd have to go to the appendix.
- Joann Elmore: I have a question, a statistical question for our vendor. It has to do with the outcome of all-cause mortality and cardiac mortality for key questions one and two. Again, let's separate them, you know? Question one is should patients get PCI with medical therapy versus medical therapy alone, and you look at the outcome of mortality. The other one is the drug-eluting stents versus bare metal stents and to look at the outcome comparing those two. It was my understanding that for the latter, the drug-eluting stents versus bare metal, those were not adequately powered to even look at an outcome of mortality. Is that correct for those comparisons? In other words, we're saying that there is

no statistically-significant difference, but weren't these studies underpowered to even look at that?

Andrea Skelly: I think it depends on the outcome that you're talking about. If we look at . . .

Joann Elmore: I'm asking about mortality, because we made a big deal about it in all of these slides and were the studies adequately powered statistically to look at mortality?

Andrea Skelly: I think that there is some question of that. Of that I think if we go back, and I'm not sure what slide.

Joann Elmore: I mean, sometimes you cannot find a difference because you don't have enough patients. I'm bringing this up because you made a big point about no difference in the thrombus, that it was a rare outcome and well, death is a rare outcome.

Andrea Skelly: Yes. If you look at the trials that are here represented for all-cause mortality in the general population, you're talking about 2600 patients, 2700 patients across the two trials, one could argue that there might be sufficient power with that size. If you look at the special populations, however, the Hambrecht – most likely not enough power. If you look at the BARI2-D, possibly. I mean, the rate of all-cause mortality was fairly high in that particular group, but that is a special population of diabetic patients. So, I don't know that there is a blanket yes or no answer to your question, and if we then go forward and look at the . . . I think for things like stroke and for definite stent thrombosis, those are much more rare outcomes, and I think that is probably where my bigger concern about lack of power may be. Most of these trials were powered to look at a composite outcome, and the definition of the composite varied across the trials, and generally the composite outcome results were driven for the drug-eluting stents versus bare metal stents by target lesion and target vessel revascularization. So, they may not have had sufficient power, but it's kind of, it's a little bit difficult to give you a clear yes or no on that. If we look at all-cause mortality here on this slide, and I apologize. It's kind of small. You know, the total numbers that we have for the patients in here are probably close to 5000 patients for the pooled estimate. So, I would think that that should be enough to detect a difference in this case. So, I think it depends on the outcome and it depends on . . .

Joann Elmore: And then my second, or do you have another question about mortality?

Michael Souter: No. I was just going to say, but again, you're making that come up within that 12-month window.

Joann Elmore: Right.

Michael Souter: We're not looking at what happens subsequent to that period when there may be a very clear distinction in prescribing patterns between those patients who are receiving the drug-eluting stents, receiving dual-antiplatelet therapy and

presumably the bare metal stents who are now well outside an appropriate period for dual-antiplatelet therapy.

Chris Standaert: I assume the studies did not record the use of antiplatelet therapy in the dual metal versus bare, that is the bare metal stents versus drug-eluting stents? Did they record that as one of their outcomes? Were there people who stayed on antiplatelet?

Andrea Skelly: No. They generally said, you know, we continued it for x-period of time or in some places, they just said we did it per protocol or per guidelines or . . .

Chris Standaert: No verification of what happened? They didn't look at that?

Andrea Skelly: Very little.

Chris Standaert: And did they do a power calculation to get at Dr. Elmore's point? Did they do a power calculation for mortality? That's the biggest study. I thought they might have done it in that study?

Andrea Skelly: I'd have to look and see what their power calculation was around. I think . . .

Chris Standaert: OK.

Andrea Skelly: . . . it may have been around, again, composite.

Chris Standaert: OK.

Andrea Skelly: But I will look.

Seth Schwartz: So, can I just ask an explanatory question? On slide 44, you do a summary of the Examination trial and the Prodigy trial, and you have two studies that were a fairly good size that both were statistically significant, and yet when you pooled it, it was not? Can you just comment on that?

Andrea Skelly: Yeah. I think the primary reason for that is that the Prodigy trial had so much variability associated with it, and because of the weighting of the trial in the statistical pooling. It was a smaller trial. It was maybe given a little bit more weight with a random effects model, and therefore, there is more spread, and I think that is part of the issue. It covered zero, and so again, I think this, you kind of have to use some judgment and say they both kind of look like they're statistically significant, and yes, they were both statistically significant, and the arrow down below points to the heterogeneity because there's a difference in magnitude and again, I think the pooled result is partly because the Prodigy is maybe overweighted a little bit in analysis and that spread, that large confidence interval for Prodigy is probably the cause.

Seth Schwartz: Sorry, just for clarification. Which trial is it that looked at the diabetic patients?

- Andrea Skelly: That's the BARI2-D trial, and it was the PCI versus medical therapy.
- Chris Standaert: Carson, you had a question?
- Carson Odegard: Yeah, I have an economic analysis question. Since 2009, well we just . . . I know in our past review we had, like, over 40 different studies that looked at cost-effectiveness. This one just shows one. Now, was that just embedded in the Endeavor-2 trial? Was that part of that or was it a separate economic study?
- Andrea Skelly: Erica, correct me if I'm wrong, but I believe that was just the Endeavor-2. There was nothing else, yeah.
- Carson Odegard: Just the Endeavor-2?
- Andrea Skelly: Yeah.
- Carson Odegard: Comparing drug-eluting stents and . . .
- Andrea Skelly: Yeah, and just the one drug-eluting stent. It wasn't across drug-eluting stents. It was just the zotarolimus.
- Carson Odegard: No other studies?
- Andrea Skelly: No, not that met our criteria.
- Carson Odegard: OK. Thank you.
- Joann Elmore: I have a question, probably for the clinical expert. I am impressed that the interventional cardiologists have pooled together and are coordinating this Ischemia trial that is ongoing, and I saw that surveys of clinicians in your field, in interventional cardiology, 80% said that they would be willing and interested in allowing their patients to be randomized into a future study of PCI versus optimal medical therapy. Since this is an ongoing study, is it available to the residents of Washington State now and if they enter in, who pays for the PCI?
- Michael Ring: So, I'm not completely familiar with the . . . all the investigators that are participating in the Ischemia study, which I believe is being sponsored by the NIH. I know that in Spokane, there is the opportunity to participate and I'm fairly sure that Dr. Malhotra in Tacoma is a participant in it as well, and I would not be surprised if it's available in other sites in Washington State, but I don't know that with certainty.
- Joann Elmore: Thank you. And the reason I asked is that historically our committee sometimes would go off on a tangent, probably because of me when I would say we've got to vote for a condition that it be studied, only patients that . . . data are being gathered. So, I was wondering, there's this, what sounds like a very important ongoing clinical trial, and I wanted to know, you know, are residents of Washington State . . . is it available to them. Thank you.

Chris Standaert: I just want to follow up on Dr. Schwartz's question. So, back on this slide 20 . . . slide 44, revascularization. So, we had said revascularization, the criteria that, and then you said it was vague why they revascularized?

Andrea Skelly: I'm sorry. I missed your question.

Chris Standaert: You said, so two points. One, I heard the comment earlier that the criteria for revascularization were somewhat vague in these studies, and there wasn't a hard point where you said we revascularize when. So, did these studies have discrete criteria, and were they . . . everyone was blinded as to what kind of stent the person had, or blinded as to whether it's bare metal stents or drug-eluting stents? So, did the treating people who decided to revascularize know what kind of stent was in there when they made the decision to revascularize?

Andrea Skelly: There was no level of detail related to that in these studies.

Chris Standaert: No level about blinding?

Andrea Skelly: About blinding for this type of outcome. I mean, for blinding in general, yeah, and we can look up how much . . . you know, which studies reported that they had blinded, but that may not be for all outcomes. It may be only for some outcomes, and again, with regard to the revascularization, there was not really any detail about when the decision was made or when it was not to be made. Some would say it was clinically driven and leave it at that. Others would say, well, per protocol we, you know, we looked at patients with angiography. That doesn't mean they got revascularized or not, but it was not clearly defined.

Chris Standaert: So, in these studies, I was just wondering what the knowledge of the type of stent could influence a subjective decision on when to revascularize. That's what I was wondering.

Andrea Skelly: I don't know.

Chris Standaert: OK. Thank you.

Michael Ring: Can I comment on that if you don't mind? Having participated in these type of trials, the typical protocol is that patients are generally randomized on the table and the investigator then is then handed a study stent. He doesn't know which one it is, what type of stent it would be, and neither is the patient knowledgeable to whether they received a, you know, stent A or stent B, so.

Chris Standaert: So, my question is on these two particular studies and the extent of blinding at the time the decision to revascularization was made. That's my curiosity, so whether she knew the answer about these studies.

Michael Ring: For the . . .

- Chris Standaert: For these two.
- Michael Ring: . . . for the Courage study, they already had cardiac catheter, oh, for those two?
- Chris Standaert: For those two.
- Michael Ring: If it was, yeah. I'm fairly confident if it was done, you know, per the usual standard it would be that they would have been . . . the patients for sure would have been blinded and typically the implanter is also blinded, as to the type of stent.
- Andrea Skelly: Even if they went and did another stent? Would they be blinded?
- Michael Ring: I mean, later on? Well they . . .
- Andrea Skelly: For the initial stent, they probably would have been blinded, but what about for revascularization further down the road?
- Michael Ring: They would also be blinded. They'd be blinded throughout the duration of the study.
- Chris Standaert: So, if we . . . if you could look at the studies and answer that for us, that'd be great.
- Andrea Skelly: OK.
- Chris Standaert: So, I know for a fact what happened there. Do we have other questions?
- Erica Brodt: So, for the comparison of drug-eluting stents versus bare metal stents, four of the seven were industry funded. For one, the funding was not reported, and two were funded by other, such as the Spanish Heart Foundation and the Swiss National Foundation for Research.
- Chris Standaert: Which two were those?
- Erica Brodt: The Basket-Prove was the Swiss National Foundation for Research. Examination was the Spanish Heart Foundation. Then, the XIMA, Prodigy, Endeavor-2 and Zeus were all funded by Medtronic, Abbott, or Merck, Eli Lilly, so on.
- Chris Standaert: Thank you. You got a question?
- Kevin Walsh: I have a question for Charissa. I'm looking at slide 13 in your presentation, the Mayo Clinic decision aid for level I and II angina, and the third grid over tells us that stents improve anginal symptoms by about 1.4% at one year, but when I look at slide 25 in the presentation, the Courage trial says about 7% improvement and the MASS-II Trial says 15% at one year. Those are big differences.

- Charissa Fotinos: I can't tell you without going to look back through some of my stuff, what exact studies this Mayo decision aid was based on. I don't know if they incorporated . . . I need to look and remind myself which studies were incorporated, but it is a big difference. They also, and I did include it, they do have a similar decision aid, I think, well I'll stop there.
- Kevin Walsh: Thanks.
- Chris Standaert: More questions, or we're going to let our brain sort of reboot for a second.
- Seth Schwartz: I just had a question, again, about the diabetic population. I'm looking at the BARI2-D trial, which looks like it's stents versus medical therapy, and I'm just curious if there, if you look at the original determination from 2009, diabetics was called out as a special population who would benefit from drug-eluting stents. So, I'm just curious, are we seeing any new data on the differential between bare metal stents and drug-eluting stents for that population?
- Andrea Skelly: Not in the studies that we included. There was no subanalysis of the diabetic population.
- Seth Schwartz: Thank you.
- Chris Standaert: Mike, you had a question?
- Michael Souter: The, and again, I'm perseverating on this question of mortality, perhaps, but the information that's been presented to us on mortality is that of coming from the randomize control trials. Do we have any insights from registry data, which one could consider to be, you know, perhaps a valid source of information in that respect to these low-frequency events, which actually add up over time.
- Andrea Skelly: For the inclusion criteria, we looked at registry and nonrandomized trials for . . . randomized studies for safety only. So, we did not include mortality data from non-observational . . . from observational studies.
- Chris Standaert: I've (inaudible) safety outcome? You had a question, Greg?
- Gregory Brown: I just had a question about the AUC recommendations that were cited and the process that's used for making up that workgroup. I know all the different societies have different processes. So, one is . . . the way that the American Academy of Orthopedic Surgeons does it is, start with clinical practice guidelines, which are purely evidence based, and then if there is no evidence, then they go to consensus recommendations. They also had very strict conflict of interest beyond the workgroup. So, I'm just wondering what the process was for developing this AUC.
- Andrea Skelly: I do have it with me if you want to take a look at it.
- Gregory Brown: OK.

- Chris Standaert: AUCs are also, by definition, in areas where there is very little evidence . . . they're not . . .
- Gregory Brown: No. No. I . . .
- Chris Standaert: . . . no, I know. I'm just clarifying, but they're not strictly evidence-driven things either, unfortunately, and they certainly are variable depending upon the pool of people who happen to be in there. I've been in several, and they can, yeah. It . . . there's a lot of opinion that floats around and personal influence that floats around there, curious.
- Andrea Skelly: They are the ACR, at least the ones I references, are explicit in the levels of evidence they're applying to the different pieces. So, they do describe how they're going to list the hierarchy of evidence and then sort of their recommendation. They also, at the end, disclose all affiliations or conflicts. So . . . but that's . . .
- Chris Standaert: The hierarchy . . .
- Andrea Skelly: . . . that's (inaudible).
- Chris Standaert: . . . of what they considered when they decided, is that what, if they have . . . the ultimate decision does not state that. So, the . . . but they have a . . . they use an evidence hierarchy in their discussion?
- Andrea Skelly: Yeah.
- Chris Standaert: Is that what you're saying?
- Andrea Skelly: Yeah. It's . . . and it'll go through . . . in the narrative, it'll say it's this level, 2B or whatever, and it will have a little bit of a narrative associated.
- Chris Standaert: OK. Thank you.
- Joann Elmore: Perhaps, since the agency medical director based their recommendations on this multicolored image in slide 11, can I ask someone to walk us through it and go over two or three example patients so that . . . just sort of as a concrete example. This is slide 11 in the agency medical directors' slides.
- Chris Standaert: So, what these things means? You mean, when you follow the grid and how to follow . . .
- Joann Elmore: Yep.
- Chris Standaert: . . . the grid and how to then decide which box you've fallen in and what that may mean.

Joann Elmore: Because they . . . the medical director took this and then wrote . . .

Chris Standaert: Is their basis . . .

Joann Elmore: . . . their three . . .

Chris Standaert: . . . for their decision.

Joann Elmore: . . . bullets. So, I want to make . . . because I . . . I'm having a hard time with this little figure, and I did not . . .

Charissa Fotinos: I'm happy to . . .

Joann Elmore: . . . have the original . . .

Charissa Fotinos: . . . walk through my understanding of it that said . . .

Joann Elmore: . . . can we pull up slide 11 please?

Charissa Fotinos: . . . It sounds like the definitions are going to change.

Chris Standaert: Excuse me, what did?

Charissa Fotinos: No, I . . . I am happy to walk through my understanding of it. It sounds, though, in the newest version, which will be out this summer, the acceptable, uncertain, and inappropriate labels were going to go away and be replaced by the other terminology. Dr. Wells, I believe used . . .

Chris Standaert: We don't have that, and you didn't use that to make your . . .

Charissa Fotinos: I wasn't . . .

Chris Standaert: . . . recommendations.

Charissa Fotinos: . . . I wasn't aware there were no guidelines.

Chris Standaert: No. So, how would you interpret this table for Dr. Elmore, so you . . . you can explain how you used it to make your determination I think is what she's after.

Charissa Fotinos: Right. So, without being . . . so, let's look at the asymptomatic side and look at low risk stress test in a person who does not have adequate medical therapy or much at all. Folks should not get PCI with either chronic occlusion of one vessel and no other disease or if they have one or two vessel disease with proximal LAD involvement. So, the red is . . . these are folks that should not have the stent placed, and you can see that recommendation goes for folks who are low-risk on stress testing who are on maximal treatment, then intermediate risk on no treatment. The yellow boxes are what sounds like they are going to be the maybe. It's not clear, and maybe that's not enough evidence. Maybe it's not as

definitive, but those are sort of judgment call places, and then in terms of the green boxes, there is evidence to support the use of stent placement in those circumstances of the type of stress test response and the type of medical therapy. So, in terms of our recommendations, not, I mean, in terms of implementing the recommendations that we made, they would be challenging. That said, it was clear from the evidence that there are circumstances in which stent placement does not benefit and is not appropriate. I think we tried to give more leeway in terms of some of the uncertain elements. Again, given the fact that every patient is a little bit different. So, I think we, in our recommendations perhaps, tried to . . .

Joann Elmore: Right. Right. I understand that you tried to follow this, but I'm trying to follow this figure. So, on the far right, you've got a whole big chunk of data that is asymptomatic. By asymptomatic, do they just mean chronic stable ischemic heart disease.

Charissa Fotinos: Yes, from my . . .

Joann Elmore: OK, thank you.

Charissa Fotinos: . . . understanding.

Joann Elmore: Then, you take somebody that has chronic, stable, ischemic heart disease, you Cath them, so you've got the columns on the right and then you also have done a stress test before that's intermediate risk, but they're not on . . . they are on minimum or no Rx. Why are they on minimum or no Rx? Don't we try to get everybody on Rx? Is that because they're allergic to the medications or something? I just want to make certain I understand this as a clinician, also.

Chris Standaert: Well, so these are, so, I wasn't in this one. The one study I've done, I went down to RAND to develop this procedure, and I was . . .

Joann Elmore: And I've . . . I've developed these . . .

Chris Standaert: Right.

Joann Elmore: . . . guidelines, too. So I . . .

Chris Standaert: So . . .

Joann Elmore: . . . I just want to understand this one.

