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Health Technology Clinical Committee Public Meeting

May 16, 2014

Craig Blackmore: Well, good morning, everyone. Welcome to the Health Technology Clinical Committee meeting. I'm Craig Blackmore, chair of the committee, and we have a quorum of members, so I will call the meeting to order. The first item of business on the agenda is to, well the first is actually the Health Technology Assessment program update. Do you have a program update?

Josh Morse: We do, a brief presentation. Good morning. I'm Josh Morse. I'm the program director for the Health Technology Assessment Program and momentarily, we'll have some slides, and I'll do a brief presentation about the program and today's schedule.

So, today's top is proton beam therapy. We also have on the agenda review of draft key questions for two topics. Neuro-imaging for dementia and screening and monitoring for osteoporosis, and we'll have an update on the next committee public meeting, which will occur in July.

So, some background on this program, the Health Technology Assessment program is located in the Health Care Authority, a state agency in Olympia; 2006 legislation designed this program to use evidence reports and this panel of clinicians to make coverage decisions for certain medical procedures and tests based on the evidence on their safety, efficacy, and cost effectiveness. Multiple state programs participate to identify the topics that are reviewed here. They include the Health Care Authority, which runs the Uniform Medical Plan for state employees and retirees, the Medicaid program, the Department of Labor and Industries, which runs the Worker's Comp program in the State of Washington, and the Department of Corrections. The agencies implement these determinations from this committee within their existing statutory frameworks. So, the purpose of the program is to pay for what works, to ensure that the medical treatments, devices, and services that are paid for with state healthcare dollars are safe and proven to work. We provide a resource for the state agencies that

purchase healthcare. We develop the evidence-based reports on the devices, procedures, and tests that are reviewed here, and we provide staff support to facilitate this, uh, independent committee to make these decisions. Overall, our objectives are better health. We strive for transparency and to minimize bias in this process, as well as to be consistent and flexible.

This is a very high level view of the process. The director of the Health Care Authority is charged to select technologies for review. These are nominated from the state agencies and ultimately put out for comments and then selected by the director. We have contracts with evidence reviewers or vendors to produce the technology assessments or reports, and we then bring them to the committee here in public meeting. The agencies then implement decisions from this committee.

So, the primary questions in the program are is it safe, is it effective, and does it provide value. Does it improve health outcomes? So, again, we value transparency. We publish the topics, draft reports criteria, and conduct open public meetings for review. We seek the best evidence in our systematic reviews and reports, and the decisions come from a committee of people who do not work for state agencies. The clinical committee decisions must give the greatest weight to the most valid and reliable evidence. Objective factors for evidence consideration include the source of the evidence, the characteristics of the studies included, and how consistent they are. Additional factors might include recency or relevance and bias.

These are technologies that have been reviewed this year or will be reviewed in the future. Today is proton beam therapy. We have changed the schedule for the fall. The thyroid ultrasound topic has been removed from the schedule based on the early review of the evidence and the scope that was developed. There was not an evidence base available to answer the policy questions, apparently. We have scheduled neuro-imaging for dementia and screening and monitoring for osteoporosis for the fall meeting.

So, how to participate, there are a variety of ways to participate with this program. You can visit our website. You can join our stakeholders' distribution list. The address is shown here to email. You can comment on topics at a variety of points in the process of any review. You can attend these public meetings. All the meeting materials are posted on the internet at least two weeks in advance of the public meetings. Anybody may present comments here to the committee, and anyone may nominate technologies for review. Thank you, very much.

Craig Blackmore: Thank you, Josh. So, the next item on the agenda is attending to business from prior meetings, and that consists of two components. First is the minutes from the March meeting, and the minutes have been provided to the committee members, and they are in our packets here, and I would solicit a motion from the committee members to approve or not approve the minutes from the previous meeting.

Chris Standaert: I saw one typo, if I'm correct. It's on page 1 under 3, it says hyaluronic acid, and it says 6 committee members approved hip resurfacing findings and decisions. That should be hyaluronic acid. It says hip resurfacing.

Craig Blackmore: Where are you?

Chris Standaert: Page 1 of the minutes.

Craig Blackmore: Oh, sorry. (inaudible).

Josh Morse: Thank you, Dr. Standaert.

Chris Standaert: You're welcome.

Craig Blackmore: Any other typos or comments or concerns?

Chris Standaert: Motion to approve.

Richard Phillips: Second.

Craig Blackmore: So, if I could just have a show of hands for approval of the corrected minutes from the March 21st meeting.

Josh Morse: All approve.

Craig Blackmore: Alright. The next item is the previous findings and decisions and at the prior meeting, we made determinations on non-pharmacologic treatments for treatment-resistant depression, and the draft findings and decisions document has been provided to the committee members and is within the packets. There are also some comments that were received that have been also distributed. So, again, I will solicit a motion to approve the draft findings for any discussion.

Chris Standaert: We got a couple of comments including one from Lee Glass about language, and should we define treatment-resistant depression and should we specify this, or major depressive disorder or bipolar depression? I know we talked about them at the meeting. I think we had trouble defining treatment-related, or a definition of treatment-resistant depression, and they're giving us a definition, but I think we had trouble coming up with an exact one if I recall from the

studies. For some reason, I can't remember the reason why we didn't choose that. We thought about that very thing, and we didn't, we selected not to go with that, because I think circumstances of actually trying two drugs in some people was not felt to be appropriate if they were totally severe. Is that what I remember? Because there are circumstances where you wouldn't want to wait 12 weeks and go through two more drugs. I thought that was the reason we didn't define it that way.

Craig Blackmore: I think we empowered the agency directors to potentially work with clinicians in the field on a definition that could even potentially evolve over time, rather than us as a committee making that more arbitrary distinction of this is how we define it. Any other thoughts or comments? Does anybody want to move for approval, or are we still contemplating?

Kevin Walsh: I'll move to approve.

Craig Blackmore: Second?