Chris Standaert: . . . but that issue of, and even what you've said is not totally accurate or correct. So, when you do these, you get a scale, and you usually vote on a scale of zero to nine, or one to nine, on how appropriate you think this is, and then it's a pooled data of all the different people in the thing, and you draw a line where you say, well, if most people . . . if our average or mean comes out at this point, it gets an A. If it comes out at this point, it gets a U. If it comes out at this

point, it gets an I. So, it's . . . it's not what you said. It's not that they think it's . . . not that they determine that it's uncertain. They don't use that word. Some people think it's appropriate, and some people don't think it's appropriate, and they aggregate it and it comes out somewhere in the middle. Some people think it's highly appropriate, and you can have something where a lot of people thought it was appropriate, something is wildly inappropriate, and it will still fall into the U. So, this is not as clearcut as you were describing it, in terms of where people draw lines. It's somewhat arbitrary-ish, and I think . . . and I suppose these scenarios are just sort of presented to them as, could this happen, 'cuz what we're not talking about is the fundamental question, why you would be catheterizing somebody who has not been treated for their stable angina.

- Joann Elmore: And (inaudible) no or minimum Rx, what?
- Chris Standaert: So, these people may not exist in the real world. They appear in the table, but they may not exist in the real world, because people shouldn't be doing that.
- Joann Elmore: OK, 'cuz there's some green boxes here with no or minimum Rx, and I just wanted to understand that.
- Seth Schwartz: This table is not based on evidence. It's based on hypothesis.
- Joann Elmore: Exactly. That's the other issue.
- Chris Standaert: So, I think we have to be a little careful about how we use this, personally, because all the vagueries of that, and it's a tool for people to help determine in a certain circumstance, not . . . and as it was pointed correctly by the presenter, not designed for policy determinations. That's not what this is.
- Charissa Fotinos: And our intent was not necessarily to explicitly this should or shouldn't be covered but was to do just this, generate conversation and some starting point, as opposed to all or none, which is more challenging.
- Chris Standaert: Why don't . . . we're going to take one more question.
- Gregory Brown: The one other thing that they do is they . . . it's not just the median score, but then there's also a consistency.
- Chris Standaert: Mm-hmm.
- Gregory Brown: So, in other words, you could have . . .
- Chris Standaert: There are two measures, yes.
- Gregory Brown: . . . you could have five, nine, and four, one, and the . . .
- Chris Standaert: Mm-hmm.

Gregory Brown: . . . median score is five.

Chris Standaert: Right.

Gregory Brown: Well, actually, technically, no. That's not true, but the average score . . .

Chris Standaert: Right.

Gregory Brown: . . . would be (inaudible) . . .

Chris Standaert: There is a high agreement and low agreement and all these . . .

Gregory Brown: . . . but, but, yeah.

Chris Standaert: . . . other variables, right?

Gregory Brown: But they're not agreed.

Chris Standaert: Right.

Gregory Brown: There's no agreement.

Chris Standaert: Right, and so how do you then determine this falls in all . . . so all these metrics go in there. So, it's . . . it's not a clearcut, we think, as a group, that it's not even a consensus determination like you'd have in a guideline. It's not even that. It's a different process. So, again, using them for policy is tricky when these are not designed for that. So, that's . . . but, we're going to take a brief break, or do you have a comment?

Josh Morse: Before the break, I have a comment.

Chris Standaert: OK.

Josh Morse: You were going to check again for any public comments.

Chris Standaert: Yes.

Josh Morse: Do you want to do that now?

Chris Standaert: I was going to do that, yes. That's what I was going to do, yes.

Josh Morse: Oh, OK.

Chris Standaert: So, we can . . .

Josh Morse: We have three minutes available for each commenter.

Chris Standaert: OK. So, we're going to take a brief break. Before we do that, we're going to ask one more time. We had closed the lines for comments a few minutes before our comment window was supposed to open for the phones. So, we'll ask if there's anybody on the phone who wants to make a comment. If you do, you will need to identify yourself, state your conflicts and financial interests and connections to all this, and you will have three minutes to let us know what you think. So, is there anyone on the line that would like to make a public comment? OK. I am assuming there are none. OK. I heard a 'no thanks.' So, thank you. Alright. We will start back up again at 2:35.

Alright. We're going to get going. So, we had several issues here. I just want to sort of put this in the right box for people and be . . . and move on to what we have to do. So, our charge is to use the literature we have and look at literature that answers our questions, right, in the prevue of what we do, and in the midst of that, we've introduced this table from AUC, which was not part of literature review. It was not part of our prevue particularly. It was not designed to do what we are trying to do, but it's relevant, because the . . . it was brought into the conversation. No, you should bring it up, because it was brought into the conversation as a decision tool used by the medical directors. So, I just want Dr. Ring to have a chance to sort of talk about the clinical application of this so we can keep it in context ourselves and where clinicians are going to use this, and then we can go back and go on to our literature base and see where . . . we go where the evidence takes us is where we go, right? And we certainly have an obligation to respect the guidelines of the medical societies and respect the existing other guidelines of payers and other things, and we'll certainly look at those, and if we fall in line, we fall in line. If we find discrepancies, we discuss them, but we will go where we go with the data we have. So, first, let's give Dr. Ring a brief second to talk about the agency for one second and how that might be applied clinically.

Michael Ring: Sure. So, the ACC and the sister organizations that developed the appropriate use criteria did so to . . . with the idea of looking at broad patterns of care to try to see how different institutions and regions compared and to try to maybe explain or perhaps decrease the amount of variability on a geographic basis, and so what typically occurs is that the ACC provides to each institution that's doing, for instance, PCI. There's a registry that's voluntary, although I believe over 99% of hospitals participate where they send their PCI data to the ACC, what's called NCDR organization that . . . it's a data repository and does the analysis, and then we'll send to the individual on a quarterly basis . . . to the individual institution on a quarterly basis, a report on how they're doing on their PCI metrics, which include outcomes, but also, importantly, looks at their AUC metrics, as well. So, they will report, you know, do they, are they providing sufficient data so that the cases can be properly adjudicated, and then we'll also give them a report on how that institution is doing from an AUC basis, you know? What percentage of their cases are inappropriate or, more importantly, inappropriate. At least, that's the current terminology. Then, we'll compare them to other . . . to the national average, as well. Now, in addition, in Washington State, we have the COPE organization that does so on a . . . to all the institutions performing PCI

and CABG in our state in comparison to each other and it maybe helps them to assess if there are discrepancies between institutions. So, those were provided to each institution and then that individual institution can decide how they want to use that data. Typically, though, because it is something that is important, it is usually shared amongst the cardiologists at that institution to help them understand their metrics and if there's opportunity to improve, that they try to do so and there has been, actually, you know, an improvement in the metrics over time, as feedback has occurred. Now, on an individual basis, it is not like when somebody gets to the Cath lab that the AUC is actually necessarily calculated with the patient on the table. Some institutions, actually, have tried to do that and make sure that the operator knows that the, you know, what the results of the treadmill were, of course, and the medications, and we'll tell them, you know, you're about to do a PCI on somebody who may not fulfill the criteria for the, um, you know, for appropriate and while they're there, and they can use that information to decide whether they want to go ahead or not, but for the most part, we do not find out about it until after the fact.

Chris Standaert: OK. So, it's a feedback, almost a self-policing tool in a way. It's a feedback tool to help . . . some people use it actively as a pre-intervention tool, but more people use it as a way to track their own sort of practice behavior following the AUC and the guideline recommendations . . .

Michael Ring: That's correct. And they . . .

Chris Standaert: . . . appropriately and then re-navigate why they may or may not be and theoretically improve their practice pattern with the (inaudible).

Michael Ring: . . . right. And that's, that's the intent.

David McCulloch: So, that's really helpful and interesting. How long has that been in place, roughly? Four years, five years, ten years?

Michael Ring: I think the initial AUC were developed in 2009 and I don't think it was part of the registry reports until likely around 2010, 2011. So, I think the timeframe you mentioned . . .

David McCulloch: So, about five years. So, is there evidence that the massive regional variation, as outlined by the Dartmouth Atlas, has that shrunk? Is there less variation or does there still remain hot spots of, you know, some places doing four, five, ten times as many for the same population as other geographical locations? Do you think it's working?

Michael Ring: I think it's working. I mean, I know that on a national basis that the rates of what's being categorized as inappropriate are coming down. There was actually a study that was published in the past year on how Washington State, in particular, is doing . . . using the COPE database and that there has been a you know, a decrease in the amount of inappropriate cases, as well as the cases that had incomplete data. So, there has been some change, at least within

Washington State, that's been documented, but I . . . to the answer that you asked is, do what I know about regional variations with the AUC criteria, I suspect there's been some publications, but I'm not familiar with it off the top of my head.

Chris Standaert: Any questions or comments from people on that? That was very helpful. Yeah, it was helpful to understand. It's a powerful tool. I guarantee most medical fields don't have an equivalent. Alright. So, we're going to go onto our key questions, and we'll come back to that if need be. From my standpoint, we have two very distinct key questions, right? We have stable coronary artery disease and stenting in general. Then we have drug-eluting stents versus bare metal stents. We can talk about them, as one, but I think we're going to get a bit confused if we start commenting ultimately on different . . . on each, and we probably should pick one topic and then the other. We need to discuss it and then we need to go through the whole vote on one and then do the other and go through the vote on that one, just so we keep ourselves clear. OK?

So, let's start with stable coronary artery disease, key question one. Does anyone want to help us get going and understand where we are so we can pull ourselves together here? We've had a lot of questions and a lot of data.

Kevin Walsh: I think Seth summarized the issue well when he said it all comes down to slide 25. The only real benefit that it seems that the evidence shows is for improvement in angina symptoms. In the Courage study, the improvement at 12 months is 7%. It goes down to about 6%. In the MASS-II Trial it's 15% over time. So, really, this is an anti-anginal treatment.

Chris Standaert: Mm-hmm, as opposed to effective . . . effecting mortality.

Kevin Walsh: As opposed to anything else. I mean, really, that's the only . . .

Chris Standaert: Benefit that . . .

Kevin Walsh: . . . thing it seems to do is benefit angina symptoms in somewhere between 7 and 15% of those patients who still had angina after maximal medical therapy.

Chris Standaert: Other thoughts or ways of looking at that one? Concurrence?

David McCulloch: I mean, I concur. I was really surprised at how underwhelmed I was with the data. I mean, I have yet to see evidence. I mean, why would you use this at all other than to make money? Why, unless . . . in somebody with stable coronary artery disease, I get it if they get symptoms and maximal medical therapy, totally reasonable to do that, but other than that, I can't think of why you would do it.

Chris Standaert: You agree, Seth? You started that one. Kevin threw you under the bus.

Seth Schwartz: Well, I'm just trying to understand.

David McCulloch: Me, too.

Seth Schwartz: Again, I expected to be much more blown away by the data than I was.

David McCulloch: Right.

Seth Schwartz: But that's not to belittle the significance of decreasing anginal symptoms in 10 to 15% of patients. I mean, that may be huge relative to some interventions. So, I don't want to belittle that, but at the same time, if patients are getting adequate control of symptoms with medications, I don't see any . . . I'm not seeing any compelling reason why you would want to give them this, do this procedure. So, unless . . . so that, that's the data I haven't seen and so . . .

David McCulloch: Mm-hmm.

Seth Schwartz: . . . that's what I'm kind of wrestling with.

Gregory Brown: So, if you are on maximum medical therapy and . . . or optimal medical therapy or however we want to phrase it, and you get a stent, your angina goes away. You stay on the medical therapy or do you withdraw some of the medical therapy?

Joann Elmore: Yeah, the guideline medical therapy is things like the statins and the blood pressure control and all the other wonderful things.

Chris Standaert: So, in anginal symptoms, this is me trying to sort out anginal symptoms equating to physical performance or physical function and quality of life and exact metrics they were using. Should we start talking about improvement or not . . . people are not . . . saying they don't see much improvement, again, towards the primary outcomes and mortality or recurrent MI. It's more the symptoms, which then correlate, theoretically, to function?

David McCulloch: I'm . . .

Chris Standaert: What do you think?

David McCulloch: . . . well, I'm . . . I'm struggling to . . . I'm anticipating that we're going to end up having to cover with conditions. I'm not saying we're going to, but just suppose that scenario happened, it's going to be hard to come up with conditions, because it's so subjective, you know? For one person versus another, what amount of exertional angina is mild, moderate, severe, intolerable? So, if we say something as vague as we will only cover it under conditions where the patient has intolerable symptoms, that's a door as wide as a barn door that you can . . . that any patient and their provider can walk through, through sheer decision making. And maybe that's the appropriate thing to do, but that's . . . I . . .

- Michael Ring: That's the world I live in every day, because nobody dies of knee arthritis. It's the pain symptoms that they can't live with, and their quality of life. So, I mean, you're right. There's no way to write a guideline that's objective, if you will. It's all reliant on the patient's interpretation.
- Seth Schwartz: And I guess I wonder if there is some guidance for that in some of the guidelines that exist or in the appropriate use criteria language that we could fall back on if we need to?
- Chris Standaert: I mean, we have things in the studies of . . . we have these categories of I, II, III, and IV, right? And you have III means they can't walk . . . one to . . . you can't walk one to two blocks without symptoms; III is under two blocks, yes?
- Michael Ring: So, can I maybe comment a little bit on or add to it, right, that that's why there's that category of uncertain where they . . . it's the . . . the question that may be scenario that's raised is . . . it can't be answered by simply the fact whether what's . . . what classification of angina, you know, how positive their treadmill test. Let's assume they're on, you know, maximal medical therapy. So, you know, somebody who has Class II angina, you know, where they get their angina after walking a couple of blocks, if they're, you know, elderly, have, you know, a bad hip are rarely in a situation where they develop the angina, their lifestyle may actually be acceptable, but if you had somebody who is, let's say, 40 years old, liked to hike, and found that they could only walk a quarter mile before they got angina, it still might be considered Class II but not necessarily an acceptable situation for them, and that's where that kind of shared patient decision would come into play.
- Kevin Walsh: But in followup to that, what I'm struggling with is, I didn't see any data that says if you do . . . if you do a PCI, they're going to go from Class III to Class II, right? Then, they're going to go from Class II to Class I. I mean, that's . . . that's what I would like to see, but I'm not seeing anything like that.
- Chris Standaert: Now, we have rates of anginal symptoms, but we don't have sort of, so if you got the stent can you walk three miles, right? So, these issues of incremental benefit of response to treatment rates . . . but what is . . . what is better?
- Kevin Walsh: Right. There's a benefit implied, but we're never really given any data to demonstrate that.
- Chris Standaert: The magnitude of that benefit.
- Carson Odegard: And that's what makes it so difficult, because this is kind of an unusual case for us, because we're not usually making decisions on subjective things, and even though there are different levels of symptoms and different levels of quality of life and lifestyle issues, that's what we're dealing with here, and I don't know how you sort it out. I don't know if you can, but it is kind of difficult.
- Chris Standaert: Well, we're going to have to.

Seth Schwartz: Well, maybe we can go to our vendor. I'm looking at 25 where they say there's an improvement in anginal symptoms, and those percentages . . . how do they define improvement in angina in those . . . in those . . . in that trial? So, primarily they're looking at the MASS-II Trial and the Courage trial. Can you comment on how that . . . how that benefit was defined?

Andrea Skelly: Right. So, in terms of clinically . . . so, this is based on the Seattle Angina Questionnaire for the Courage trial. If . . . actually, you are looking at . . . you are looking at this, yeah. They really didn't define freedom from angina in terms of clinically significant here, but if you look at the Seattle Questionnaire, which I believe is maybe the next slide or the, yeah. It's the next slide. Yeah, it says, yeah. So, in terms of the Seattle Angina Questionnaire, they defined clinically important difference for anginal frequency of a change of 20 points. So, that's, that seems reasonably substantial. I mean, that's an off-the-cuff remark, but . . . so, for anginal frequency, at least 20 points, for anginal stability at least 25 points, treatment satisfaction 12 points, quality of life 16 points, physical limitations 8 points. So, that's what they consider a clinically important difference, but for the slide previous to that, we do not have information on how they defined . . . how it was . . . how it was . . . freedom from angina, what did that mean? What did that mean in terms of . . .

Kevin Walsh: How many possible points were there in the questionnaire?

Andrea Skelly: . . . that I don't know.

Kevin Walsh: I mean what is . . . I'd be interested in knowing what 20 . . . what percent?

Joann Elmore: Yeah, you described it in your report, but this is based upon patient self-report among patients who knew that they had a stent put in.

Kevin Walsh: Right.

Andrea Skelly: Correct.

Joann Elmore: Compared to those that knew they had a Cath and did not get a stent put in.

Kevin Walsh: Right. So, they had the procedure placebo.

Seth Schwartz: But I have a couple questions here. So, first of all, is the Seattle Angina Questionnaire, was that what was used in that trial?

Andrea Skelly: In Courage, yes.

Seth Schwartz: In Courage, but not in MASS-II Trial?

Andrea Skelly: No.

- Seth Schwartz: And is that the only, has it been clinically validated for other situations or has it only been . . . was it only used for this trial?
- Andrea Skelly: No. It's been validated in other situations. It's widely used.
- Seth Schwartz: And so, is that clinically important difference generally defined for that questionnaire, or is that just what they used in this trial?
- Andrea Skelly: That, I would need to go back to the front part of the report where we talk about the outcomes and their liturgy, so give me a second.
- Seth Schwartz: OK. And then just to follow up, just to be clear. So, is that . . . so is that 20 to 25 point difference what they're defining in the Courage 2 trial as a different . . . as an improvement in angina, or was that totally an independent statement?
- Andrea Skelly: That's an independent statement.
- Seth Schwartz: OK. So, we're saying there is absolutely nothing in that trial that indicates how they indicated an improvement in angina? Was it like a yes, no question? Is your angina better or not, or?
- Andrea Skelly: We're looking that up.
- Seth Schwartz: OK.
- Kevin Walsh: The Seattle Angina Questionnaire has got a range of a 100 points, so.
- Chris Standaert: So, but it says also it was inconsistent in the Courage trial. Angina frequency they said yes, but they said angina stability, quality of life, physical limitations, satisfaction really not stunningly different at all. So, I guess a similar question is, how do we measure this idea of better?
- Michael Souter: So, I think the point being made of, that's being very subjective and depending on individual circumstance . . . patient circumstances, this is really an important one. It's difficult to ignore that, and I do take note of the impact of this and a 40-year-old whose got, you know, children to run after versus a 68-year-old who enjoys a more sedentary lifestyle, and, you know, I don't want to be leaping the, you know, to inappropriate conclusions here, but I just wonder whether or not, as has been posited, we may be ending up covering with conditions whether we can, in plain language that really accommodates the relevance of anginal symptoms to that person's lifestyle and function. It may be a large door. I see David shaking his head. It may be a large door to drive through, but nonetheless, I don't know of any way in which we can make a meaningful distinction that's actually going to cover the population that we have to serve. And I think we have to have something that accommodates somebody's function and lifestyle or that, you know . . .

- David McCulloch: Well, I'm . . . I'm agreeing with you Mike. I don't see this . . . I can't think of a way we could write conditions that aren't basically just saying any patient in discussion with their cardiologist can decide to have this or not, because they're going to decide that for me, my symptoms are bad enough, I want the stent, and that may be all we can do.
- Chris Standaert: So, go ahead. Joanne?
- Joann Elmore: Well, I want to follow up on that point, in that I suspect, I have not seen any data on this, but I suspect that many patients undergoing angiography who then realize that they could or couldn't get a stent, they may not realize that that stent is not going to change their mortality. I don't think patients realize that this is an antianginal drug.
- Chris Standaert: And again, we have several things to consider, right? We have more than one prong to our stool. So, if we look at slide 27 again, it talk about outcomes. We go back to 7% of the people are better. What does that mean? They have the RAND 36 they said at six months, people who are stented were better but not at twelve months. Other RAND domains no different than the BARI2-D trial, FX-36, physical functioning and vitality better at twelve months but not after that, and not anywhere else. Again, the magnitude of these is there. Then, we have to consider safety issues. Do we have safety concerns?
- Michael Souter: Yeah, well I think there is that question of periop- . . . peri-procedural MI. That would be particularly true of the diabetics in the BARI2 . . . the BARI2-D trial does reflect that population. So, that may . . . that question may already be answered for us in some way.
- Chris Standaert: Mm-hmm.
- Joann Elmore: I'm on page 100 of the report, and I just saw something that worries me. So, I want to . . . 101, page 101. It's a little footnote. It's the angina, freedom from angina, table 21, PCI versus medical therapy, and it gives the results of all the different studies, and there are a lot of P-values that are significant, but then the footnote says, freedom from angina not further defined by any of the studies.
- Andrea Skelly: That's what we're trying to verify, but that is my understanding, as well. And in terms of the Seattle Angina Questionnaire, on page 41 of your report, it appears that where it has been validated, the MCID minimum clinically important difference is 10 points. So, the values that I gave you must have been related to that particular study, what they considered a clinically important difference, and it's above that ten points.
- Gregory Brown: Based on that, in the Courage trial, page 4 has a complete page of all the report for physical limitation, angina, stability, angina frequency, treatment satisfaction, and quality of life. So, there are a number of statistical differences, but based on that for, like, anginal stability, at three months the difference is 77

versus 73, 76 versus 73, 74 versus 70, 73 versus 69. They are statistically significant, but they don't meet that MCID if it's ten points. Same way with anginal frequency scores, you know one . . .

Joann Elmore: I think this is percent of patients that are reporting angina, and that's different from the percent who had an improvement in the Seattle Angina Questionnaire scale. Those are two separate ways of assessing angina.

Gregory Brown: Correct. I agree, I guess. I'm shortcutting and defaulting. From my perspective, patient reported outcomes on an absolutely scale is much better than trying to find a difference in the binomial variable yes/no. So, based on that, although there is statistically significant differences in their scores, there is no clinically significant differences in their scores based on a ten point MCID. So, that's . . . that was my point.

Chris Standaert: When you go to the safety data on revascularization, it's interest . . . we've talked about the term. It's interesting. So, if you didn't get stented as a primary revascularization. And we've done this with other things. You can say that in the Courage trial, let's add slide 28, through 55.2 months, PCI 20%, medical 30%. So, that means 70% of the people in the medical arm never got stented at all and that essentially 120% of the people in the PCI group got stented, because 20% got stented twice, right? So, it's, you know, you sort of go with the risk of needing revascularization. It's still one out of five if you vascularize them, and it's actually the other way around. The numbers are flipped in the MASS-II Trial. So, that concept, in terms of safety and things, seems to . . . it does not argue that it's unsafe not to stent people to my view, but . . . because you still have a fair number that get re-stented.

Andrea Skelly: Again, there are a lot of differences in terms of the patient populations between Courage and MASS-II Trial.

Michelle Simon: Didn't you say with MASS-II Trial, there were a lot more patients included that had positive treadmill tests and previous procedures?

Andrea Skelly: Yes. So, some of the differences in the baseline characteristics were that more Courage patients were male. More Courage patients had single vessel disease, and fewer Courage patients had three or more diseased vessels, and there were more Courage patients who had undergone prior PCI or prior CABG, and then in terms of the baseline characteristics, you know, Courage was fairly well randomized. There were differences in the baseline, but of MASS-II Trial, significantly fewer patients . . . more PCI patients had prior MI in the PCI group versus the medical group. Fewer patients had diabetes in the PCI group versus the medical therapy group, and significantly more PCI patients had a positive treadmill test in the PCI. So, that's for the 47% versus 33%, and that was in the MASS-II Trial. That is not in comparison to the Courage trial. That was the baseline characteristics difference between the two treatment groups in MASS-II Trial.

- Chris Standaert: So, everyone in both of these studies got a catheterization, yeah? Then they got a treadmill test?
- Andrea Skelly: I believe so, but I'd have to check. Mike says no, but let us . . . let us check.
- Chris Standaert: Didn't they break out these outcomes we're looking at by the effects of the stress test to the heart, so by myocardium at risk or no risk? Did they make that split in terms of them looking at outcomes, so we know who benefited from the procedure?
- Andrea Skelly: Not that I'm aware of. I'll have to look, but I don't believe so.
- Louise Kaplan: I'm curious also, the MASS-II Trial was done in Brazil. Was the recruitment different than how people were recruited for Courage? I'm just thinking when you're comparing studies across different health systems. Part of Courage was done in the U.S. and Canada, but that system is going to be more similar, those two are more similar than Brazil. I'm just wondering about recruitment and population differences, how people got into this study.
- Andrea Skelly: I couldn't answer that question.
- Gregory Brown: Canada and U.S. were that similar.
- Chris Standaert: Yeah, no.
- Gregory Brown: I've been trained in Canada.
- Louise Kaplan: I think I said they might be more similar than . . .
- Chris Standaert: More similar.
- Louise Kaplan: . . . more similar than Brazil and the U.S.
- Gregory Brown: Maybe not similar enough is the way I should say it.
- Chris Standaert: One question, we can . . . that might help us. It's sort of what Joanne brought up before, that we can't . . . this idea of we have somebody with stable angina and not functionally limited with no perfusion deficit or myocardial risk on stress testing, why should they be catheterized. They shouldn't even be in this algorithm. It should be in the people we're talking about, right, because that gets tricky, because they're the ones who would say more obviously, they're not really limited. They're not terribly at risk, and we're not going to effect the mortality at all by stenting them. So, why are we even going to catheterize them, right? So . . . so, they'd be the people you might, you know? So . . . but that's not called out for.
- Gregory Brown: So, here's the MASS-II Trial, so methods, patient selection. Patients with angiographically documented proximal multivessel coronary stenosis of more

than 70% by visual assessment and documented ischemia were considered for inclusion. Ischemia is documented by either stress testing or the typical stable angina assessment of the Canadian Cardiovascular Society. Patients were enrolled in randomized . . . there was agreement on the part of the surgeon and interventionist that revascularization could be obtained by either strategy.

Joann Elmore: And that stable angina could be Class I, II, III, or IV. So, it could be of variable severity. Is that right?

Gregory Brown: Yeah. It doesn't . . .

Joann Elmore: OK.

Chris Standaert: . . . but they are people with myocardium at risk. They are people with myocardium at risk on stress testing. So, it's a distinct subpopulation of stable angina.

Joann Elmore: Mm-hmm.

Chris Standaert: Inclusion criteria of the Courage study?

Gregory Brown: Yeah. So, evaluate the relative efficacies of three possible therapeutic strategies for patients with multivessel coronary artery disease, stable angina, and preserved ventricular function. So, multivessel coronary artery disease, stable angina, and no CHF, I guess, is . . . reasonable ejection fraction.

Chris Standaert: Right, but at risk myocardium.

Gregory Brown: Based on angiography, because they all had angiography.

Chris Standaert: Yeah. They had a stress test, too, you said?

Gregory Brown: No. No, so they, the patients had angiographically documented proximal multivessel coronary stenosis of more than 70% and then ischemia was documented either by stress testing or Canadian Cardiovascular Society assessment.

Chris Standaert: Yeah. Separately?

Gregory Brown: Yeah, one or the other.

Chris Standaert: Can you do the same for the Courage study so we can have them? Or can Andrea help us with the inclusion criteria of the Courage study, one or the other?

Andrea Skelly: There is a list of inclusion criteria in your report, as well, directly taken from the studies themselves.

- Chris Standaert: What page?
- Andrea Skelly: Let me see what page it's on.
- Gregory Brown: OK.
- Joann Elmore: All patients had to have angiographically-defined ischemia.
- Josh Morse: Please use the microphone, thanks.
- Joann Elmore: And what were the exclusion criteria, though? I'm sure there were some.
- Andrea Skelly: Let's see. Eligible patients include those with chronic angina, Class I through III CCS, stable post-MI patients, and asymptomatic patients with objective evidence of myocardial ischemia. All patients must have angiographically-defined coronary artery disease with at least one vessel meeting the AHA/ACC Class I or II indications for PCI, and then major trial exclusions are persistent CCS class IV angina, refractory to medical therapy, unprotected left main stenosis of greater than 50%, left ventricular ejection fraction of less than or equal to 30%, or less than or equal to 35% with severe three-vessel disease, including greater than or equal to 70% proximal stenosis of the LAD or a markedly positive exercise stress test.
- Chris Standaert: So, is my impression then correct that, again, these are patients with myocardium at risk with ischemia of some sort or myocardium at risk on stress testing, and that's these studies.
- Kevin Walsh: So, right. I mean, it goes back to David's point. So, if we're going to, you know, if we're all kind of leaning towards approving with conditions, and the question is what conditions? What we've just found out is that all the people in these two studies that we've been looking at that had improvements of angina between 7 and 15% over a year, whereas a population of people that had disease on catheterization, and we're trying to make a determination for people who just present with angina? That seems kind of not comparable to me, right, because somebody can present with angina and end up with a stent based on what we're saying. If their angina is . . . if they've . . . if they come in with angina, they have maximum medical therapy, they have worsening angina, worsening, oh yeah, you can have a stent because these studies said you had an improvement of 10% in your angina symptoms or 10% of you will improve year out, but we're basing that decision on a subgroup of people who have already . . . we already know have coronary artery disease because not only do they have angina, but we've catheterized them.
- Chris Standaert: And they have significant issues with risk, right?
- Kevin Walsh: Right.

- Chris Standaert: So, this is a distinct subpopulation of our topic population, which is stable coronary artery disease.
- Kevin Walsh: Right. So, we're trying to make, I'm saying we're trying to make a determination for a large group of people, only a small percentage of whom are going to have a catheterization at the time that this decision is made.
- Andrea Skelly: By the way, on page, starting on page 29 of the appendices is an exhaustive list of inclusion/exclusion criteria for all studies included.
- Seth Schwartz: Can I just ask our clinical expert, in practice, how this happens, you know what I mean? Do these patients . . . they come in with angina. They've been on medical therapy. They're not happy with their treatment. If you're going to talk to them about a PCI, are they all going to get catheterized, or is that going to be a small subset that gets catheterized? How is that going to work?
- Michael Ring: Sure. So, when we're talking now about patients with stable coronary artery disease. So, recognize that the overwhelming majority of those patients never get to the Cath lab. You know, you see many patients a day with stable coronary artery disease that the primary emphasis of that visit usually is, you know, prevention of future progression of the disease, you know, and guideline driven medical therapy. So, the typical patient that you say, see in the office, that reports angina or possible angina typically will get medical therapy and then will have a treadmill test, and if that treadmill test is either normal or low risk, generally you will continue a trial of medical therapy. On the other hand, if the stress study is considered, you know, intermediate or high risk, especially if they're on, you know, optimal medical therapy. That's the type of person that would end up going to the Cath lab, which is relative rare. I mean, we do, you know, many treadmill tests a day and just a very small percentage of those patients actually end up eventually in the Cath lab. So, it's . . . the normal flow is that there are a lot more patients getting medical therapy, a smaller number getting stress tests, and even a much smaller number that eventually end up in the Cath lab. Now, occasionally, you will see patients who continue to have symptoms despite medical therapy and a normal stress study, and those patients may end up, you know, with a cardiac catheterization at that time. So, once they get to the catheterization lab, you know, we . . . sometimes we'll see anatomy that we're not clear as to what it means. So, there's, you know, other things we do besides the treadmill test. We have things that we call pressure wires where we can put a wire down a lesion to determine if it's what we call hemodynamically significant, to see if that could be causing, you know, obstruction of flow, and we do have pretty good data on that, as far as being able to predict, based on that determination, if a patient has a good prognosis with continued medical therapy versus a much higher likelihood of having an MI or needing to have subsequent revascularization. So, that's the . . . that's what usually happens in day to day practice.

- Chris Standaert: Well, the interesting thing is, despite the (inaudible) very high risk with known vessel disease is, this didn't impact mortality. And it has relatively modest effect on quality of life and angina.
- Gregory Brown: But I think you explained that with the . . . they may rupture a plaque some place else. So, even if you stent one occlusion, it's not going to affect their mortality.
- Michael Ring: Yes. That's correct for the majority of lesions. Now, the one thing that we're . . . a territory that we don't know, and that's really the subject of the Ischemia trial is that, you know, based on the stress studies, we know that you can risk stratify patients in terms of how they're going to do, you know, from a survival benefit, or you know, risk of MI. So, we know that low risk patients generally have less than . . . have zero to 1% annual chance of major cardiac event. If you have a high risk study, then you have approximately 5% annual chance of subsequent large MI or death. In the intermediate, of course, is in between those two numbers. So, we do know that the stress study can predict. What we haven't determined yet, and that's the subject of the Ischemia trial is, can you modify that risk with revascularization? And that's why there is a certain amount of . . .
- Chris Standaert: Right.
- Michael Ring: . . . you know, consensus or, you know, uncertainty about these guidelines.
- Chris Standaert: Because that's what's not clear from this. Those people may be at risk, but it is not clear that that risk is mitigated by stenting.
- Gregory Brown: But that's not the group we're asking about in our key question, is it?
- Chris Standaert: No, not all, no, but even stable angina, you know.
- Gregory Brown: So, well, I guess, to move us forward, if we're . . . what I'm hearing is thoughts about approval with conditions, then the conditions could be intermediate or high risk based on stress test.
- Chris Standaert: Well, the tricky part there is, we don't have . . . we don't know that their mortality is improved by the stent, which is what the other trial is about, and we don't know that they're the ones . . . we don't know who is more likely to improve function. They didn't stratify these people in the analysis.
- Gregory Brown: Mm-hmm.
- Chris Standaert: Dr. Skelly, they didn't . . .
- Gregory Brown: I guess, my . . .
- Chris Standaert: . . . so, that's my question.

- Gregory Brown: . . . my . . . I guess from my perspective, as a clinician . . .
- Chris Standaert: Right, understood.
- Gregory Brown: . . . is if I have someone with stable angina in a low-risk study, I don't have a problem saying that I don't think that should be covered, but if I've got someone with an intermediate or high-risk study, and I don't know if it's helpful or not, to say we're not going to cover it is a very different decision, at least for me.
- Chris Standaert: Mm-hmm. Yeah. You can play devil's advocate and say do you . . . that statement you made. You don't know if it's going to help or not, and then you have some risk. You have the higher perioperative event if you stent them. So, are you putting them at more risk by sending them than less . . . than you are mitigating the risk of mortality or recurrent MI, you know? I'm just throwing the . . .
- Kevin Walsh: Right, but we're not requiring that they be stress . . . this isn't required that they be stress tested or given a coronary artery angiogram before the procedure is done. So, you're not asking the right question.
- Gregory Brown: No, we are. So, if we cover with conditions, we can state as a condition that they've had a stress test.
- Kevin Walsh: Based on what?
- Gregory Brown: Well, I . . .
- Kevin Walsh: I mean, what . . . where's the evidence that shows us that makes a difference?
- Seth Schwartz: Yeah, but I think that we've done this a lot, though. I think when you look at the inclusion criteria for the trials, I mean, we've done that a lot. We've defined our patient population based on the inclusion criteria of the trial. We are seeing evidence as soft or as weak as it may be, that there is some benefit. We have decided to cover with the conditions, and we use the criteria for entrance in the trials, as our conditions. I think that's . . . we have precedent for that, and we can pull out that subset, which is at least more restrictive than just anybody with stable angina, but, I mean, we can debate whether that's enough, but that's . . . I don't have a problem with that . . . with that.
- Gregory Brown: . . . I'm sorry if I'm moving (inaudible) discussion. That wasn't my intent, so.
- Chris Standaert: No. And that gets tricky here, because the inclusion criteria for the Courage study are voluminous, right? So, it's prior PCI or CABG with ischemia, chronic stable . . . any one of these, chronic stable angina, post-MI without class IV angina and LV dysfunction, asymptomatic ischemia detected by stress testing of some sort of various other methods, 80% lesions in greater than one vessel. I

mean, that's . . . it's lots of things, and then how we translate that into something that's actually an effective policy that can be monitored gets very tricky. I agree with you. In principle, I agree with you.