Michael Souter: Second.

Craig Blackmore: OK, could I have a show of hands for approval of the draft findings and decisions document on non-pharmacologic treatment for treatment-resistant depression, in favor.

Josh Morse: All approve.

Craig Blackmore: The second topic from the previous meeting was facet neurotomy, which we determined would be a covered benefit with conditions, and there is a host of conditions for lumbar and cervical, and again that document is provided, and we did receive some comments, which are included. Any discussion?

Chris Standaert: I'm going to bring up one issue, just because I think it's worth noting. There were a lot of comments to this, and a lot of signatures, including a number of providers in the state, and I think most of the things they comment on, like, three months instead of six months for pain, including the thoracic spine, I don't think there's real justification for it. I don't think anybody presented any evidence why we should go for three months instead of six. The only concern I had was the C2-3 joint issue, and I know why we voted, I was the only one to vote for it, and I know why, because there was no RCT on C2-3. I just thought I'd explain my rationale for voting for it and why I think that was really one of the key things people were complaining, or trying to address in their comments, and I think C2-3, there are a few things different about it. It's partly C2, which is distinct anatomic structure, and so the nerve supply to the joint is different, which is why it wasn't included in the Lord study largely. It didn't have a procedure for ablating that joint, and they do have that now. That was established after that study, but fundamentally, I don't think, I don't know why I think differently. The only difference about it otherwise was it causes headache and not neck pain. C2-3 does not go to your neck. It gives you a headache. So,

in my own head, I don't physiologically think of it as different than C3-4. I don't know why one would. The nerve supply's a bit different. It's a little more obnoxious to neurotomize it, because people get numb in the back of their heads. So, this is more of a down-side. I get that, too, but my rationale was just that it seems like it is like the other joints, and I agree with everything else we said about the Lord study and 100% response and all that sort of stuff. I personally would have put, gone from C2-3 down to C6-7 for that reason, but I was clearly in the minority at the time.

Craig Blackmore: Yeah, and I think we did go through that at the last meeting.

Chris Standaert: So, I bring it up because that was a part of many of the comments of the public.

Craig Blackmore: Yeah.

Chris Standaert: And again, the other comments I'm less persuaded by personally.

Craig Blackmore: Any other thoughts?

Marie Brown: Is that something we would reconsider? I mean, is it possible to reconsider the, just to rethink it based on comments and your follow-up comment?

Chris Standaert: Yeah, I mean, my, the only thing I would do is, I would change C3-4 to C2-3, because we say right now limited to C3-4 through C6-7 and personally I would make that C2-3 through C6-7. It really doesn't apply to C1-2. That's a whole different joint structure, and you can't really even do the procedure.

Craig Blackmore: So, none of these comments presented evidence. Is that...

Chris Standaert: They all...

Craig Blackmore: ...evidence that wasn't available in an earlier study on headache.

Chris Standaert: Yeah.

Craig Blackmore: I mean, there was nothing that was missing in our decision-making process that is now brought to light. We understand that there's...

Chris Standaert: What they do is...

Craig Blackmore: (inaudible)

Chris Standaert: ...well the, the literature report we got did not cover a lot of the non-RCT studies, and so a lot of these are case series of various sorts and descriptions of the technique, and it just, there is no RCT on this particular issue. Nobody's bringing that up, but the big issue, from my standpoint, is that the technique to do this procedure just did not exist in 1996 when Lord came out, and people have since defined the anatomy and figured out how to do it reliably, and Lord

did not know how to do that when they did their study, and they say that is why they did not include it in their study, although as Carson pointed out they did study the prevalence of headache associated with C2-3.

Carson Odegard: And that was my concern too in the last meeting. I mean, I voted against it, but I, because I brought up the issue, I mean, the fact that it wasn't in the Lord study and, so I'm with you. I would...

Craig Blackmore: I'm thinking from the standpoint of process. So, we, we gather in a meeting. We look at all the available evidence. Based on that evidence, we make a decision, and then we give an opportunity for public comment, because that's important, and I guess I would see the public comment as an opportunity to make sure that we did not miss something in the evidence, in which case we might need to revisit it. Now, if we missed something in the evidence, then that can be interpreted in a lot of different ways, obviously. We are not, necessarily, going to make everyone happy with our decisions, and I, you know, I think it is important to consider the comments, as we are doing. I am personally not going to be persuaded by comments unless they are bringing to light something that was not already a part of, bringing to light something that was not part of our discussion. I do not see this as an opportunity, I'll just leave it at that point. So, I mean, I think it is important that we are having this conversation, and I would take what you're saying but not see, see that there is anything new that has been brought to light that wasn't already encompassed by the prior meeting. Other perspectives on this issue?

Michael Souter: I would just say I agree. I do not see anything, I do not see any new evidence that was not there before, and I do not see any reason to change our vote. I mean, this is a common scenario for us to be in, that people are unhappy with our decision, who present some very passionate arguments, but I think we made our decision based on the evidence at the time. Our only justification for change is if something new arises that wasn't presented us before.

Seth Schwartz: I think we are, I think we are all open to new evidence and reassessing the previous decision, but without new evidence, this is just discontent with the decision.

Michelle Simon: I understand there is no new evidence being presented. I think the comments do carry some significance and it is worth another look at I think for me personally. I understand that the C2-3 joint is a little bit different in that the architecture (inaudible) understood, and the procedure is more well understood now than it was when the study was done (inaudible). So, I think it is (inaudible).

Marie Brown: I agree with Michelle and Chris.

Chris Standaert: I do not think, I do not know, from the evidence, I do not know if, because it said most of the comments I found unpersuasive regarding many of the other issues that were brought up from the evidence standpoint. I think people were trying

to find a different way to provide perspective on the evidence and how it could be interpreted in light of the existing RCTs and other data we have, you know, what is different about C2-3 is what they're trying to do, but I agree. There is fundamentally something different, but they are trying to present in a way of how to put it in the context of this procedure in caring for these patients is what they are trying to do.