Seth Schwartz: But I think we've done that before, too. We've said with the same inclusion criteria as X, Y, or Z trial. We've said that, and we could say that. I mean . . .

Chris Standaert: Yeah.

Seth Schwartz: . . . there's ways to handle that if we . . .

Chris Standaert: Yeah.

Seth Schwartz: . . . decide that's the direction we want to go. I'm getting a sense we're starting to beat a dead horse. I'm wondering if it makes sense . . .

Chris Standaert: Yes, I know. We're going to move on.

Seth Schwartz: . . . to take a straw vote and know where we are.

Chris Standaert: So, other people, so Tony? I just want to make sure we're hearing everybody before we go there.

Tony Yen: So, practically speaking, I just don't imagine a person just with chronic stable angina is automatically going to get a stent. I just don't see that practically happening. I think, you know, as our medical expert over here had said, there is actually a process people go through. People have chronic . . . they present with angina. Typically, they will go through a trial of some sort of medication. They will try to have that medication optimized. Only if they fail medications or they are having changes in their symptoms, which actually does not meet this criteria, because then it's no longer chronic, stable angina, right? Then, they'll probably go to catheterization. So, what I'm . . . what I'm trying to think about is that, are we making policies for, I think, a variety of different scenarios that probably aren't even realistic or not even clinically relevant. I do see this . . . when I see patients coming through, I think, you know, chronic stable angina, I think . . . I think what's going to happen essentially is that they will get a catheterization. That catheterization shows something that's hemodynamically significant or not. Then that becomes a discussion. Maybe they do a stent right there and then if their symptoms are overwhelming, but I just don't see, like, if they have no coronary artery disease, they're, of course, not going to get anything at all.

Gregory Brown: Well, I think this sounds very similar to the discussion we had last session on lumbar spine fusions for isolated degenerative disk disease, and the spine surgeon said, well we never do that. Well, OK, then if we never do that, then it shouldn't matter if we don't cover it. We vote for no coverage. So, similar, I guess, question for the cardiologist is, if you never do a catheterization just for

isolated, you know, stable angina, then it shouldn't matter, clinically, to patients if we didn't cover that specific condition. Is that a misinterpretation?

Chris Standaert: No, that's . . . that's some of the issue that yes, he can say we won't even address restricting people, but then things that shouldn't happen still happen. We all know this in medicine, things that shouldn't happen. Louise?

Louise Kaplan: So, I . . . I keep coming back to the utilization data, and even though we don't have the comparison from 2009, which I would still be very interested in, when you think about the number, you know, coronary artery . . . coronary artery disease is the leading cause of mortality still, correct, yes?

Michael Ring: In the United States, but not in Washington.

Louise Kaplan: Oh.

Michael Ring: Interestingly, in 2004, cancer deaths surpassed those due to cardiovascular disease. And, you know, that gap has widened.

Louise Kaplan: I stand corrected, but nonetheless, given the number of people covered by the state system, it just doesn't strike me that there are large numbers of . . . there is not a large number of utilization to me when I think about the number of people who have coronary artery disease, and I wonder if the issue is really not the number of unique patients who are getting the procedures, but the cost itself. So, I'm just trying to make sure that we're not driven by how expensive this procedure is rather than how many people really need it, and if . . . I just keep looking at the numbers of people who are getting the procedure, and it just doesn't seem like it's . . . like we're going to cut out a whole lot of people if we say don't cover under these conditions. What are we going to do, eliminate one or two, five? I mean, that's what I'm trying to figure out is, what would we really change if we make a decision with a coverage condition. And that's what I'm trying to figure out, and what in the data tells us that that's going to make a difference.

Chris Standaert: I'm finding some group where maybe there is over-utilization or inappropriate utilization. You're saying it's hard to find.

Louise Kaplan: Right.

Chris Standaert: And so, we may not, and drawing lines is hard to find, because we don't see a lot of data to help us draw lines anyway. Michelle, what do you think?

Michelle Simon: I'm unhappy. So, the reason we do this, presumably, is we want to help people, and we want them to not die, right? You would think?

Chris Standaert: Mm-hmm.

Michelle Simon: That's a good reason, but it seems like the data shows that that does not really affect either cardiac death or MI or all-cause mortality or any of those things. It does affect the symptom of angina, primarily, and even that effect, if you look at the . . . if you drill down on that data, it washes out after arguably 36 months, perhaps. These are in people who know they had a stent. So, there is this placebo effect that I'm concerned about influencing a subjective measurement that we're using a clinical measure. So, that part is concerning for me. If we could figure out a condition, I would be most interested in discovering that, but I don't think we have the data here to determine any condition that is not subjective to make a decision on.

Chris Standaert: Joanne?

Joann Elmore: I'm also struggling with this first part of our two questions we have to vote on today, and it seems as if we can either just say we'll cover them all or cover with conditions, yet given all of the evidence we've reviewed, we are having and will have a very hard time defining the conditions, and then the other option is to say, well, we're not going to cover it, because there is no mortality, and there is just very little improvement in angina. So, I have a question about if that were to occur, I have heard that there is the Ischemia trial that patients in Washington State can sign up at the University of Washington and Spokane. I don't know how many other sites. So, that would be one option for these patients if the angina, even though it's stable, it's really bothering their quality of life. My question is for the medical director, though. If it is a vote to non-cover, they can still contact the medical director and ask for prior approval. Is that correct, and I want to know how long that process takes, because these are stable patients. It's stable, chronic ischemic disease. There is no urgency, but how long would that process take, and could they get approval on a case by case basis?

Andrea Skelly: It would probably easy . . . more reasonable to consider a prior authorization process in that case, because if something is not covered, then we have to review it as an except to rule, and that requires, if I'm correct, an appeals process. So, from an implantation perspective, it would almost be better to say under these circumstances, you know, we would require prior authorization. Then, that . . . if they felt that that wasn't . . . our decision was not in the best interest of the patient, then they can just call us up and say here, what's going on, and that would be a more expedient way to do it. Is that . . . is that correct, Lisa?

Joann Elmore: No. So, my question is, if we were to say non-cover, there is still the possibility for patients in our state and their clinicians to contact you and ask for approval. And how long does that take?

Andrea Skelly: Lisa is going to explain the appeals process for noncovered conditions and how that works. She knows the dates and I'm going to mess it up.

- Lisa: So, if something is noncovered, the only way the agency can consider it is under an exception to rule. Under our exception to rule rule, we would not actually review for medical necessity, but it turns into a 'how is this client different from the rest of their population that we would cover this?' It also does not give hearing rights to clients. So, I do agree that the PA route would be better for our clients.
- Josh Morse: And Lisa, what program that does exception to rule apply to?
- Lisa: Yeah, Medicaid fee-for-service, but then if it's a noncovered, then I mean, I don't know how the rest of the plans would implement that.
- Josh Morse: Right. So, if it's noncovered, it becomes not a benefit for Uniform Medical Plan and it does not have a similar process.
- Chris Standaert: So, the prior authorization is an issue because they're going to take somebody and put them on the catheterization table and decide there is something they could or should stent, but then they have to stop and call for preauthorization? I mean, they're going to get catheterized twice. I mean, that doesn't . . .
- Joann Elmore: Well, candidly, I was thinking that this might reduce the number of catheterizations, but it won't work.
- Chris Standaert: Yeah. Why don't we try to quantify this a bit, and we'll go through our decision tool for this one. Let's see if we can go . . .
- Carson Odegard: I have one more question.
- Chris Standaert: Yeah.
- Carson Odegard: Do we have any information, any data when the patient has to go to the catheterization lab, what's the ratio of stent versus no stent? Do we have any kind of idea of . . .
- Michael Ring: Right. So, again, it's helpful to break this down into patients who present with acute coronary syndrome versus . . .
- Carson Odegard: Yeah, right.
- Michael Ring: . . . stable coronary artery disease. So, it's a small group, right? Because you know, we've . . . I think it's already been predetermined that actually patients who present with acute coronary syndrome actually do have their mortality and risk of MI, you know, decreased with stenting. So, I think that that's not even a question.
- Carson Odegard: Yeah. No I got that. That small stable . . .
- Michael Ring: Yeah.

Carson Odegard: . . . group.

Michael Ring: Right. So, that and, and just to get some additional perspective, that number, that ratio has decreased without any governmental organization, you know, coming out with any regulations pertaining to it. So, there is already occurring a decrease in patients with stable coronary disease that are undergoing PCI that's occurring maybe as a result of data, like, from the Courage trial, as well as the AUC. So, if you look at, you know, and this is very general, but I'm sure it's probably pretty close to the target is that probably about 25, 20% or 25% of the patients who go to the catheterization lab this type of situations. You know, we think stable coronary artery disease actually turned out not to have significant disease. So, you know, remember the stress studies are not perfect.

Carson Odegard: Right.

Michael Ring: You know, they may, they, you can have false positives or . . .

Carson Odegard: Sure.

Michael Ring: . . . people continue to have symptoms that you just feel you need to get sorted out.

Carson Odegard: Mm-hmm.

Michael Ring: So, and then I would say of the remaining 75% that do have significant coronary artery disease, roughly about a third are treated medically, continuation of medication, because they have sort of low-risk anatomy or maybe disease that is well treated with revascularization. Approximately another third to maybe a little bit higher percent, we'll say 50% of the remaining people will probably have a PCI if they're brought to the catheterization lab for appropriate reasons. Then, roughly about one in four of those patients will probably end up with bypass surgery.

Carson Odegard: Oh, that's great. Thank you. That helps.

Chris Standaert: OK.

Joann Elmore: Can I throw another wrench into this? Sorry guys. You know, it seems that maybe we're sort of moving around trying to figure out what could conditions be and then it's going to be hard and we don't have the evidence to guide it, and this is a, you know, clinical practice. It's changing, and you notice that at the national level, the guidelines don't even talk about what the interventional cardiologist sees on the angiogram. They're talking about FFR. So, study . . . for those of you that are not familiar with the FFR, this fractional flow reserve, you know, the interventional cardiologist that's interpreting the angiogram might sort of decide how much vascular occlusion there is on the different vessels, but then when you stick this wire in and calculate the FFR, 25% of the time, they will

change their treatment recommendations based upon the additional FFR quantitative data. So, at the national level, they're sort of saying, oh, and if there's FFR evidence of sort of a lesion that needs to be intervened on, that's where a stent should be put in. Right now, in Washington State, I would guess it's about 10%. At a national level, it may, I don't know, 10 . . . I've seen studies say . . . oh, higher? 10 to 20%. I know the industry people say that it's 20% of all people getting caths are now getting FFR. So, as we're sitting here contemplating, you know, what are the possible criteria, we haven't even talked about FFR, and we don't have any good data on it.

Chris Standaert: We're in the midst of evolving practice. I think we have to keep ourselves moving. Let me go to our tool, and that may help put some clarity of where people want to go with conditions or no conditions potentially.

Carson Odegard: So, can I ask. If we were to approve with conditions . . .

Chris Standaert: Mm-hmm.

Gregory Brown: . . . and we have . . . are in a changing environment and our medical director gave us an AUC that they're considering using as a way to make a decision, do we allow . . . can we allow them to have preauthorization criteria?

Chris Standaert: We can't . . . well, we shouldn't totally punt to them and say you do whatever you want to. That's not really the idea, um, what we say is sort of . . . should be their guideline for what they do. We can't be totally vague, because then it's very hard for them to implement. So, we should do our best to come up with implementable, if that's a word, criteria for them, and I think the issue, you know, when we get to conditions, if we have conditions, the choice then would be do people want to accept those conditions we vote for. They say cover or don't cover independent of that, and those two votes would skip all conditions that even are proposed. Yes?

David McCulloch: One way to get around that would be to say, the conditions would be that patients meet appropriate use criteria, as defined by . . . knowing that that may change and modify over time with new data, but at least . . . I don't know that we'll be able to do it much better than that, Chris.

Chris Standaert: I mean, I will accept everybody else's opinion, but I have concerns of . . . that's not part of our data set. We have one page . . . we have one box from the AUC on a slide. That's all we have. So, it's not part of our data set to consider at the moment.

David McCulloch: Right, in that . . . in that case . . .

Chris Standaert: So, therefore, it's part of . . .

David McCulloch: . . . I would say we should defer this and come . . .

Chris Standaert: . . . and go back and . . .

David McCulloch: . . . and talk about this . . .

Chris Standaert: . . . look at the agency.

David McCulloch: . . . yeah, and base. I mean, I don't think we're going to be able to do anything better than trust that the appropriate use criteria and the policing tool of implementing that . . . that's about as good as we're going to be able to do, and I would say, to me, that would be a reasonable. We'll cover use of stents for people going through this reasonable, but you're right. It would be nice to see what that was, and this one here says 2012. My guess is that this is updated more often.

Chris Standaert: So, let's . . . we've got to . . .

David McCulloch: OK.

Chris Standaert: . . . we're going to go through the tool, right? We have to do this. We have to say this. And then we can put the data in front of us, and people can make more of a qualitative look of what they see.

David McCulloch: OK.

Chris Standaert: And we can see what people say. Let's go to page four of our tool, our decision document. Let's get some idea of what people think, and maybe we can pull this back together a bit. So, if we start with safety, so I believe there actually are some safety concerns here that some people expressed. So, we have to worry about safety outcomes, and we'd like to know not just do we have the right outcomes, but are there concerns about some of these outcomes. Could somebody help me? OK. So, if we accept the list, are there concerns in there? Are there areas where this . . . there are safety concerns for this particular technology. So, people brought up, we brought up peri-procedural MI before. That seems to be somewhat higher when you put the stent in? I didn't see a difference in stroke. The thrombosis rate was so uncommon that they didn't get that one either as a major concern, but some concern on bleeding. So, issues that Mike brought up earlier that we don't have documentation on potentially bleeding complications from prolonged use of medications to go along with the use of . . . oh, that's right. That's a different side. That's drug-eluting, but stent. Again, with a stent some of these people have drug-eluting stents, they'll be on anticoagulants, antiplatelet therapy, potential issues there.

OK. We'll move to outcomes. So, people do you have other . . . do you have another safety concern?

Louise Kaplan: So, I just, so, the key question relates . . . well, so, I . . . the reason I'm hesitating here is, the key question is, is PCI with stenting and medical therapy more

effective than medical therapy alone. So, do we have to consider any of the potential side effects or safety issues related to medical therapy?

Chris Standaert: To the choice . . . to the opposite choice. So, if you didn't stent, yeah. Potential complications or safety issues there.

Joann Elmore: They should get medical therapy in both groups.

Chris Standaert: Right. Theoretically, they are the same, but they may not be necessarily, but theoretically they should be . . . they should be on added therapy, the stent plus medical therapy as opposed to just medical therapy.

Louise Kaplan: But nonetheless, do we have to consider any of the safety. So, we're just considering the . . .

Chris Standaert: If you're aware of any.

Louise Kaplan: . . . safety issues of (inaudible).

Michael Souter: (inaudible) clarification again, as well, if we're talking about major bleeding as a safety factor. That's really not germane to the first question we're asking, which is, you know, the issue of medical therapy versus stenting because you are going to get antiplatelet therapy.

Chris Standaert: As part of your medical therapy.

Michael Souter: In the circumstances there, yes. The issue only comes up when you go down the pathway of deciding between the second question . . .

Chris Standaert: Mm-hmm.

Michael Souter: . . . of, you know, between drug-eluting stents and bare metal stents.

Chris Standaert: OK.

Gregory Brown: Well, no. You're not going to get dual-antiplatelet therapy if you don't get a stent, are you?

Michael Ring: That would be unusual. There are occasional situations where you will recommend dual-antiplatelet therapy if someone has an extensive atherosclerotic burden, disease in their carotids and peripheral areas or some patients actually have coronary . . . diffuse coronary artery disease that you elect not to revascularization and you will still prescribe dual-antiplatelet therapy for that type of patient, but the majority of patients probably would be on aspirin alone.

Chris Standaert: Yeah. We heard before, with a dual . . . with a bare metal stent, you can come off after about a month. You can come off of the therapy.

- Michael Ring: You could. The reason they would . . .
- Chris Standaert: Come off of a dual . . .
- Michael Ring: . . . get a bare metal . . .
- Chris Standaert: . . . the dual, come off of clopidogrel.
- Michael Ring: . . . the reason they got a bare metal stent is because you're worried about continuation of long-term dual-antiplatelet therapy, but there . . . if you're not concerned about it, there's good reason to continue, especially . . . that's actually a Class I recommendation for patients who have an acute coronary syndrome is that they get dual-antiplatelet therapy for a year irrespective if they got medical therapy, drug-eluting stents or bare metal stents.
- Chris Standaert: OK. Thank you. So, effectiveness or efficacy of our outcomes? Are there other outcomes people want to add?
- Gregory Brown: Symptom relief is going to be angina from Seattle Angina Questionnaire.
- Chris Standaert: I would assume so. It doesn't call it that questionnaire. It just says symptom relief, patient reported and function, patient reported. So, out of these, what did we find? Mortality?
- Andrea Skelly: No difference.
- Chris Standaert: No difference, all-cause and cardiac, no significant difference. Myocardial infarction other than beyond peri-procedural, it's just higher on the stent?
- Andrea Skelly: Right, the stent.
- Chris Standaert: And quality of life and symptom relief, some benefit but questionable of how large and meaningful that magnitude is, correct?
- Andrea Skelly: It has sustained (inaudible) over time.
- Chris Standaert: That's what . . . how sustainable it is. And then the issue of revascularization, is that . . . which way does that fall? Does that support stenting or not stenting?
- Gregory Brown: I would actually argue that it's irrelevant in my mind, because that's an intermediate outcome to me, and if it's . . . there's no difference in mortality, then I don't really care what the stent or vessel does. Well, I mean, that's the problem with a lot of quality measures is their process papers, you know?
- Chris Standaert: Right.