Craig Blackmore: So, we all agree that there is something different about C2-3, I think. We all agree that the randomized clinical trial data and the evidence that we have evaluated did not show any evidence of benefit, or at least not strong evidence of benefit at that level, and based on that information, we made a decision, and so I guess I am not still clear what has changed in the interim, except that a lot of people had said that we should cover C2-3 because they think it works.

Marie Brown: Is it a way of thinking about the evidence? Sometimes just changing perspective or point of view when you really look at it, that it can help you reconsider a decision. It is the perspective or the context that may be somewhat different.

Chris Standaert: You know, I mean, the only thing that's really fundamentally different about this C2-3 facet joint is the innervation. The structure of the joint, the actual articular facets, the cartilage structure, the ligaments, everything, it is not fundamentally different than C3-4, C4-5, C5-6. All those are different than thoracic facets. They're a totally different structure, but anatomically, it's not fundamentally different other than the nerve supply, and so that, again, that goes back to why Lord did not include it in that particular study.

Michael Souter: But we did not, we did not come to our decision based on differing anatomy. We came to our decision based on answering key questions. The key questions haven't changed. The evidence has not changed. I don't see why the answer should change.

Craig Blackmore: We are, we are always going to have arguments, you know, if, our job is to draw a line to say here is the evidence for or against up to a certain point. Sometimes, it is going to be clearcut and we are going to say there is no evidence for any of this. Sometimes, it is going to be clearcut and we are going to say, this clearly works everywhere, but in all the other circumstances, our job is to draw a line, and it is hard, but that line is to be based on the best available evidence, and we have a lengthy process to go through to try to understand what that evidence is, and we have a meeting and a deliberation, and we make some judgment that the evidence supports up to a certain point. Nobody is ever going to be completely happy with where we draw that line, and if it were easy to draw that line, you would not need a committee, and you would not need Josh and his whole team, and you would not need to go through this comprehensive evaluation of the evidence, you know? And wherever we draw the line, we are always going to get push back, and there are going to be all sorts of arguments based on reason and based on physiology and based on emotion, but our job is to stay focused on evidence, and I think we did in the last meeting, and I haven't seen anything to suggest that we did not act on

evidence in the last meeting. I can definitely see some disagreement among the committee members, and that is appropriate and understandable, but from the standpoint of process, has anything brought to light that tells us that we did not make a decision based on the best available evidence or that the best available evidence was not provided to us or some other problem.

Carson Odegard: Well, the only new evidence that we have are two Lord Studies and a (inaudible) study that is related to the arguments that have been presented. So, how convincing, you know (inaudible). Basing this on new studies, how convincing are these studies. I personally have not read them.

Craig Blackmore: They are new studies that (inaudible).

Joann Elmore: It was interesting reading the many responses to our minutes and our decision, and it made me pause thinking that I now needed to pull up the entire evidence report from that last time and sift through it and I am wondering if it is appropriate that we ask the evidence vendor and our clinical expert to join us via teleconference at one of our next meetings and address two or three of these very narrow, specific questions that we let the current decision stand, but I would like to ask the evidence vendor and the clinician to address these, just because I felt like it, I agree with Chris. I think there are some interesting biologic and clinical issues, and the three issues that I see are the greater than six months versus greater than three months. The second is the C2-3, and the third was that they felt it was unrealistic to set 100% as the criteria to select, 100% improvement in pain.

Kevin Walsh: I felt like we evaluated the evidence and had a thorough discussion and made a decision, and I am comfortable with letting that decision stand.

Craig Blackmore: We, we put some restrictions on a technology, and, you know, obviously not everybody wanted us to do that, and I think each of the restrictions we put on caused some discomfort. I think any time we put a restriction on a procedure, we are going to get push back, and our job is to look at the evidence and draw a line that says this is what the evidence supports, and somebody is always going to want to be on the other side, and there is always going to be potential benefit on the other side of that line, but the reason you have the clinical committee is to look at the evidence and to say it goes up to a certain point. I mean, procedurally, I think we have a few choices. I think we can approve our prior decision or we can start over. We can say we need to bring back together the evidence vendor and the committee and we need to re-review the evidence and we need to reconsider our decision. I don't personally see that as productive. I don't think we should throw every decision into question just because there is push back from the people who do the procedure and are convinced that it works without evidence to support it. I do not think it is a good precedent and to be quite honest, I think it would make the committee substantially less effective if we re-review decisions just because people objected. With that being said, if the committee has sufficient discomfort that our interpretation of the evidence was incorrect, then that's what we have to

do, and that's why we have checks within the system, but I do not think we can sit here and say, oh, let's just expand it because people think we should without going through a complete re-review.

Marie Brown: Can we do a narrow re-review just based on, like...

Seth Schwartz: No, no. I, I don't think, I think that violates the process.

Craig Blackmore: You say we, the committee went through this entire process and got it wrong, and we are going to do it again.

Seth Schwartz: I make a motion that we approve the decision.

Michael Souter: I second.

Chris Standaert: Discussion?

Craig Blackmore: More discussion?

Carson Odegard: My only concern, and this isn't related to this particular study or it really relates to all of them, and that is really if the evidence provided to us is really the best set of evidence, I have no doubt that we can consider all the evidence that was in front of us, and I thought we did a reasonable job. The thing that bothers me is that I'm not sure we've got all the relevant evidence, not being a content master in this field, I have no idea how to assess that, and we have to assess, accept the fact that our vendor has basically done what they were asked of them. If there are some real concerns that the evidence was not presented, I'm open to investigating it, but, and going further into that, but I'm certainly not at the point of saying let's look at the same evidence again and see if we make a different opinion. I don't want to do that.

Craig Blackmore: I mean, I think that's the question before us. If we believe that we made the decision based on the best available evidence, meaning the evidence was before us, we had deliberation, we had discussion, we decided, then we should approve this decision. If we believe that there is some important piece of evidence that the committee was not provided with, then I think we are obligated to go back and re-review all the evidence because we didn't make a decision based on the best available evidence. I am not...

Carson Odegard: Has anybody even brought that...

Craig Blackmore: ...seeing new evidence.

Carson Odegard: ...to us that says, hey, we haven't considered some essential data, I'm not aware that that's the case.

Chris Standaert: The basis for the argument they make in the, for the C2-3, they bring in studies that were not brought in, but they are case series. They are technical descriptions of how to do the procedure. They are not good clinical studies.

Carson Odegard: Right.

Chris Standaert: So, but that is what they're bringing in and the argument being evidence is what it is. You go to whatever level, as we have, and we did not even get that, and that is what their argument is from that evidence standpoint. I, personally, I don't, re-reviewing, I think, is fraught with all sorts of problems, and I don't like that, and frankly, I think we did a nice job, and I think we went through a lot of things very carefully, and I think, you know, with 100%, that's what Lord used in their study. It was a very well-done study, and that's what they used, and that's what we said, and I, people don't like these other studies that have been done, but that is the best, that is the only study we had that we could base a decision on, but that is where the C3-4 and C2-3 thing came in as well, and so I certainly agree with the overwhelming majority of our decision, and now we are in a point where we have to vote on our decision. I'm in the awkward spot. Do I vote for it or against it, even though I agree with almost everything we said? The only thing I would have proposed for re-review is just changing the language to C2-3 to C6-7, but that is not where...

Craig Blackmore: We cannot go back and revisit a decision and change it without going through a formal evaluation again. We had, we had people presenting information.

Chris Standaert: Mm-hmm.

Craig Blackmore: It is completely one-sided, and we already had deliberation over the evidence that is available. This is, this is a quality check.

Chris Standaert: Mm-hmm.

Craig Blackmore: Did we miss something, and that's a judgment, and some of us may believe that we did miss something and that this case series was important, um, U-turn we are not here to say, oh, you know, upon further thought and upon further, you know, input we are going to just change what we have already done.

Chris Standaert: And, I am not trying to be contentious. I brought this up because we had a very, a number of very well thought out and clearly people put a lot of time into generating responses back that we had not, we owed them. We were obligated to make sure we address their concerns.

Michael Souter: (inaudible)

Seth Schwartz: And they had the same opportunity to present that, that before.

Chris Standaert: Mm-hmm.

- Seth Schwartz: They could have come here and presented it here. This is not, this is not the only opportunity they had to voice this issue. They were not here.
- Craig Blackmore: So, there is a motion on the table to either approve or not the minute, or sorry, the draft findings and decisions on facet neurotomy and, you know, again, not approving them is an option and, and, and this is a quality check and if we have made a mistake and have not considered, if we have made a mistake by not considering the best available evidence, then we should revisit it and we should re-review it, but if we do believe we reviewed the best available evidence at the previous meeting, and the wording of the documents reflects our decision, then we should approve it. So, again, I would like a show of hands of all those who are in favor of approving the draft decision on facet neurotomy.
- Josh Morse: Five approve.
- Craig Blackmore: So, now I need a show of hands for those who believe we should re-review the facet neurotomy question.
- Joann Elmore: Only C2-3.
- Craig Blackmore: No. We re-review, re-review.
- Seth Schwartz: Or nothing.
- Chris Standaert: So, that was what I was about to ask. I don't know if we have ever not voted to approve one of our things. What is the consequence of not approving our own, what happens if we don't, I mean, does that mean we change the language, I mean, we have changed the language in other statements before?
- Craig Blackmore: We had changed language to reflect previous, we didn't change the context. We changed the language to make sure the language reflected what we had really meant by it. We didn't change a decision. So, to change a decision, we need to go back to a committee meeting. We need to have the evidence presented to us again, and we need to deliberate again and come to a new decision that we can approve that would be an acknowledgement that our prior decision had been a mistake because of whatever reason because we did not have the best available evidence, because for whatever reason. The one time in the past we did not approve a decision was the stenting case, and we came to the conclusion that we did not have enough information to define the technical parameters around which the limitation applied, the millimeters, the length of the stent, the diameter, the number of stents, etc., and we convened a subcommittee to help us define those clinical parameters, and then we brought that back to the committee and we re-formulated the decision, as a consequence, but I, I do not believe it would be in keeping with our process for us to make a change in the decision without having the evidence available before us, including the vendor, including our clinical expert, including all of that material and to go through a formal re-review and make a decision based on the (inaudible).

- Carson Odegard: If we do a re-review, say in six months, say that there's new evidence that's, uh, appeared...
- Craig Blackmore: We always have the option to do a re-review. We are required to consider a re-review at 18 months, and we are always able and empowered to do a re-review if somebody brings, you know, if new evidence is identified that we feel might have a significant impact on our decision. Josh, from the process standpoint, am I, am I mis-stating, or?
- Josh Morse: No, I agree with you.
- Craig Blackmore: So, you know, if a big randomized clinical trial comes out, then we would have the opportunity, and it did not support our decision, we would have a re-review and, again, we would have one of our vendors evaluate, bring all the evidence to the committee, and we would consider the question again. In a year and a half, we are required to look and see if there is new important evidence and we could do that sooner or at any frequency if something was brought forth.
- Joann Elmore: It certainly would have been helpful to have this conversation before we had that vote, because I, we having such a black and white issue, re-review or (inaudible) I think I might have voted differently. I thought if we had the option to do a targeted single key question re-review I would be interested in that.
- Chris Standaert: Mm-hmm, right.
- Joann Elmore: Without that option, I don't want to do an entire re-review.
- Group: I agree.
- Chris Standaert: Yeah, I am not interested in a full review, but yeah...
- Craig Blackmore: I, I don't, from a process standpoint, I do not know how we would do that.
- Carson Odegard: Right.
- Joann Elmore: Well, part of transparency is that we ask for feedback, which we did, and we received voluminous feedback, and many of them pointed out the C2-3 question. I am uncertain that we reviewed adequately the case series and so I am uncomfortable, I mean, I am very satisfied with our decision, except for the C2-3. So, I wish there was a way around it that we could just do a narrow C2-3. I would be very happy to vote to provision to a narrow C2-3.
- Michael Souter: Has the key question changed? Back to what I was saying earlier, has the key question changed? No. Has the evidence that we reviewed? No. I do not see any justification at all other than, you know, our...
- Group: No.