- Gregory Brown: And so, you can suppose it has . . . hypothesize, but it clearly hasn't effected all-cause mortality.
- Michelle Simon: It actually becomes a safety outcome when you're re-exposing that person to another procedure.
- Chris Standaert: Yeah. So, they all get . . . they get 120% procedures when they get stented versus 30 or less when they don't. Costs, we haven't talked about costs at all I don't think. Do we have a handle or an opinion on the cost data?
- Carson Odegard: Other than it was no more cost-effective.
- Chris Standaert: It wasn't more cost-effective. Was it less cost-effective? I just saw not more cost-effective.
- Joann Elmore: Yeah, I know. When they said that, I thought, OK, double negative. Let's go over that. I'm assuming that meant that it cost more.
- Carson Odegard: That's what I thought, too.
- Chris Standaert: Is not more cost-effective the same as equivalent cost-effectiveness, or does that imply less cost-effective and . . .
- Carson Odegard: Less cost-effective.
- Andrea Skelly: I'm sorry. What was your question?
- Chris Standaert: The cost-effectiveness. Your slide said it was not more cost-effective. So, that leaves two options. It could either be equivalent or it could be less cost-effective.
- Andrea Skelly: The data for the drug-eluting stents . . . or the medical versus PCI indicated that because there was no difference in benefit, most of them, you know, didn't find that PCI was cost-effective over medical therapy alone.
- Chris Standaert: Because there is extra cost with the PCI but really not much discernable benefit . . .
- Andrea Skelly: Right.
- Chris Standaert: . . . that they could quantify.
- Andrea Skelly: Exactly.
- Chris Standaert: It goes back to issues of . . .
- Carson Odegard: (inaudible) costs.

- Chris Standaert: Yeah. OK. Alright. Let's vote on these, and then we'll start talking about what we're going to do. So, effectiveness. This is for stenting in the setting of stable coronary artery disease compared to maximal medical therapy alone, and is there sufficient evidence under some or all situations the technology is effective? More, less, or equivalent.
- Gregory Brown; These . . . are you?
- Chris Standaert: So, is there sufficient evidence under some or all situations that the technology is effective, either more, less, or equivalent, or unproven effectiveness compared to medical therapy alone?
- Louise Kaplan: And the operative is some or all.
- Joann Elmore: Exactly. It may not be clinically important, but there were some findings.
- Chris Standaert: Some or all, yes.
- Joann Elmore: We all paused on that.
- Josh Morse: There are ten more and one equivalent.
- Chris Standaert: Same question for safety, and this is some or all situations. This is in your aggregate opinion. This is under some or all situations, is it safe?
- Josh Morse: Ten less, one equivalent.
- Chris Standaert: Cost-effectiveness. So, again, under some or all circumstances is stenting cost-effective compared to maximal medical therapy?
- Josh Morse: Ten less and one equivalent.
- Chris Standaert: OK. So, now I'm going to move on. We're going to have to vote at some point here and decide what we're going to do, and we're either going to wind up . . . we have three choices, no cover, cover, or cover with conditions.
- Andrea Skelly: May I make a statement after talking to folks from the Health Care Authority and representing Regence, if you decide on a coverage with conditions, if that condition never comes up, we effectively have eliminated that person's ability to get that procedure. What we could do is, and what we've done sometimes is say a prior-auth and then go back and review and say, did you meet the criteria that we sort of set out? And if the answer was, gosh, you really didn't and they ended up one of the shouldn't have done this, we could deny payment at this point. So, it's sort of a technical consideration as to cover with conditions means that in that rare instance where maybe that person should have had it, but that condition was not met, they have no appeal rights. They can't get it. Did I represent that accurately?

- Chris Standaert: Yeah, that depends how we phrase our conditions and whether . . . how big our umbrella is, really.
- Andrea Skelly: Exactly. I'm just . . . I'm just letting folks know that that's a consideration, that's all.
- Chris Standaert: Yeah. We're aware of that. So, I need to know how people, I . . . frankly, I could see . . . I see every perspective here. I see every possibility. I see cover, no cover, or my own just gross sense of listening to people. So, the way we do this is, if we decide we have several choices. We can come to a conclusion that we think, maybe we want to talk about conditions and see if people want to do that and be able to convince themselves or each other they can come up with them and then vote to accept them or not, essentially, or we can vote ahead, and if it's clear that we're going to one way or the other without conditions, those with conditions would be in the minority and we would move forward with what the bulk of people want.
- Michael Souter: So, you're talking about having a nonbinding vote to test the temperature?
- Chris Standaert: I'm about to ask for a nonbinding vote to get some idea whether people want to talk about conditions, because we could say . . . we could do a mandatory vote, and if the minority of the people say conditions, we're done. We're not talking about them even. So, before we go there . . .
- Josh Morse: May I ask, just to interject one comment about expert treatment guidelines, and you may want to review those. They aren't pasted into your decision document, but they are the references in there, as far as where they are in the report for your review, because if you don't . . . remember when you get to the end of this, if you don't align with those guidelines you . . .
- Chris Standaert: We have to.
- Josh Morse: . . . you, yeah.
- Chris Standaert: We have to say why.
- Josh Morse: Right.
- Chris Standaert: Medicare does have a guideline. We have a national coverage determination.
- Josh Morse: Well, yes and the professional society guidelines are in there, as well.
- Andrea Skelly: And I do have copies of the guidelines available with the exception of the appropriate use, but I see Dr. Ring has one.
- Joann Elmore: They're in the evidence report, not in here.

- Andrea Skelly: Starting on page 60 is the summary. Again, this is a summary. It's not the complete guideline. A complete guideline would be several hundred pages, and there are multiple guidelines. So, you've got stable coronary artery disease, which is the Fihn 2012 and 2014 and then on table 7, ignore table 7 because that's outdated guidelines. STEMI . . . patients with STEMI start on page 65, and then N-STEMI start on page 67, but this is for the stable . . . the bulk of the data . . . the bulk of the information starts on page 60.
- Chris Standaert: And that was in the medical director report, had the Medicare policy.
- Louise Kaplan: It's page 73 of the final evidence report.
- Chris Standaert: Was the Medicare statement?
- Louise Kaplan: That's what it says here in our document.
- Andrea Skelly: Yeah, starting on page 73, and the tables on page 74.
- Michael Ring: Would that be starting on page 62, though? That's where the society guidelines are.
- Chris Standaert: So, we have a strong obligation to address the Medicare issue, and we have an expectation to essentially align with that, unless we have data or reason to think we're not . . . we have to be explicit about why we don't align with Medicare coverage decisions.
- Kevin Walsh: Why are we talking about it before we vote?
- Chris Standaert: Because Josh brought it up, and . . .
- Josh Morse: You don't have to. I'm just pointing out that it's . . . because it wasn't in your decision aid. You went past that . . .
- Chris Standaert: Right.
- Josh Morse: . . . to the vote and just because of (inaudible).
- Kevin Walsh: But you're asking for a straw vote before a vote.
- Chris Standaert: No, I haven't . . . I haven't asked for anything yet. So, and the point of looking at the Medicare thing, I was going there, but then, yeah. So, the point of looking at the Medicare is that . . . so as you look at that, if whatever we do we have to sort of either align with that or justify why we're not aligned with that quite explicitly. So, it's worth looking at before we go there. So, now this issue of how are people leaning. Are we going for conditions or not? I guess the easiest way to do this is a hand of people who would like to see a discussion of conditions before they vote so that we can decide how to do this. Seven, it looks like the majority with conditions. Can we pull up a screen up there so we

can see what we're all saying? Now, somebody who raised their hand has to start talking. We need to start getting hand . . . so people who want to hear conditions. Tony, what do you think?

Tony Yen: So, I think it's reasonable to talk about conditions. First of all, the floor would be, you have to be on guideline-directed medical therapy number one. That's the first condition. It may not be a medical condition, but it's a . . . it's a . . .

Chris Standaert: Mm-hmm.

Tony Yen: . . . maybe a therapeutic condition. Then, the second condition may be the severity of the patient's angina. I don't know if that's arbitrary but . . .

Chris Standaert: Meaning Class I, II, III, IV?

Tony Yen: Right, Class I, II, III, IV, should it be . . . should we really strongly consider it by class? There's Class I angina, we're going to cover for that? Probably not, at least in my opinion, but strongly consider moreso for Class III or above.

David McCulloch: I don't think this committee can dive into that level of detail. I think if we're going to cover with conditions, the conditions should be appropriate use criteria as currently defined by . . . huh?

Chris Standaert: No, go ahead. I'm listening.

David McCulloch: Because I . . . there's no way that we're going to sit . . . who do we think for Class I with . . . I just don't think we can do that. I mean, I think we should say something reasonable.

Gregory Brown: I agree with you, David, but I agree with Tony in that we do, I think, have the obligation to say every patient should be treated with maximal medical therapy before they undergo a procedure.

David McCulloch: Completely, yeah.

Gregory Brown: So, I mean, that may be different than the AUC, but it's certainly not inconsistent with the AUC. I mean, they have other recommendations. Obviously, that's why they have optimal medical therapy. So, we're simply asking them to say use your AUC and follow your guidelines for optimal medical therapy.

Carson Odegard: Or you could say that you use the AUC or other appropriate measures.

Chris Standaert: Well, I don't know. Yeah, what does that mean?

Louise Kaplan: Could, could I ask . . .

Chris Standaert: Louise, go ahead. Louise?

- Louise Kaplan: So, if we are . . . if we look at the guidelines that are here and we say there has to be optimal therapy. So, what happens for the individual who cannot fully participate? For example, you're the ortho surgeon so one of the guidelines is physical activity, 30 to 60 minutes of moderate intensity aerobic activity five days a week. So, what if the person is physically unable to do that? So, do they get denied because they physical cannot?
- Chris Standaert: Well, it's going to be optimal for that person, right? These are personal decisions about what's optimal. So, optimal . . .
- Louise Kaplan: So, I'm just saying . . .
- Chris Standaert: . . . is a relative term based on the individual.
- Louise Kaplan: . . . well, but if you say optimal, and you say based on this guideline, I . . . there has to be specificity so somebody does not get their procedure not covered because somebody decided that they did not do something.
- Gregory Brown: But, I mean, that's not how a clinical practice guideline works. I mean, there is strong evidence that nonsteroidals work for knee arthritis, but there are certainly medical contraindications for taking nonsteroidals. So, you know, they get a pass on that recommendation when I'm going for preauthorization for a knee replacement.
- Chris Standaert: Right, yeah, exactly.
- Gregory Brown: So, I mean, that's how it would function here, you know? If you can't walk two blocks because, you know, you've got Grade IV knee arthritis, then . . .
- Louise Kaplan: So, then, who makes that decision? Are you back to the clinician making the decision about what's . . .
- Chris Standaert: Mm-hmm.
- Louise Kaplan: . . . recommended?
- Chris Standaert: Yeah. It's a clinician deciding optimal medical treatment.
- Louise Kaplan: So, if we do it with conditions, then do they have to be preauthorized to have met these conditions? I'm just trying to get this process down. So, the clinician decides that they've met the conditions? I could see a lot of passes on the conditions.
- Gregory Brown: Well, I mean, but that's the nature of a clinical practice guideline. They're not mandates, they're guidelines.

- Chris Standaert: So, can we put up something up there. So, we had one proposed topic of optimal medical therapy.
- Tony Yen: Actually, the Medicare guidelines are not bad. It says over here, optimal medical therapy, objective evidence of myocardial ischemia, lesions amenable to angioplasty.
- Michael Souter: I'm not so sure that the lesion's amenable to angioplasty, because I don't think that's actually going to do anything. I completely agree that, you know, in many ways it's there in front of us.
- Chris Standaert: Yeah. It's a starting point. It talks of people who would have more medical concerns that you might think that if you're not stenting them you're more worried about what you're not . . . what you're missing I would think. Who else raised their hand?
- Seth Schwartz: I think the Medicare is a reasonable place to start. I think what I like about it is, it's general and yet it covers the two main issues we're concerned about, which is, we want to make sure that they've gone through and adequate medical trial, which is unlikely to be missed but important to state, and then secondarily that they actually have objective evidence of coronary artery ischemia. So, for us to define whether that's a stress test or whether that's a, you know, a catheterization or whatever it is, we can get into that, but that might be beyond what we need to do. I think that captures the concept without us having to get too deep into the weeds.
- David McCulloch: I totally agree.
- Chris Standaert: So, can we put these up? Do you have access to them to type them up there for us, or do you want me to read them to you? So, in accordance . . . so, objective evidence. Cover PCI both with and without placement of . . . well, with placement of stent. So, we will cover the placement of a stent in accordance with the FDA approved protocols. No, that's myocardial infarction.
- Seth Schwartz: You know, I think I might even be a little bit more specific and say persistent symptoms despite optimal medical therapy or something to that effect.
- Joann Elmore: Or angina impacting quality of life. It's vague, but it gets at that issue of even with a class I or II. I mean, we just need to (inaudible) this up to the (inaudible). And I don't think that this is anything easy for the medical directors to implement, but all of us, I think, realize that we wanted to make certain that the angina was really quite bothersome to the patient before they actually underwent this.
- Michelle Simon: This may be a dumb question, but is . . . is the guideline directed medical therapy, which includes lifestyle modification in addition to medication, is that one of the FDA approved protocols that we're agreeing to? What are the FDA approved protocols is my only question?

Joann Elmore: Well, her question is about medical therapy. We use the word optimal medical therapy and I've noticed that they like to use the word guideline directed medical therapy, and there is a big long list of all the guidelines.

Michelle Simon: Of the specific things.

Joann Elmore: It's very specific, very detailed, and it gets at all the other cardiac risk factors. So, I don't know whether we want to say optimal medical therapy or use this other term.

Michelle Simon: I prefer the other term, because it does actually mean something.

Joann Elmore: Guideline directed medical therapy.

Michelle Simon: Right.

Chris Standaert: Do you guys have . . . do you need the . . . can we put these up. So, the . . . just finish getting the terms up. So, it's lesion . . . well, we're going to change it, lesions amenable to stenting, yeah, not angioplasty. So, but refractory . . . next line, angina refractory to medical treatment is just what they say. We can change the words. Angina refractory to medical therapy.

Joann Elmore: I'm not certain that's what we want, stable coronary angina.

Michelle Simon: That's what the Medicare decision (inaudible).

Chris Standaert: Right. I'm going to put up the words of Medicare, then we . . .

Joann Elmore: Yeah, OK.

Chris Standaert: . . . can play with the words.

Joann Elmore: OK.

Chris Standaert: So, at least we start with what they, what people are talking about. Then, they have lesion . . . single . . . single coronary disease essentially is what they have. Then say, for patients whom the likely alternative is coronary bypass surgery, which we're probably not going to have. Single vessel coronary disease is roughly what they have. So, this is the terms they are using, roughly. So, we can change them and stay aligned with them.

Seth Schwartz: So, just in light of the discussion we have had, I think I'd throw out the last one, because I don't think we saw evidence about that, that I would feel comfortable making that statement today.

Chris Standaert: OK. So, you propose . . .

- Seth Schwartz: So, I think the fourth and the first are effectively saying the same thing. We just need to decide which one of the two we prefer.
- Chris Standaert: . . . so you can say angina refractory to guideline directed medical therapy?
- Seth Schwartz: I struggle slightly with that term. I don't know that the definition is as specific as we think it is and they can always ask what guideline.
- Chris Standaert: Mm-hmm.
- Seth Schwartz: So, I mean, I think you can say angina refractory to what did you call it, maximal medical therapy or optimized medical therapy or whatever, but I think those terms leave the wiggle room that we want clinicians to have here.
- Michael Souter: The use of the word optimal actually allows for individual patient specifics, which gives some clinician ability in that setting.
- Chris Standaert: So, type the word optimal right where you are. Get rid of the line below. Get rid of the top objective medical . . . optimal medical therapy.
- Michael Souter: And what about lesions? I mean, do we really want the lesions amenable to stenting. We want that to be gone, don't we?
- David McCulloch: It's lines one and three. (inaudible).
- Chris Standaert: Yeah. The only line that restricts is the objective . . . is the myocardial ischemia, you know, which, unfortunately, wasn't really drawn out by our studies.
- Seth Schwartz: That's not true. I think that was an entrance criteria for all the studies.
- Chris Standaert: Not all of them, no.
- Seth Schwartz: The two that we're relying on evidence from, which is . . . Courage had that, because Courage has that and . . .
- Chris Standaert: They had a whole slew of them, and that was one of them, and the other one said you could use a scale, too, or you could have a functional test (inaudible) evidence we didn't have, but I . . . yeah. The clinical logic of it makes sense.
- David McCulloch: Right. I mean, the . . . you could include that. I mean, you wouldn't . . . I mean, cardiologists wouldn't put a stent in unless, in addition to those two, when you do the catheterization, there are lesions . . .
- Chris Standaert: Right.
- David McCulloch: . . . amenable to (inaudible).