- Joann Elmore: We, we did not review the case series, I mean, I know the case series are not high quality.
- Michael Souter: Yeah, and we had many instances previously where case series have come to us, and we have just said, that is just a case series. This is a significant volume of complaints, yes. I do not think that we should allow volume to determine a qualitative decision. I would move that we re-vote, again, on the question.
- Richard Phillips: Can I ask a question, too, of Josh, and that is would, if indeed you have a number of people who are unhappy with our decision, do they have a means of addressing that issue with the, with you as the, the program director and perhaps bringing this for, up for review at an earlier date? Do they, does that pressure have anything to do with how decisions are re-evaluated down the line?
- Josh Morse: Well...
- Richard Phillips: You know, in other words, we have that 18-month re-review statement there, but does the fact that we have this kind of a situation where people have provided feedback contrary to our point of view, does that put any pressure on you, or does that open the door for you to, you know, look at this down the line as another review?
- Josh Morse: The re-review would depend on newly-available evidence.
- Richard Phillips: Exactly.
- Josh Morse: So, if something emerges in the next six...
- Richard Phillips: Well, that's what I'm thinking. Is it just, I'm not asking, and I'm going along with everybody saying about, you know, we, we look at what evidence was here, but if they are going to say that there is new evidence and they bring it to you, then you can, indeed, bring it back to us with new evidence for re-review then.
- Craig Blackmore: Right.
- Josh Morse: Or they can come to you and ask for a re-review if they wish.
- Craig Blackmore: But we, we, we can re-review, if new evidence comes to light, then the committee can be asked to do a re-review, you know? We, we can do this whole process again if some big randomized clinical trial came out next week and, and, you know, we as a committee could recommend that. I don't think we could force it, but we could recommend it. Any of the, you know, any of the stakeholders could come to the (inaudible)...
- Richard Phillips: 'Cause sometimes these decisions are, you know, whether to include case review, case studies and these analysis is really a decision of the vendor. It

really is not something we can do anything about. I am not going to, you know, we cannot really retract our feelings because some things are not included in the, for our review, but that does not mean that some of those studies may not have been reasonable to put in front of us. I do not know how to assess that issue, but I do think it is a legitimate concern.

Craig Blackmore: And, and we could lower the bar, you know? We could say if you have a case series of ten that you seem to believe shows benefit, we will cover the technology. We have set a bar that is a little higher than that. I will not say it is incredibly high. We are not requiring a meta-analysis with 16 randomized clinical trials that show unequivocal benefit. I think to lower the bar any further and say a case series with, you know, all the limitations is sufficient proof of effectiveness would be not something I would be comfortable with in terms of believing the process has value.

Chris Standaert: I do not want to drag this out. I mean, I do not think we have used case series as a way to justify coverage for an entire technology. I believe we use them on the margins, subpopulations or other sorts of things or other categories may fall in there. I think they influence that some, which is where their value may be, and that is, again, I have the same problem with this one particular issue, and I do not know if it comes, I do not know that there is going to be new evidence to present to warrant a review. I suppose if we pass it as is, there certainly is a high incentive on somebody to do an RCT of C2-3 facet, which would then open up the availability for re-review. I just was not aware that we could, we could not actually just change our language that fit.

Joann Elmore: I am going to second Michael's motion.

Craig Blackmore: So, we had a nonconclusive vote. There are exactly ten of us, and five is a nonconclusive vote. So, I think we can redo it. There is a motion on the table to do so, and it has been seconded. So, I will ask then for a second vote on approval or nonapproval of the drafts, findings, and decisions for facet neurotomy. So, if you're in favor of approving the draft findings and decisions, you could please give me a show of hands.

Josh Morse: Ten approve.

Craig Blackmore: This is never going to be easy, right? They are all different. They are all hard, and we are not always, as a committee, going to agree. OK.

Josh Morse: So, there is an issue with the phone, if we could take a ten-minute break.

Craig Blackmore: Yep.

Josh Morse: And get queued up for the next session.

Craig Blackmore: So, we will do that. We will take a two-minute break. We are still in session but this would be a good opportunity to grab a coffee if you want to do so.

Alright. Now, if I could ask the committee members to resume their seats, and we will start with the next item on the agenda, which is our new topic for discussion, which is on proton beam therapy, and we are going to start off the proton beam therapy session with public comments, and we have, we have received a number of requests in advance in the meeting from people who wished to address the committee. So, we are going to have those individuals. We also have the opportunity for people who have not told us in advance that are present, either here physically or on the phone who want to address the committee, after we sort of have the pre-scheduled presenters, we will have an opportunity for anybody who is kind of a walk-in to also address the committee. There is a signup sheet, there was. I think it is still out there, or? OK, there is still a signup sheet out in the hall. If you want to address the committee and you haven't already told us that, please just sign up on that sheet and we will give you an opportunity at the end. We have also had a number of, a number of individuals who want to address the committee coming from the same institutions and the same groups who want to sort of pool their time, which we allow. So, if there are 20 people that want to address the committee, we allocate the time among those 20 and then three or four of them want to pool it together, they can have a joint presentation of, you do the math, instead of individual presentations. So, that is what we are ironing out, and so, so what have we got?

Marie Brown: Could we also look at this? I have had several requests for us to speak closer to the microphone and more slowly and clearer.

Craig Blackmore: Very good point. Everyone should speak into the microphone. Committee members, it is good to identify yourselves when you are speaking, at least the first few times. There will be a transcript of the meeting, and the transcriptionists need to know who is speaking. When, when members of the public, people are addressing the committee, if you could please identify yourselves, tell us if you are speaking as an individual or if you are representing some group, and please also tell us if you have any financial conflicts or if people paid to have your transportation or to have you come or whatever, and for the speakers, we have, we will tell you when there is one minute left, is that right? Margaret will, Margaret will let you know, and we are good to go.

Josh Morse: We are. So our, the first scheduled speaker is Shannon McDonald and, you have three minutes, please.

Shannon MacDonald: Good morning. I would like to thank the committee for their time in evaluating this therapy for our patients. I am a pediatric and breast radiation oncologist from the Massachusetts General Hospital in Boston, and I am going to focus on the treatment of breast cancer this morning.

Craig Blackmore: And, if you could, please, tell us if you are representing yourself or some group and if you have financial conflicts of interest.

Shannon MacDonald: So, I am here as a visiting professor at the University of Washington, which I attended yesterday, and then I am here today for this meeting funded and traveled by the University of Washington.

Craig Blackmore: Thank you.

Shannon MacDonald: So, for locally-advanced breast cancer, we feel that protons is appropriate for selected patients and as part of our group at MGH, we have met with ethic boards and others to figure out a way to appropriately select patients and one thing that makes breast cancer patients potentially, patients that are potentially to benefit from this treatment is that they live for a very long time, and they do suffer from late morbidities of radiation from breast cancer and more often patients with locally-advanced breast cancer who require treatment of the regional lymphatics have exposure of the heart and lungs to relatively high doses of radiation that have been proven to translate to cardiac morbidity.

So, areas of the heart that have been shown to be sensitive are the coronary arteries and mean heart dose has also been shown to correspond to late cardiac morbidity, and an article by Darby that was published in the New England Journal of Medicine in March of 2013 showed that for every gray of radiation therapy, there is an increase in major cardiac events, meaning MI, revascularization, or cardiac death of 7.4%, and that continues to go up with every gray of radiation. There is clinical data from our institution that shows a mean heart dose for protons is less than 0.5 gray meaning an almost zero increased risk of cardiac morbidity and other institutions for modern proton therapy for locally-advanced breast cancers show cardiac mean, heart mean doses of 5 to 16 Gy, which would translate into an absolute increase in cardiac risk of around 5% but a 50% increase in overall risks.

So, as part of the cooperative groups of proton therapy centers and sort of a consortium that we have together, we have applied for a PCORI grant to study this in patients and we are proposing a randomized trial of about 2000 patients where we will look at these patients to see if we will find a decrease incidence of cardiac morbidity for these patients.

This shows you the differences in photons versus proton. These two images show photon therapy on the left. The pointer is not working, and protons on the right. So, just demonstrating graphically the difference in cardiac doses and also pulmonary doses. Other potential benefits from protons may include a decreased risk of lymphedema due to the soft tissues that are avoided and a better coverage of the treatment volumes that we need to cover with this treatment.

So, in summary, the patients that we feel are ideal for this type of treatment are those with locally-advanced disease that require treatment after mastectomy or for breast conservation but regional nodal involvement. Internal mammary node treatment is not always included at this time, because of fear of cardiac morbidity, but there are two, two papers that will be published within the next

year supporting a survival benefit for IMN involvement. So, I think this is something we will see more of. So, these patients are exposed to anthracyclines and (inaudible) so cardiotoxic chemos. Additional cardiac risk factors have been shown to further increase the risk of cardiac disease and other patients that can benefit are those with permanent implants. Many institutions do not allow for a permanent implant to be placed prior to radiation, which is an impact on the psychological benefit to the patient, as well as costs. So, thank you, all for your attention.

Josh Morse: Next scheduled speaker is Don Denton. Is Mr. Denton here?

Christine Masters: No, Mr. Denton isn't. He left a letter.

Josh Morse: OK, Mr. Denton's letter is in your packet. The next is George Laramore. Dr. Laramore and others from the University of Washington have pooled their time for 18 minutes. There are six people here that are represented.

George Laramore: Thank you, very much. Just so I understand how everything works here. I would briefly appreciate the opportunity to talk to this committee about proton radiotherapy. As was said, we have pooled our time. I am George Laramore. I am the founding medical director for the proton center and a former chair of the Department of Radiation Oncology. I was intimately involved in bringing the proton center to the Pacific Northwest. The other speaker will be Ramesh Rengan who is the current medical director, and we originally had planned to have Jim Apisarnthanarax speak, as well, who is our GI radiation oncology specialist. Jim's wife had a baby last week, and he is otherwise preoccupied. I, nor anyone else on this slide, has any conflict of interest. The proton center is merely one of five sites at which we practice. We have no equity interest in any of the sites. It is entirely revenue neutral as to where we treat our patients.

Why protons? Why did we think it was important to bring this technology to the Pacific Northwest? This is a slide that I think you probably have in your report in one form or another. It is basically a physical dose distribution. The vertical axis shows the percent absorbed dose from radiation coming in from the left. The depth on the right is basically depth in water or in tissue. If the current technology uses high energy photon beams, Linac 8 MV and Linac 25 MV accelerator. The point is, if you are going to treat a tumor at about 20 cm depth and you want to give 100 units, the high dose close to the skin is over 200 units with an 8MV accelerator. It is interesting because we have also on this slide had a comparison orthovoltage. This means low energy x-rays. Orthovoltage was the first form of radiation that was used therapeutically, and you can see it is a substantially higher skin dose. The point I would like to make is, people shifted going from orthovoltage to megavoltage when it became available, not on the basis of any randomized trials but because the radiation dose distribution looked so much better with the higher energy x-rays and also the patients had substantially fewer side effects. There were not randomized trials that led to this advance.