- Chris Standaert: That's what that language is (inaudible). Yeah. That's implied. They're not going to put stents where they can't put stents.
- Gregory Brown: Are we allowed to ask our expert if we think there's a case that would be appropriate that we're somehow excluding?
- Michael Ring: I think that the scenarios that you've listed there probably cover the majority but not, you know, all of the cases that are potentially relevant there. So, I would assume by objective evidence, myocardial ischemia would mean either a stress study or the FFR is not correct. So, I mean, there are situations, just so you know, that you may find somebody that has what's, as an example, 99% stenosis of their proximal LAD and, you know, decreased flow visually beyond, you know, so that would be sort of an obvious no brainer that that's significant and needs to be treated. You would then, thus, require that they, you know, do an additional test that's not inexpensive. That FFR is, you know, approximately \$800 that you would add to the cost of care.
- David McCulloch: We're not saying that. We're saying they have objective evidence of myocardial ischemia. Would you think that . . . what you described would be objective evidence of myocardial ischemia?
- Michael Ring: Well, um . . .
- David McCulloch: A 99% occlusion of the LAD?
- Michael Ring: . . . if you consider that objective, yes, now the problem is that angiograph . . . well, the thing is that I do caution that, in that anatomy in subjective assessment of an angiogram is not as objective as you'd like to be in all circumstances. On the extreme end, yes, but how about, is an 80% significant, or is a 70%, or 50%?
- Chris Standaert: OK, what do you do now? This is more lenient than Medicare. These (inaudible) done on Medicare and this is, to me, seems more lenient than Medicare has. You have these same criteria already. Cardiologists already exist with them, and everybody over 65 on Medicare, yeah?
- Michael Ring: Again, anatomy, though, is not the same as ischemia.
- Seth Schwartz: But we're not talking about anatomy. The point is, it just needs to be something objective. That can either be anatomic. It can be a high risk stress test. It could be, you know, it could be a catheterization.
- Gregory Brown: It says ischemia. It doesn't say . . . you could say at risk or myocardial ischemia. The at risk would . . . what I'm hearing is at risk . . . you need at risk to say anatomy, because you can be at risk for ischemia but not there yet.
- Chris Standaert: But if you go back to our data, we don't have evidence of improvement in MI or mortality and we have . . . we voted less safe and less cost-effective as a group.

- Michael Souter: I'm happy with this as it stands.
- David McCulloch: Yeah, I mean I . . . I think that the other way around, that we're saying they should certainly cover for patients who have angina refractory to optimal medical therapy and then in addition, you've got, you know, Kevin's point is that you would . . . in clinical practice you would then do a catheterization and see . . . find objective evidence and then you would do it.
- Joann Elmore: I'd like to hear from our few committee members that did not raise their hands for the conditions, and the reason being is that these conditions are . . . they're not really going to limit much, you know? All they do is sort of encourage medical therapy and we . . . I think needed, if we were going to go this approach, to be vague because the evidence, it's more than, you know, not every patient can get a noninvasive stress test. It's variable, the cardiologist interpretation, and there's going to be new FFR. So, we can't do too much specification here. So, can I ask the committee members that did not raise their hand, I'd love to hear their comments at this point.
- Michelle Simon: I'll go first. I feel like this is a technology is not achieving what we want it to achieve. We just voted as a group that it was not as effective. It's, perhaps, less safe. It's not as cost-effective either, and here we are talking about guidelines, which actually open it up even wider. So, my feeling is, if we're going to include guidelines, let's include things like what's in the (inaudible) study, which is a Medicare approved program, diet and lifestyle showing coronary artery disease regression over time. Let's include that as something we are going to include as a condition. We haven't mentioned anything about that kind of thing. We didn't look at that evidence, but that is in this guideline that I mentioned before, the guideline directed medical therapy, which is from 2012. It has about seven different organizations that were involved in development of that. It speaks to diet and lifestyle, and I think those are important factors to consider when we're talking about a technology that is very expensive, in my opinion, and not very effective.
- Michael Souter: Can I just make the comment, though, that when we voted for the . . . the voting pattern that we did, the words that we have to adhere to is any and all circumstances.
- Chris Standaert: Mm-hmm.
- Michael Souter: So, that does not necessarily mean that we're giving, you know, that we judge that something is completely unsafe or completely inappropriate all the time. It just means that there is, you know, if you think that there's an occasional circumstance where something isn't safe, that's the way you actually have to vote. That doesn't mean that that's how you conceive of the whole there. Do you see what I mean? So, I . . . I just think, you know, I wanted to just interject that, about how our voting patterns have to go.
- Chris Standaert: Right.

- Gregory Brown: And I thought the vote was actually ten to one that it's more effective.
- Chris Standaert: Under any and all circumstances.
- Joann Elmore: But that was under any and some of us said, well, it was statistically significant but maybe not clinically.
- Michelle Simon: In the discussion, it clearly . . . it seemed to me that the gestalt of the group was that it's not any better, really.
- Chris Standaert: So, Kevin, what do you think? You were in that crowd, too.
- Kevin Walsh: What do I think?
- Chris Standaert: Mm-hmm.
- Kevin Walsh: I don't think the improvement in angina justifies the use of the technology. I feel like many people don't adhere to maximal medical therapy. We don't have any lifestyle inclusions. I think those are probably as powerful as this technology is over the long run.
- Chris Standaert: Mm-hmm.
- Kevin Walsh: So, I'm not going to vote no for the conditions you've come up, but I don't really care.
- Chris Standaert: Yes, Louise.
- Louise Kaplan: Well, I think the guidelines are excellent guidelines. I think the reality of people's lives is not that they choose not to adhere. I think all too often, people are in life circumstances that don't allow them to adopt these guidelines that would make all of us much better. So, you know, I think it's a . . . there is more than just an individual responsibility. I think we have a societal structural challenge in terms of how we live our lives and how our societies are structured in our communities and, you know, our . . . you know, I have all sorts of people who tell me that they live in Olympia. They commute to Seattle. They're up at 3:00 or 4:00 in the morning. They get home at 6:00 or 7:00 at night. Life is hard for a lot of people, and I don't want to impugn that people are not doing the right thing simply because they say they don't want to bother. So, I think guidelines are there to help clinicians and patients make decisions that are patient centered based on what they can actually do in their life, and I feel that the parameters that are up there are really not helping me think about how it's going to really change what happens. I just don't want to exclude somebody who would benefit from something . . . I mean, despite the fact that the evidence is really, in my mind, you know, insufficient and lacking.
- Chris Standaert: Mm-hmm.

- Louise Kaplan: But, I think if we simply say don't cover, then we're . . . I would never not cover, but to find conditions, I think, is problematic in and of itself.
- Joann Elmore: But, if we say don't cover, they can sign up for the Ischemia trial.
- Louise Kaplan: Depending on . . .
- Chris Standaert: They could.
- Joann Elmore: Depending upon whether it's available in their area.
- Louise Kaplan: Right. Well, we've got a very big state, you know?
- David McCulloch: I can go the other way and say, well, we should just cover unconditionally and leave it up to the policing of all the things we have heard about today.
- Joann Elmore: They have to prove an attempt at guideline approved medical therapy. I mean, that's my only request . . .
- David McCulloch: Yeah.
- Joann Elmore: . . . if we have a condition, because I see a lot of patients that they aren't, at least, attempting to make certain that that's being fulfilled. I think that's what I'm hearing.
- Michelle Simon: Yeah, quitting smoking, perhaps some help with that, some diet information to . . . most people know what to eat. I don't think that's true. I don't think that's happening out there necessarily in the real world.
- Chris Standaert: They can't buy it. So, you like optimal or you like the guideline where . . . guideline driven medical therapy.
- Michelle Simon: I think this guideline directed medical therapy is fairly decent, and it's got a lot of backing. There's a lot of people involved in that . . . the development of that. It moves us in the right direction, I would say.
- Chris Standaert: So, you prefer guideline directed, as opposed to optimal.
- Michelle Simon: It's a specific thing, table five on (inaudible). It was written in 2012, authored, primary authors Fihn.
- Chris Standaert: Table five on which page?
- Michelle Simon: Page 60 of our report.
- Gregory Brown: I mean, every medical condition improves with smoking cessation. Has that been a required thing in every one of our recommendations, that you're

required to quit smoking before we'll authorize treatment? I mean, that . . . that's what you're saying. I agree that . . .

Michelle Simon: (inaudible)

Gregory Brown: . . . it's absolutely best. I don't smoke, so I agree with that, but as a clinician, you know, there are certain . . . I mean, I counsel my patients, I do a lot of fracture work. It delays bone healing. I counsel every one of them, stop smoking, but I can't say I'm not going to treat your acute fracture until you stop smoking.

Michelle Simon: I'm not saying that either.

Chris Standaert: Well, then again, this isn't an acute issue. This is stable angina.

Gregory Brown: I understand that, but that's . . .

Chris Standaert: It's a different issue. So, I don't know, other people want to change optimal, we can change optimal. I heard good arguments for optimal earlier.

Tony Yen: I favor Michelle's approach in terms of guideline directed medical therapy, that it seems to be a bit more of a holistic and comprehensive approach rather than just . . .

Chris Standaert: OK.

Tony Yen: . . . focusing on, oh, are you are on your atorvastatin or whatever.

Chris Standaert: So, back to what the Medicare guidelines said, guideline directed medical therapy.

Gregory Brown: That's fine.

Chris Standaert: OK. I think we got to go on and vote. I don't know how much more we can get out of this. You have more?

Louise Kaplan: I just want to ask. So, how does this get operationalized? So, if these are the conditions, how does it get operationalized?

Chris Standaert: It's going to be up to these kind folks over here to figure out on how they monitor what optimal is and what people have and what guidelines they're following. I don't know.

Louise Kaplan: Does this mean it becomes a prior authorization that you have to see documentation before you authorize?

Charissa Fotinos: I don't necessarily think that would be reasonable. It may be a condition where we go back and just do a random check and say, oh, gosh, you know what, you

didn't meet our criteria. We're going to look and see if we paid you or not. I don't . . . PA doesn't necessarily make sense in all circumstances.

Louise Kaplan: But then, could you deny payment after somebody's had the procedure because you did a chart review and . . .

Charissa Fotinos: Yep. Yes, we can.

Chris Standaert: Yeah. And this is relative . . . this is relatively aligned with Medicare. So, the people doing these should be used to these. This is relatively the same language as the Medicare guidelines with actually less restrictions.

Gregory Brown: Not when you say guideline directed, it's not.

Joann Elmore: If anything, it's actually . . .

Chris Standaert: It is the same wording.

Joann Elmore: . . . potentially more restricting.

Gregory Brown: It's much more restricting.

Chris Standaert: The thing is . . .

Joann Elmore: If they were to do a review, they could actually go back and say, wow, you know? Look at all of your patients that . . .

Gregory Brown: Yeah, I . . .

Joann Elmore: . . . I have a minor tweak. Can we change angina refractory to number one, because that seems like that's the first thing, and then the second is the objective evidence? Is that OK, Chris?

Chris Standaert: Mm-hmm. Sure. I thought Medicare used that same phrase, though, use the guideline directed therapy.

Michelle Simon: They say FDA approved guideline.

Chris Standaert: Alright. We're going to move on, so, unless other comments, we're going to have our binding vote.

Josh Morse: This is for key question one.

Chris Standaert: Key question one, stable coronary artery disease. And so, we are approving coverage for cardiac stents with the following conditions.

Louise Kaplan: So, are you asking us to vote yes or no on this or just to tell you what (inaudible).

Chris Standaert: So, if you vote . . . so if you vote no, you vote no.

Joann Elmore: You could vote . . .

Chris Standaert: So, wait.

Joann Elmore: . . . no coverage.

Chris Standaert: . . . so if you vote no, you vote no. If you vote cover, it doesn't have to be with these conditions. You just put a blanket cover. You vote cover condition you get this. OK?

Louise Kaplan: Just checking.

Gregory Brown: So, just so I understand. So, if . . .

Chris Standaert: Cover with conditions is this.

Gregory Brown: . . . yeah, and so . . .

Chris Standaert: Cover is no conditions, cover everything.

Gregory Brown: . . . right.

Chris Standaert: No cover is don't pay at all.

Gregory Brown: Right. So, if you vote for this and a patient doesn't quit smoking, you can turn around and deny payment to the person who did this?

Chris Standaert: People who have (inaudible) they're following their guidelines.

Gregory Brown: Well, but the guideline says stop smoking.

Joann Elmore: To counsel them.

Chris Standaert: Counsel.

Joann Elmore: We can't change patient . . . we try to change patient's behavior, but we can't always.

Chris Standaert: So, we're not . . .

Charissa Fotinos: One of the . . .

Chris Standaert: . . . we're trying to stay out of the weeds here on that one, right? We're going to let them deal with that. We're trying to say we're following basic medical guidelines.

- Charissa Fotinos: Yeah, the concept that's written in the guidelines and is sort of implicit is that it's optimized for the patient. Whether that patient stops smoking or not, you've at least attempted to and have attempted to optimize it.
- Louise Kaplan: It's one thing to write a guideline into your conditions. It's another thing to operationalize it, and I just think you have . . . we really have to recognize operationalization. I just need to say that.
- Chris Standaert: OK. Understood.
- Gregory Brown: Could we . . . we didn't have a formal vote with optimal versus guideline directed. I would like to have a vote for those two. I am not . . . I am not comfortable with that.
- Chris Standaert: You don't like guideline directed versus optimal?
- Gregory Brown: I do not like guideline directed. I think optimal is implied, you're doing what's optimal for the patient and that includes smoking cessation and weight management and everything else.
- Chris Standaert: You could say optimal guideline directed.
- Gregory Brown: As soon as you put in guideline, it's whose guideline, what does the guideline say? What's it change, you know, if we pick a guideline and it changes, do we have to readdress this decision?
- Chris Standaert: We don't.
- Gregory Brown: Oh, you don't.
- Chris Standaert: So, so you're . . . some of this we just leave to them to determine. We're trying to . . . I believe the Medicare language was the same thing, FDA guideline approved sort of thing. So, we're following the language.
- Michelle Simon: It's FDA approved protocols is what they said.
- Chris Standaert: Yeah. So, we're following some of their language to them, and it leaves some flexibility to the medical directors. They generally are adhering with common medical practices, essentially, is what you're following, too, with guideline.
- Michael Souter: But I agree with Greg. A protocol for a procedure . . .
- Chris Standaert: OK.
- Michael Souter: . . . we didn't . . . we didn't actually get, yeah.
- Chris Standaert: So, we will do this.

- Gregory Brown: The protocols are for stent placement, not for optimal medical therapy.
- Chris Standaert: So, we're going to have two choices. We're going to have either the word optimal, we'll go there, or the words guideline directed, we'll go there. You don't have to vote for either one if you don't want either one. If you don't care, you don't have to raise your hand, either way. If you want one or the other.
- Louise Kaplan: Is there only one guideline?
- Josh Morse: Yeah, that's my question. Do you want to reference the guidelines that you're, or?
- Gregory Brown: You don't want to? OK.
- Michelle Simon: I do.
- Joann Elmore: The report refers to a specific guideline.
- Josh Morse: Then, maybe you want to add that so that the agencies know which guidelines.
- Seth Schwartz: I would just make the comment, if you're going to reference . . . if you're going to say guideline, I think you need to reference a guideline.
- Michelle Simon: Yeah.
- Seth Schwartz: I think it's too vague if you just leave it like that. So, either you reference the guideline that we're referring to here, or we just go with optimal.
- Michelle Simon: Right.
- Chris Standaert: Alright, so . . .
- Michelle Simon: So, the guideline that I was referring to is the 2012 Fihn guideline directed medical therapy.
- Chris Standaert: . . . to guideline directed medical therapy per the Fihn 2012 guideline, multi-society. Yeah, it's a multi-society guideline, it looks like.
- Michelle Simon: Yeah.
- Andrea Skelly: There is also a 2014 update. So, Fihn 2012 plus 2014.
- Chris Standaert: That just may answer our question for us. So, if we chose guideline, then we will pick guideline. If we don't pick guideline, we don't have to do it. So, all in favor of guideline directed as language. Four. All in favor of optimal as language. We're going to put optimal up there.

- Louise Kaplan: I'm abstaining just for the record.
- Chris Standaert: That's OK. Abstentions? One abstention. So, change optimal, then we're not . . . to optimal medical therapy. OK. Other comments before we vote?
- Michelle Simon: The other comment is, there . . . this is likely to come up for a third visit, I'm guessing, if there is some significant data that will be coming out this summer. So, you all can relax about that.
- Chris Standaert: We'll be back at it in a year and a half doing the same thing, yeah.
- Michelle Simon: Yeah. We'll be back at it again.
- Chris Standaert: OK? Let's vote.
- Josh Morse: Ten cover with conditions and one cover.
- Chris Standaert: OK, and again, we have to say whether we are in alignment with our guidelines with Medicare. We are relatively in alignment. We took out a couple of clauses because they weren't really supported by our data or operational within our system, but we stayed, I think, with the intent of the Medicare guidelines, yes? And there are numerous other clinical guidelines that we looked at and considered in making our decision. OK.
- We have one more topic now. Alright. Do people want to stand for three minutes, or are we going to lose critical mass if people stand up?
- David McCulloch: I think so. Let's just keep going.
- Chris Standaert: We'll keep going. Let's not lose, oh yeah. I'm on a roll. Alright. Key question two, we're moving on. So, now, we have a whole other discussion. Newer generation drug-eluting stents versus bare metal stents. This is a re-review. So, we are supposed to consider it in the context of our prior review. So, this question starts on page 17 of the vendor report, of the slides at least. We can start looking through that one.
- Michael Souter: And this is for the same population, stable?
- Chris Standaert: No. This is stable or unstable presentation.
- Michael Souter: Oh, this is all-comers, huh?
- Chris Standaert: This is all-comers and the use of drug-eluting stents versus bare metal stents.
- David McCulloch: If you're going to use a stent, under which conditions will we cover it being . . .
- Chris Standaert: Bare, yeah, essentially, right. So, bare metal stents would be the default. So, when would we cover the use of drug-eluting stents, because we're not going to

get into the parameter of the coverage of bare metal stents? That's only when, this is going in. We will pay for it, drug-eluting stents instead of bare metal stents. Maybe less contentious? Maybe?

Seth Schwartz: I would start by saying I don't think we saw any data on any of the conditions that were used for coverage in the 2009 determination. So, I don't see any way that we can meaningfully change the existing recommendations.

Chris Standaert: You don't see any way to meaningfully change it. Do you see anything to support those recommendations?

Seth Schwartz: No, but I didn't look at any . . .

Carson Odegard: We didn't review that evidence.

Gregory Brown: We didn't get that . . .

Chris Standaert: We didn't review all that evidence.