Protons represent an advance further down the line in terms of dose distribution. Because of the physics of a proton beam, it does not deposit much energy until it gets near the end of its path, then it deposits a lot of energy. We squeeze this peak of energy through the tumor and we get this spread out red peak that is shown in red. The point is, we have a lot less radiation dose on the way in and the beam does stop abruptly so we have a zero exit dose. That means there is a lot less normal tissue being radiated.

A situation where this is particularly important is the pediatric population. There is a type of pediatric tumor called a medulloblastoma that arises in the posterior fossa or the cerebellum. This tumor spreads along the spinal axis. So, along with chemotherapy, we give radiotherapy to the spinal axis. If we are giving the radiation with photons, or x-rays, it gets the picture on the right with a lot of radiation dose going through. This can irradiate the heart resulting in cardiac toxicity. It irradiates the bowel so that the patient going through treatment has a lot of GI side effects. If it is a young girl, you are irradiating the ovaries, so you have ovarian dysfunction. You have similar advantages in treating the brain. You can spare the inner ear. You can spare a lot of the optic structures and overall, if you look at the complication rate, kids that are treated with photons have about a 40% improved incidence of overall complications. These are neurocognitive difficulties, cardiac toxicities, endocrine dysfunction, hearing loss, and a risk of second malignancies.

The slide with the curve on the right shows the incidence of in-field second malignancies for retinal blastomas. These are tumors of the eye. With x-rays, the incidence, overall, of getting a second malignancy is in the range of about 20%. These tend to be very aggressive malignancies, typically osteogenic sarcomas, essentially 0 with protons, and so we have implemented proton radiotherapy for the great majority of our pediatric patients with solid tumors working with Seattle Children's Hospital. We think that dosimetric studies, in comparison, are essential for clinical decision making. In fact, when we are discussing with insurance companies about whether protons are beneficial, we run a comparative plan. The best we can do with standard radiation, compare it with protons, look at the difference in dose to critical structures, and show this information.

We agree there is need for clinical evidence. As your study noted, clinical data is really lacking for many sites, and we take responsibility for that, as a community. In 8 of the 16 cancers surveyed in the report, there was really no evidence, an additional 7 of 16 had low evidence. I would point out that we are an academic center, and we are going to try to improve upon this. We are participating in a study called PartiQOL, which is a randomized trial of IMRT versus proton radiation for patients with low-risk locally-confined prostate cancer. This is a study that was started by the Massachusetts General Hospital and University of Pennsylvania. It is one of the studies that we want to join. As Dr. MacDonald said, there is a PCORI grant that is being out, and we are in the finalists in terms of consortium group. The idea here is to develop prospective clinical trials for common tumor situations. Breast is one. Post-prostatectomy

patients who have positive margins who have locally failed is another, and breast cancer. The clinical data, in terms of getting these for long-term results, because we are looking at normal tissue side effects, which often manifest themselves a decade or longer after were treated, means that we have to get these clinical trials started and we need support in order to follow these patients. Unlike the situation where there are pharmaceutical companies who have a lot of financial return if a drug is approved, that is not the situation when you are looking at a technology. So, we really do not have vendor support for these, these studies. We would like to see coverage of patients with the intent of gathering evidence so that a decade from now, we will not be having this conversation without having a lot of data that we can talk to.

What I would like to do now is turn the table over to my colleague, Dr. Ramesh Rengan who is the current medical director. Dr. Rengan will talk about some specific data on some common tumors, like lung and GI, and then talk again about the need for evidence development.

Ramesh Rengan:

Thank you, again, to the committee. I also have no conflicts of interest to disclose, other than my leadership position as the medical director of the proton facility. I am a faculty member at the University of Washington and an associate professor in the School of Medicine, as well as an associate member of the Fred Hutchison Cancer Center.

As an oncologist, as everybody in this group, perhaps, is aware, what we focus on when we have a patient come into our clinic is this curve here, and this is what the patient's also focus on, which is, how likely are we to control the cancer. How likely is our technique, whatever that technique may be, to sterilize the disease that sits in front of us, but one of the things that is often forgotten is this, which is the red curve, and this is, perhaps an even more important determinate of clinical outcome for the patients that we see in our clinic, and as a radiation oncologist, the sole contributing factor to this red curve, which is the toxicity that patients experience from the treatment that we deliver, is radiation dose to normal tissue. All of the side effects that we can attribute to radiation comes from collateral radiation dose that is being delivered to areas outside the tumor and it is intuitively obvious that what we want to do is minimize any dose deposited to the normal tissue and only deposit dose to the cancer and the differential ratio between the dose deposited to the tumor and the dose deposited to the normal tissue is really the primary determinate of survival and outcome. It is not simply about tumor control, and so if we try to intensify our therapy, there is no such thing as absolute resistance to radiation. If I give a high enough dose of radiation, I can sterilize any tumor, but the problem is, I need to do that safely.

So, treatment intensification, although that is the primary technique and intervention that is available to us as a radiation oncologist to improve control of disease, only works if it comes with a commensurate widening of that therapeutic ratio, and if it doesn't, we are not going to improve survival. So, if you look at a patient with lung cancer, the ratio is probably more like this. It is

very, very narrow. We have a very narrow therapeutic window for these patients. So, although we do a very poor job of controlling our tumor, lung tumors in particular, with radiation, the approach of treatment intensification may not be an effective strategy because we are not able to widen our therapeutic ratio and we put this to the test as a thoracic oncology community in that we initiated a phase-three randomized trial in 2006. It is not yet published, but the results are known. They have been presented in multiple venues where we randomized patients between the standard dose of radiation that was established in the 1970s, which is six weeks of radiation with concurrent chemo for a patient with locally advanced nonsmall cell lung cancer and then we felt we could do better with modern radiation techniques, such as IMRT. Give a higher dose of radiation, 74 Gy, so almost seven and a half weeks of radiation with concurrent chemo, and we felt this is going to yield an improvement and outcome, and they actually stopped this trial early without allowing it to continue, because there was a difference between the survival curves. The unfortunate thing was, it was a detriment. There was a detriment to giving the higher dose. So, they had to stop the trial because it was unethical to continue, because it had crossed a futility boundary. So, delivery of the higher dose of radiation not only did not improve outcome, it was detrimental to survival, and again, that is because we narrowed the therapeutic ratio with our treatment intensification strategy, not widened.