Gregory Brown: We only went to new, the new drug-eluting stents and if I heard right, you said the first analysis had meta-analysis with up to 32,000 patients in them?

Andrea Skelly: Yes. Some of the meta-analysis had 17 randomized control trials. I don't remember how many thousands . . .

Gregory Brown: Right. Well, here we have . . .

Andrea Skelly: . . . of patients.

Gregory Brown: . . . we were talking about two or three trials at most.

Andrea Skelly: Yeah.

Gregory Brown: MASS-II Trial, Courage and . . .

Andrea Skelly: Actually, those were in medical therapy . . . compared to medical therapy. So, we're looking at . . .

Gregory Brown: Oh.

Andrea Skelly: . . . Examination, Prodigy, that list.

Chris Standaert: Can you put on the screen our existing conditions, please, our existing coverage determination so people can see that.

Josh Morse: And the complete document is right before your decision tool or right after Dr. Skelly's slides.

- Chris Standaert: Put one up there so people can see it.
- Seth Schwartz: I guess the only question I would have, because I don't think we saw, was there any controversy in regard to the existing recommendations from the 2009 decision?
- Chris Standaert: There was a lot of controversy at the time. There was extensive controversy and a very difficult time coming to consensus to say the least.
- Seth Schwartz: No. No. No. I don't mean during our . . . post, were there meaningful criticisms of the recommendations of the 2009 panel that we should be aware of?
- Carson Odegard: Well, there were some problems with it that we had to come later after, what did we have? We didn't have a . . .
- Joann Elmore: But on the other hand, we don't know how it changed practice.
- Carson Odegard: Right.
- Joann Elmore: We don't know that people are actually doing anything different.
- Kevin Walsh: But that's not . . . that doesn't matter.
- Carson Odegard: We haven't had any major objection to it that I . . . after we made the final recommendations.
- Kevin Walsh: Seth, are you at all impressed by the fact that the new studies did not address the criteria that were the limitations of coverage?
- Seth Schwartz: No. I think the point is exactly that. That I did not see any data on stent diameter. I did not see any data on length of vessel disease. I did not see anything on . . . meaningful on diabetes. I did not see anything on restenosis, you know, placement in that circumstance, and I did not see anything on what vessels were involved . . . what coronary vessels were involved. So, if you guys are . . . if they already did an evaluation of these 17 randomized trials that actually looked at these things, I saw nothing that would allow me to comment on these decisions, and I find no . . . I saw no great data that drug-eluting stents were any better than bare metal stents. So, I was just looking at what we saw today, and I'm not very impressed, but particularly given that it may need longer, you know, dual-antiplatelet therapy and things like that and all that stuff, but I . . . I don't . . . I can't meaningfully say why I would change any of this stuff, since I saw no data today to comment on any of it and I trust that the panel looked at all the data that was existing prior to this evaluation.
- Chris Standaert: Dr. Skelly?
- Andrea Skelly: You know, my memory goes as I age, but if I remember correctly for the first go around, the 2009 go around, a lot of those criteria were based on the FDA

related indications and contraindications, not strictly on the data that were available in the evidence report, and I will stand corrected, you know, if I am wrong, but there was . . . there was some extra . . . there were extra sessions after the committee met last time to look at some studies in some of these special populations, but again, it was not part of the full evidence report at that time. So, I . . . I don't know to what extent those recommendations for coverage were really supported by the main evidence report. I'm going to . . . the caveat again is that my memory may not be as clear without going back to the report.

Chris Standaert: Yeah, Louise?

Louise Kaplan: The question doesn't ask whether or not those conditions were appropriate. The question asks whether or not the new generation drug-eluting stents were more efficacious than bare metal stents. So, are we debating the conditions or are we debating the stents themselves?

Carson Odegard: There's two different things we're looking at. Those were the conditions to perform the procedure. Now, we're looking at outcomes, and I think it's a totally different, you know, we're . . . I mean, the only . . . the only thing we really have is the MI outcome data and . . .

Louise Kaplan: Well, the original conditions were when a drug-eluting stent could be used.

Chris Standaert: Mm-hmm.

Louise Kaplan: I don't see this second question as asking us whether or not those conditions should be revised. I just want to be clear . . .

Chris Standaert: Mm-hmm.

Louise Kaplan: . . . what we're doing. That's understood.

Chris Standaert: OK. Mike, you had a comment?

Michael Souter: I was just going to say that the process we went through before was one, as you said, of extensive, very difficult decision making here and then going to further sub-committee to utilize the sub-committee makers and a lot more involved discussion with expert members of the cardiology community coming in and offering consideration.

Chris Standaert: Mm-hmm.

Michael Souter: So, I'm hesitant to leap in and just sweep everything that was decided before after the way, as Seth has said, in the face of insufficient evidence to actually change my mind. I don't see anything there in the new studies that would encourage me to revise our guidelines.

- Chris Standaert: OK.
- Michael Souter: Because I . . . I don't see . . . there's no evidence base to do that.
- Carson Odegard: Can I ask . . . Dr. Ring and I were speaking during the break, and my understanding is, the economics have changed significantly from when this was initially done to now in the sense that back in 2009 there was a big price differential between the two, and now it's much smaller. So, my understanding is that actually the preference for the cardiologist is to use drug-eluting stents in everybody they can and really only use the bare metal stents in the patients that can't do dual-antiplatelet therapy.
- Michael Souter: But that wasn't our only criteria for making that decision, though. There were elements of safety, again, and the requirements for the dual-antiplatelet therapy, etc.
- Chris Standaert: So, I guess I could see two circumstances that could change the criteria from before. So, several issues. One, these are different stents. So, the stents we were using that the original report was on are no longer . . . those stents are no longer made. So, the FDA indications, they're different. These are different things now, and the ones we commented on before are no longer really used. So, under . . .
- Michael Souter: Where's the data then?
- Chris Standaert: . . . I'm just throwing out several ways to think about this. So, under that, if you were convinced that these worked beautifully under all circumstances, you could readily expand coverage. Or if you're convinced that, you know what, this does not seem to work at all, and I'm not sure why we're covering this . . . why we're covering drug-eluting. I could see you taking one extreme or the other quite readily, but . . . if that's the way you saw the . . . saw the data.
- Kevin Walsh: So, Seth, I have a question. Your interpretation is that since there's no data about these specific criteria, we shouldn't revisit the decision?
- Seth Schwartz: No. It's different than that. So, I think it falls more in line with Chris's second statement, which is that I haven't seen any data that drug-eluting stents are any better than bare metal stents, so I would be inclined to say no coverage, but we haven't looked at any of the subgroups . . . the subgroups that they're talking about here, but I wouldn't know subgroup analysis.
- Kevin Walsh: I understand what you're saying, but I'm . . . so, the question I want to ask is, but these are . . . these are the studies that have been done, since the vote, what that says to me is, these criteria don't matter anymore, that they are clinically irrelevant.

Seth Schwartz: Well, no, because the criteria that were created at this committee were not applied to the studies that we're looking at today. It was just in the State of Washington. So, we have no idea about that.

Michelle Simon: The studies we looked at in 2009 did have these criteria elucidated. We were looking at muscle lengths and lesion length and all of that, and that's what was so hard for us, and that's why we had to go to an ad hoc committee, but you're right. The new studies don't even address that. I don't know why. I don't know if that means it's not clinically relevant.

Kevin Walsh: Can I ask Dr. Ring? Am I . . . am I interpreting this wrong?

Michael Ring: So, the field has changed dramatically, since 2009, in that the current generation of drug-eluting stents are significantly better in terms of safety issues, including mortality, over the previous generation that we compared to. So, the rea- . . . there's really very little, you know, debate in the field about if drug-eluting stents are better than bare metal stents in most categories. I think it's unequivocal and that's what's occurred as the standard based on trial data that most of the studies that we did not review today actually have occurred since 2009 had not been drug-eluting stents versus bare metal stents. It's been various generation, different models of drug-eluting stents versus each other, and if we looked at that, you would see that the new generation drug-eluting stents are clearly better than the ones that we looked at in 2009.

Kevin Walsh: Let me . . . let me word my question differently then, please. So, the criteria of stent diameter or length of stent, I mean, are those clinically relevant anymore?

Michael Ring: No. It comes down simply to the fact whether or not the patient is a reasonable candidate for long-term dual-antiplatelet therapy and whether they will be compliant with it. That's really the only things that come into play here.

Kevin Walsh: So, Seth, I see, the question you're asking is irrelevant.

Seth Schwartz: Well, maybe that's the case, but then I see a totally . . . I see complete contradiction, which is . . . I'm hearing that they're so much better now than they ever used to be, and yet I'm seeing no data at all that they're any better than bare metal stents.

Kevin Walsh: That's a different . . . OK. I . . . I don't want to go there right now. I just want to ask, do we need . . . prior to making a decision about them versus bare metal stents, is it really . . . do other people really think it's true that we cannot go back and revisit the question, because the studies that we're looking at did not specifically address the issues that we . . . that were conditions in 2009?

Michael Souter: I would just offer the point, I just don't know, and in answer to the point that the majority of studies now are concentrating on comparing different generations or different models of the modern stents. That's probably because the majority of them are being funded by industry in that respect. They've got

no real . . . you know . . . they're all trying to kind of push one brand of . . . benefit one particular stent versus another. So, I don't have a great deal of confidence in the merits of, you know, of these studies in those respects. I would have liked to have seen some evidence that there . . . if truly angiographic diameter and length of lesion, etc., is truly now irrelevant, then, you know, it would be nice to see some proof of that or some factual basis of that. No disrespect to our clinical expert but, you know, that's just what we're hearing and we're being asked to take on faith here at the moment.

Chris Standaert: Mm-hmm.

Michael Souter: There's a lot of, you know, debate on these previous topics beforehand, the exercises, a great deal, and I don't want to completely want to throw that away without good objective evidence that yes, we can . . . we can disregard this. No need to worry anymore, by my concern . . . oh, let's just take the position, OK, we decide, OK. There's truly no difference now between the drug-eluting stents and the bare metal stents. We'll just get rid of that, sweep away all the previous conditions and then, if we have failed to take account of, you know, studies that have examined lesion length, etc., I just don't know if they're out there or not, because it's not there raised in the key questions that were asked.

Kevin Walsh: So, am I hearing that there is a gap between what we think we're being asked to do and the way that the question was framed by the medical directors?

Chris Standaert: I think that's what you're hearing. It's not an uncommon thing for us to run into, unfortunately. So, again, but there are other way . . . other potential outcomes even with the way the question was asked. I mean, we have data. We have data to look at, but Dr. Skelly, so . . . I asked this question when you were up there, the fact that we talked about lesion length and diameter. So, these weren't inclusion or exclusion criteria for studies. These are not discussed in the literature anymore. You don't . . . did you go looking for things that might relate to this under special populations that would help us discern out whether this is still a relevant clinical issue per . . . part of our problem is that the technology has changed. The device we're talking about today, drug-eluting stent, is not the same device it was seven years ago.

Andrea Skelly: We made no exclusions for length or lesion size or diameter of the vessel.

Chris Standaert: We don't find (inaudible) up that way.

Andrea Skelly: In terms of the drug-eluting stents versus the bare metal stents, no. I think we would have included it. If it was a newer generation drug-eluting stent. I don't know if it's of help, but on page . . . starting on page 55 of your report is the list of the indications . . . FDA-approved indications for stents in terms of the diameters of vessels and lesion lengths, etc., but no. In terms of explicitly looking at . . . we did not exclude any studies. If there had been studies that met the other inclusion criteria, which were fairly broad, we would have looked at them. We would have included them. If there had been sub-analyses that

had been in diabetic patients or related to vessel length. I mean, the only thing that related to vessel size is the one RCT that was included, the Basket-Prove, and you can see the data for the Basket-Prove, but that's the only one that specifically addressed vessel size.

Seth Schwartz: So, I'd like to ask the clinical expert. So, as a clinician, how do you make the determination of whether you use a bare metal stents or a drug-eluting stents?

Michael Ring: Like I mentioned earlier, it has to do with whether or not the patient is a likely candidate for dual-antiplatelet therapy long-term, both in terms of medical and compliance issues.

Seth Schwartz: So, I'm hearing, essentially, if they can tolerate a bare metal stents or I'm sorry, if they can tolerate a drug-eluting stent, you would do a drug-eluting stent?

Michael Ring: Right, and that has to do with the fact that they are superior at preventing restenosis and the cost differential is fairly minimal these days.

Louise Kaplan: So, could I ask then, since we had a coverage decision that specified conditions, so does nobody look at these conditions when they make their decision?

Michael Ring: Yes, that's right.

Louise Kaplan: OK. So, the effectiveness . . .

Seth Schwartz: So, then can I . . . can I ask Dr. Skelly? So, taking us to slide 43, is that the one looking at revascularization rates? Is that . . . is that the superiority of the drug-eluting stents or the bare metal stents? Is that the only thing we're seeing?

Andrea Skelly: In terms of the efficacy piece? Is that the only thing that's statistically significant? Is that what you're asking?

Seth Schwartz: Yes.

Andrea Skelly: So, you're looking at . . . I'm sorry, you said slide?

Seth Schwartz: 43.

Andrea Skelly: 43? So, slide 43, yes. Target lesion revascularization is much less with the newer drug-eluting stents. It was true also with the older drug-eluting stents. So, this finding is consistent with what was seen. Now, the Basket-Prove, we don't have data for Basket-Prove in here, which was in the large diameter vessels. If we look at number 44, that's where we got into Prodigy and Examination, the problems with heterogeneity there, but . . . so, that does not help us. In your report, and I'll have to take a minute to find, there is also a target . . . so, we reported both target lesion and target vessel revascularization, but again, drug-eluting stents, they are favored with regard to less need for target lesion or target vascular revascularization.

- Seth Schwartz: I'm sorry to be dominating the questions here, but do we have any objective data about the real cost difference?
- Andrea Skelly: We were not asked to look into that.
- Seth Schwartz: Then, finally about safety, the slide I'm seeing about safety differences is slide 50, and it looks like, with the exception of the stroke difference at 30 days, there was no difference . . . or six months, whatever that was?
- Andrea Skelly: Yes, and that was among the octogenarians. We did not see any difference in the other safety factors.
- Seth Schwartz: You did look for cost-effectiveness data though?
- Andrea Skelly: We looked for cost-effectiveness, but that's not the same as looking at the differential costs between drug-eluting stents and bare metal stents.
- Seth Schwartz: OK. And the agencies did present cost data during their slides.
- Chris Standaert: And so for cost-effectiveness, you had one study on slide 52, right, so one cost . . . cost-effectiveness study?
- Andrea Skelly: I'm sorry?
- Chris Standaert: So, on slide 52, that's your cost data that we have?
- Andrea Skelly: Yes. Slide 52 there was one study that looked at cost-effectiveness and there is more detail on the report . . . in the report on the economic pieces starting on page 168, but the bottom line is that the one study by Epstein et al., they concluded that there were no differences in . . . that it wasn't cost effective. There were no differences in survival or quality adjusted life years over a four-year horizon.
- Chris Standaert: So, per QALY? So by QALY? So, it was not cost-effective to use drug-eluting stents.
- Andrea Skelly: That's what . . .
- Chris Standaert: So, again, that's our double negative again. So, it was . . .
- Joann Elmore: To clarify, so it costs more. It's more expensive.
- Chris Standaert: . . . right.
- Andrea Skelly: Yes. And if you look at the data on page 165, the initial cost of drug-eluting stents was higher compared with bare metal stents but not by a lot. It was \$17,422 versus bare metal stents, which is \$16,641.

Chris Standaert: There we go. That's what he's after.

Seth Schwartz: Thank you. That's what we wanted to know, thank you.

Andrea Skelly: And, yeah, but that's . . . that's not cost-effectiveness. That's just the difference.

Chris Standaert: Page what?

Andrea Skelly: Page 165, it's about the last sentence of the . . .

Chris Standaert: OK.

Andrea Skelly: . . . about the last paragraph, about maybe three-quarters of the way down.

Chris Standaert: So, not more cost-effective but not wildly more expensive either.

Gregory Brown: Right. That's not really an issue.

Chris Standaert: So, let's go back to . . . so we'll get to this issue of whether we can change this or not, because actually some of this there are FDA criteria for when you can use these things that do reflect stent value and similar things. I don't know if it would help us or not, but let's just look at the data for one second. So, we have these issues of cost-effectiveness we just talked about, which is limited, obviously.

Gregory Brown: Yeah.

Chris Standaert: So, if we look at outcomes and outcomes that are important to people here, just in terms of the data we have, what does it help us understand? So, we had one graph that seemed to show improvement on revascularization?

Michael Souter: At 12 months.

Chris Standaert: At 12 months. How do people feel about the data and other venues for outcome? Is this an effective . . . is it more effective to use a drug-eluting stents in some way? Some of the things you worry about are mortality and symptoms and all the function, all those things.

Seth Schwartz: I guess I have a comment, which is, I'm wondering if we even need to separate bare metal stents from drug-eluting stents. In other words, if they effectively cost the same amount, have the same risk profile, are either the same or marginally more effective, we've made a comment about stenting in general, do we even need to break this out? We just cover stenting with the conditions that we specified and don't even say whether it's . . . what stent they use and let them sort it out.

- Chris Standaert: So, this is . . . this is a different condition. This is essentially all conditions where you would use a stent. So, it's not the same as we had before. We can't apply it to the same thing we said. This isn't stable angina patients. This is anywhere you would use a stent.
- Seth Schwartz: Oh, I'm sorry. OK.
- Chris Standaert: Right? I understand the issue was what . . . can we do this, can we not do this, all that sort of thing. We are obligated to go through our data and say what we . . . can we wrap our heads around what we have and what we don't have, and what we think is helpful and what is not, and if we can do that in relatively short order, we can start putting this in order and decide what we can really do. So, let's talk about what we have before we talk about what we can or can't do with it.
- Seth Schwartz: So, just to be clear. So, we're . . . what we're going to ultimately vote on is any condition where . . . where a provider would do a stent . . .
- David McCulloch: Correct.
- Seth Schwartz: . . . would we cover a bare metal . . . would we cover a drug-eluting stent under either . . . under any condition when they would use a stent. Is that basically . . .
- Gregory Brown: Correct. Right.
- Seth Schwartz: . . . what I'm understanding? OK.
- Chris Standaert: That's what we're voting on.
- David McCulloch: Correct. Yes.
- Chris Standaert: So, are they effective? Mortality? Kevin, what do you think?
- Kevin Walsh: I think there's an economic decision, and there's an effectiveness decision. I think the effectiveness is . . . it's a wash. I can't see that there's a whole lot of benefit to drug-eluting stents, but if there's also no price difference, then I don't know . . .
- Chris Standaert: Unless there's a safety concern.
- Kevin Walsh: . . . why it matters. Unless there's a safety concern.
- Chris Standaert: Sure, unless there's a safety concern.
- Kevin Walsh: I don't remember seeing a safety concern that was significant between bare metal stents and drug-eluting stents.

- Michael Souter: I don't know what the prescription patterns are that require, you know, how much consumption or, you know, what's . . . what's the pharmaceutical bill for it to continue dual-antiplatelet therapy that they would have to take. I can't . . . I don't know what the dollar figure is on that. It may not be much, but (inaudible).
- Kevin Walsh: But the . . . but is that relevant, because any patient who can . . . it sounds like any patient who can be on dual-antiplatelet therapy is whether they have a bare metal stent or a drug-eluting stent.
- Group: No.
- Joann Elmore: Bare metal, you usually just put them on for a month.
- Kevin Walsh: That's not what I thought I heard.
- Joann Elmore: Well, it's starting to increase more.
- Michael Ring: So, again, it depends on . . . all things being equal, if a patient can take it, you typically will continue dual-antiplatelet therapy, but recognize that, you know, we do have the option for generic clopidogrel. So, the cost is pretty minimal. It's not like it was back in 2009. So, the cost of the medication isn't the issue. There's the potential for safety events.
- Kevin Walsh: Right. It's safety related not economic, hardly economic anymore.
- Michael Ring: But there's also an opinion, you know, the thing why people . . . why we like to continue it is just that it does . . . dual-antiplatelet therapy does reduce the incidence of stroke and MI. So, you have to balance that versus the safety issues. That has to be individualized, of course.
- Michelle Simon: We do have data from the state utilization that addresses cost somewhat, and if we look back on the medical agency presentation on slide 19, we will have the Uniform Medical, and we see that the cost comparing the bare metal stents to drug has actually, at least in that set of data, has been going up, the difference has been going up. So, in 2014 we're looking at about \$30,000 per procedure for the bare versus \$38,000 per procedure for the drug-eluting stents. It's a little different for the Medicare and certainly fee-for-service. You don't see that, but I think cost is somewhat of a concern in that it's been increasing in that population from 2011 to 2014.
- Michael Souter: I do have safety concerns from the point of view of the bleeding risk associated with them beyond that year of use. You can argue that medications may be getting . . . dual-antiplatelet therapy (inaudible) be bare metal stents or drug-eluting stents for that first initial period, but again, I would have liked to have seen some registry data on what the accumulated experience is, because just, you know, in my own clinical field, I see a lot of people who have been

significantly injured as a consequence of trauma who may have worse outcomes from, you know, concurrent use of dual-antiplatelet therapy.

Chris Standaert: Mm-hmm. It complicates medical care in a number of ways. If we look at our outcomes, we have cardiac mortality and all-cause mortality. They don't look wildly different. Myocardial infarction and re-infarction, not wildly different. Stent thrombosis, not even wildly different. The big difference seems to be in the target lesion revascularization over 12 months, though any MI over 12 months is close. I think we'll have to decide if . . . I think that degree of efficacy versus safety concerns versus cost is relevant and would anything we say be able to sub-plant this one way or the other? You said Medicare pays the same for these either way?

Michael Ring: Professionally, right. The . . . the . . .

Chris Standaert: Oh, the professional fee is the same, oh.

Michael Ring: But the reimbursement . . .

Chris Standaert: But the reimbursement for the stent . . .

Michael Ring: . . . there is a different DRG for drug-eluting stents versus bare metal stents, but again it depends if the patient is inpatient versus outpatient. It's a very complicated issue that I'm not the expert, but I can tell you from a system perspective that the acquisition cost is not much more than about roughly \$500 or \$600 difference.

Chris Standaert: The acquisition for the person purchasing it, not for the . . .

Michael Ring: For the hospital system, right . . .

Chris Standaert: Right.

Michael Ring: . . . that's purchasing it.

Chris Standaert: Which is likely amplified by the time the patient gets it, I bet.

Michael Ring: Oh, yeah, multiple fold.

Chris Standaert: Yes, Andrea.

Andrea Skelly: To address Dr. Souter's question, on Page 161 of the report, the only registry information that we had was one registry study at high risk of bias, and they looked at patients 80 years old and older who had STEMI, and the incidence of in-hospital major bleeding following newer drug-eluting stents was 1.2% compared with bare metal stents, which was 2.7. It was not statistically significant, but we do not have data beyond that 12-month period that you're looking for.

- Gregory Brown: So, bare metal stents were higher?
- Andrea Skelly: Yes, it was, but it was not statistically so at 1.2% versus 2.7%.
- Tony Yen: Can I ask our clinical expert over here, is there a reason why drug-eluting stents are used so prevalently? Is it . . . is it truly for the reason of target lesion restenosis or are there more clinical reasons behind that?
- Michael Ring: That's the main reason. I mean, if you look at this data here that you were just looking at, I mean, the restenosis rates are very low. They are in the range of, like, 3 to 5%, right? And that compares to what we were looking at with the Courage data, which was done with bare metal stents and they had a 20% restenosis rate.
- Tony Yen: And the second part to that question, because I don't see it within the literature that we have available, does that correlate with symptoms at all, because I just, I don't . . . it seems like . . . are we achieving an angiographic result or . . . because I don't see a whole of mortality difference.
- Michael Ring: The TVR, target vascular revascularization, is typically, in these studies, driven by clinical symptoms, typically. So, if patients are coming back with a reason to have it done, which is quite a bit different than when we looked at 2009, which a lot of it was angiographically driven that part of the study protocols, as they came back to the catheterization lab at six months, and a lot of patients ended up having repeat revascularization, even in the absence of symptoms. It was kind of the ocular reflux, as some people term it, but the incidence of ischemia driven revascularization, it tends to be quite low, less than 5%.
- Carson Odegard: Dr. Ring is . . . can you just give us kind of a brief description of what the major difference between 2009 and the . . . with drug-eluting stents, and now? Is it the coating that's the difference, or is it the architecture of the stent itself?
- Michael Ring: Probably three things, but the most important, yes. The stents have changed. They are a little bit different. They have smaller struts, so they're a little bit safer, we think, but the main difference is that the polymer that's used is probably felt to be more biocompatible and less likely to induce late inflammation and possible stent thrombosis, and the drugs used now, the principle drugs used are everolimus and zotarolimus, as compared to previously in 2009 it was Taxus or Taxol, and Sirolimus for the Cypher stent. So, both of those stents are off the market now. So, we have different stents, different polymers, and slightly improved stents, as well.
- Chris Standaert: Why are they off the market?
- Michael Ring: Because they . . . they were inferior to the ones that are used now. They were associated with worse outcomes from a stent thrombosis perspective and late MI.

- Carson Odegard: Thank you.
- Chris Standaert: Yes, Louise?
- Louise Kaplan: So, can we answer the questions and then just change our criteria, since it sounds like we need to address the reality of today rather than what was going on six years ago.
- Chris Standaert: We do. I was just looking at our language. We said bare metal stents are covered with conditions. Obviously, we had no data brought up to address that one or the other, and we addressed the specific condition today that would probably sub-plant that, because we didn't cover it in all conditions for stable angina. We put conditions on our coverage. So, we have already sort of amended that, at least in the stable angina population. We're not putting our . . . we're not addressing, specifically, restrictions within the unstable angina population. So, I assume we're going to have to use language of some sort saying when stents are indicated, and I guess what we have to decide is do we have evidence, and do we want to broaden these conditions so that it becomes more open? Or do we restrict it tighter, and the things like stent diameter length, I looked at the FDA indications, there are maximal lengths for which they should be placed but not minimal, and most of the stent diameters hover around the 3 mm range. They are 2 to 3, they are 4. They are hovering around that range in the FDA indications. We can certainly say FDA indications . . . the stent should be used within its FDA indications. We can certainly say that.
- Joann Elmore: Yeah.
- Chris Standaert: But just so that they are . . . the newer stents are used for what they're supposed to be safe at, and we don't have any other data other than the FDA indications on that. Yes, Kevin?
- Kevin Walsh: I was just . . . I was just going to ask Dr. Ring, does anybody look at that?
- Michael Ring: Do they look at the labeling, you mean?
- Kevin Walsh: No, the FDA indications?
- Michael Ring: Not . . . not . . . I mean, do we look at that . . .
- Kevin Walsh: So, we don't really . . .
- Michael Ring: . . . the problem is that there's a number . . . many clinical scenarios that, unfortunately, have not been tested in randomized clinical trials. They never made it to . . . you know, to be submitted to the FDA for an indication, but I will also remind you, too, that clopidogrel never received an indication for use in stenting until relatively late in the game. There was never actually trials, you know, by industry to get that indication. So, that's just clinical practice is that

there are scenarios that just don't quite meet the labeling indications, but the majority of things do, and that's, you know, I think that the way stent trials are designed now is that they tend to be more what we call all-comer, and they include everybody rather than trying to be too narrow in the type of inclusions/exclusions.

Chris Standaert: OK. Other general comments. We're going to move onto our tool, and I will try and figure out what we do with this. Basically, our language says that the re-review is chosen because there is new evidence that wants to be considered, and upon re-review, consideration shall be given only to events made available, since the previous determination. It does not necessarily say we have to refute, do, support, do anything to what we had before. So, we have some latitude, I think, in terms of how we think about this. We don't have a mandate that we have to keep this, but we have to address what we have. If we're convinced some way . . . one way or the other by the new data that we should do something different than we said . . . we're certainly entitled to say that. If we're totally unconvinced, we can leave it where it is, and the new data just doesn't explicitly get at what we want to get at. So, we have to figure that out.

Alright, we're going to jump to our tool again. So, issues of safety. We had bleeding, which Mike brought up, delayed bleeding from the medication, from the adjunctive therapy.

Gregory Brown: If I heard the data correctly, the bleeding was higher in the bare metal stents.

Michael Souter: That's when they're being placed. I don't think we've got good data, you know, it may be that there's no difference, but we don't have good data to, you know, to say that when subsequent to the placement.

Gregory Brown: I agree we have inadequate data, but the data that we do have actually supports drug-eluting stents for safety.

Tony Yen: I don't know if that study was statistically significant is the point.

Gregory Brown: I'm not arguing that. I'm just saying, that's the only data we have. Is there any other data?

Andrea Skelly: The data on slide 49 summarizes the major bleeding, and it's across any time period, and that's in the RCTs, and there were no differences between drug-eluting stents and bare metal stents, but again, all we had was data at one month or . . . and one type of drug-eluting stent 12 months. Then, on page 161 of the report, we had one registry study that reported in-hospital bleeding, and it was statistically similar, even though, yes, there was less in the drug-eluting stents than the bare metal stents, it was not statistically significant. The P-value was 0.3, but the risk difference was, you know, 2.7 versus 1.2%.

Michael Souter: And I go back to the point, I mean, really you can only address these issues as a combination of getting this stent and then by necessity getting the drugs, and

then experiencing other coincident life events that put you at risk with good registry data, and I don't think we've got that data. So, I don't think you can answer that question one way or another.

Chris Standaert: And the onus is on the device to say it's safer, and it just doesn't seem to be.

Gregory Brown: I understand. I guess what I'm hearing from our clinical expert is the . . . you . . . when you look at the tradeoffs of stroke and MI issues on dual-antiplatelet therapy versus bleeding risks, they tend to fall on the, we would rather do dual-antiplatelet therapy and so to just say, but for the stent question we're only going to talk about bleeding. So, they're picking their stent based on whether they can do the dual-antiplatelet therapy.

Chris Standaert: Yeah. I mean, so one, that's not really in the prevue of what we're saying. I think what Mike is saying is, it is more mandatory to have the dual-antiplatelet therapy. So, you have to require that. So, there's an extra risk that goes with it theoretically, in the long-term, and this is just coming up as a concern. Whereas you are not obligated to stay on them as long if you have a bare metal stents. So, it's a consideration for longer-term outcome, and the peri-procedural outcomes seem relatively similar in terms of safety? OK.

Effectiveness? So, we have things on here. We already said mortality, all-cause mortality, cardiac mortality, not much difference, no advantage to one versus the other? MI's? We don't really know much about function do we? Did we get function data, patient reported outcome data? We didn't get any. And revascularization? It seems the one area they showed some advantage. Were people impressed by that? No. OK.

And cost, we have it as more costly, and it has not proven to be more cost-effective. We don't know about less cost-effective, necessarily, but it is more costly. Other comments on these, or we'll see how people feel about them. OK.

Gregory Brown: I guess I'm impressed by the fact that it sounds to me like the 2009 decision has become irrelevant and the subspecialty has moved on irrespective of that.

Chris Standaert: I can see that perspective. So, let's vote on these three things. So, effectiveness? So, under any or all circumstances . . . under any or all circumstances is there sufficient evidence that drug-eluting stents are more . . . are more effective?

Josh Morse: Five equivalent and six more.

Chris Standaert: How about safety? More or less?

Josh Morse: Two less, nine equivalent.

Chris Standaert: And cost-effective?

- Josh Morse: Two equivalent, two, three, four unproven. That leaves five less.
- Chris Standaert: So, our questions are, since 2009, is there evidence that new generation drug-eluting stents are more efficacious than bare metal stents in reducing MI, death, etc. So, are they more efficacious? We're going to have to decide if we're going to cover them, and we have the same choices we always have. One of our choices would be to keep this and say we don't have any need to change this and we should stay with this. One would be to change our conditions. One would be to cover unconditionally, and one would be to not cover.
- Seth Schwartz: And just to be clear, if we were to say cover unconditionally, were we talking about only . . . we're not talking about indications for stenting in general. So, just . . .
- Chris Standaert: Right.
- Seth Schwartz: . . . if . . . if it's . . .
- David McCulloch: If you're getting a stent . . .
- Seth Schwartz: . . . they can use a drug-eluting stents.
- Chris Standaert: So, what we would say, I think is, if there are clinical indications for stenting, you can use . . . if we were to cover conditionally, if we cover unconditionally. So, is anybody in favor of keeping what we have? We'll start there? One? No. OK. So, then that, we have to figure out where we go. So, it's the same process. We're going to talk about conditions. So, I'm not quite sure how people are leaning again. I haven't heard enough to convince me. So, who wants to talk about conditions? We can start there.
- Gregory Brown: Could I propose a straw vote first?
- Chris Standaert: A straw vote before a straw vote?
- Gregory Brown: A straw vote of how many people want to cover unconditionally so that if there's a majority we don't even need to discuss conditions.
- Chris Standaert: So, you got to . . . you got to kind of go one way or the other, right. So, I'm just using the inverse of the language, right? So, if only two people want to talk about conditions we can just vote, and if for some reason we have a split vote then we got to figure it out. So, who would like to talk about conditions? No one. One. One person.
- Michelle Simon: I wish there were conditions to talk about. I would like there to be conditions.
- Chris Standaert: Right.

- Michelle Simon: I mean, besides what we had in 2009, we haven't really seen evidence for us to make that distinction, I don't think, but I'd love to hear what you had to say.
- Tony Yen: The only problem is that I just don't have the literature over here to really develop good conditions right now. I wish that there was better literature out there in terms of maybe stratifying by (inaudible) etc., folks who may be at higher risk for in-stent restenosis, or something to that effect. I don't see anything about symptoms, at least within the data that I see over here in front of me. We do have the expert opinion, and that is well appreciated, but this seems like, you know, right now we're left in this space of everybody gets drug-eluting stents pretty much, except if, you know, you can't tolerate dual-antiplatelet therapy for whatever reason. It seems to be the medical approach at the moment.
- Joann Elmore: And I'm concerned that I wasn't here in the prior review, because of some of the early literature did show some data, if I remember correctly, on anginal symptoms, quality of life, those kind of things, whereas now, we don't have any of those data.
- Louise Kaplan: It seems almost irrelevant, because we're not talking about the same intervention.
- Chris Standaert: No.
- Louise Kaplan: The intervention has changed.
- Chris Standaert: And actually the intervention we approved with some conditions turned out to be worse. Right.
- Seth Schwartz: Only one person wants conditions, should we go ahead and vote?
- Chris Standaert: Yeah.
- Chris Standaert: Thank you. That's what we're about to do. So, any other comments, or people we're going to vote. OK. So, our decision will relate to the use of drug-eluting stents in circumstances where coronary stents are otherwise clinically indicated.
- Josh Morse: One no cover, ten cover.
- Chris Standaert: I don't believe we had a Medicare guideline that related to drug-eluting stents. We follow the one with stents in general already. Did we have society guidelines we are supposed to look at regarding drug-eluting stents?
- Josh Morse: I recall the information that was provided, and maybe Dr. Skelly can remind us.
- Chris Standaert: Were there society guidelines on drug-eluting stents?
- Josh Morse: Did they address the question?

Andrea Skelly: Bare metal stents versus drug-eluting stents?

Chris Standaert: Mm-hmm.

Andrea Skelly: No.

Chris Standaert: No. So, we have nothing to talk about.

Andrea Skelly: It's just stenting, PCI.

Chris Standaert: Alright. So, we are done. That was a lot . . . that was a lot to work through. I appreciate your patience. They were hard to wrap our heads around. So, you are all done.

Josh Morse: Thank you.