Now, one of the trials that you have in your evidence report is the Phase 2 trial from MD Anderson where they delivered that exact same high dose of radiation, except with protons, and in the Phase 2 setting, alright, it's not a Phase 3 setting, but in the Phase 2 setting, they saw a very different survival number, 29.4 months versus the 19 months, which was seen in the Phase 3 randomized trial with x-rays being delivered to that same dose.

So, there is, at this point, no clear way out with x-rays to improve outcomes in lung cancer patients. We cannot really improve upon the dose that we established back in the 1970s. We tried it, but there is no clear way to improve outcomes. Protons may allow for these narrow therapeutic window tumors a way for some patients to improve outcome, and that is a common theme that you are going to hear again, and how do we test that? We have to test it in a randomized fashion and we, as a proton community, have initiated with the cooperative group infrastructure, a randomized trial of IMRT versus protons for exactly these patients, locally-advanced nonsmall cell lung cancer patients, comparing protons versus photons. This trial is something that we want to open at our center, but this trial will not move forward unless we have payer support. That is the only way we can run these clinical trials, and that is different than the way drug company trials work. With technology, we cannot run these trials unless the insurance provider is willing to pay for the patients to receive their treatment, and so that is why this committee has a powerful opportunity to provide support for the very clinical evidence that they say is lacking, which we completely agree is lacking. It cannot happen without payer support.

There are also patients in whom I cannot treat with x-ray, patients in whom photons are contraindicated. One example of a class of patients in whom we do not have suitable solutions with x-rays are patients who have had prior radiation. So, re-irradiation comes with all sorts of risks and most radiation oncologists will not re-irradiate unless they are really pushed, but this is an emerging patient population. You are going to hear from one of those patients later today. This is an emerging patient population, because we are actually getting better at controlling disease systemically. So, when we get better at controlling systemic disease, local progression becomes a bigger problem. So, once you've radiated and then the disease progresses locally, what do you do? Well, you could operate, but that is fraught with risk, or you can re-irradiate, but that also has challenges, and this an area, a niche area, where protons actually can potentially come in. There is an example of a patient who had an infield recurrence of their sarcoma, and we tried to deliver, come up with a plan to deliver a high-dose conformal radiation with x-rays, we could not achieve a plan that was deliverable, because the dose to the bowel was going to be too great, put the patient at too much risk for complications, but with protons, we could treat. This was not a patient who could be salvaged with surgery. They had an inoperable recurrence. So, they had no therapeutic option outside of proton beam radiation, so we did, and this is an emerging patient population, and this is something that the report is silent on, at least at this moment. So, we would encourage you to consider classes of patients in whom x-rays do not even offer an option.

Brief discussion about GI tumors, very similar to lung tumors, very narrow therapeutic window because the treatment that we deliver is not terribly effective, and it is very toxic. Side effect rates are very high. So, even with the fittest pancreatic or rectal or esophageal cancer patient, our likelihood of complications are high, 30-50%, severe complication rates with x-rays, and we are talking about complications to vital organs, such as the lung. So, we have to be very mindful of that when we pick a patient and this is an example of a dosimetric comparison that we would do to pick what the best treatment would be for a patient. For example, esophageal cancer, you can see clearly here when you compare protons to 3D conformal or even modern IMRT based x-rays, you are able to exclude a lot of normal tissue. Again, the red curve. You are able to exclude a bout of normal tissue from being irradiated, and this is intuitively something that we feel will benefit a patient.

So if we look at the data, the Phase 2 data from MD Anderson shows that the heart and lung complication risk with protons was lower than benchmarked historical controls with what we see with x-ray, about 50% lower, but again, that's Phase 2. The next step is a Phase 3 trial, and that is being opened, and that is also a trial that we want to participate in. Again, we cannot do that without payer support.

So, there is, we completely agree that clinical data is lacking, but we want a way forward, and I think that this committee has within its power to help us find a way forward to provide that data and as Dr. Laramore said so eloquently, so we

are not having the same discussion ten years from now saying why aren't, why isn't there data? So, in conclusion, what we would, with all humility, suggest to the committee here is that we would recommend that we tie in payer support to obtaining clinical data, and that gives us a path forward, and so we would recommend extending payer coverage policies for patients who are enrolled on clinical trials, enrolled in prospective outcome registries so then we have this covenant that we are going to get the clinical data that we say that we need. We also would suggest that it was, we agree that clinical data trumps dosimetric data, but dosimetric comparisons is a fundamental component of radiation oncology clinical practice. That is the way we make clinical decisions in the, in the clinic. When I see a patient, I come up with two or three different radiation plans, and I pick the best one. So, we would suggest that where the clinical data is lacking, it is appropriate to include dosimetric studies, which were excluded from this report. We think dosimetric studies are important and frankly, pediatric tumors would not be treated unless we believed in dosimetric data with protons, and we would suggest that for tumors with narrow therapeutic windows, such as lung and GI, that the committee considers offering greater recommendations for coverage with protons, because we do such a poor job with x-rays. We need a way forward for these patients.

Finally, the patient populations in whom we cannot treat with x-rays, patients who had prior radiation, whose a re-irradiation patient, patients who have hypersensitivity syndrome, such as Crohn's, ataxia, telangiectasias, these are patients in whom x-ray radiation is completely contraindicated because their likelihood of side effects are very high. These are small patient populations, but these are patient populations who are real who, when they have a cancer, we don't have an option for them and protons offer a way out because it allows us to exclude normal tissue to a greater extent. So, these are the modifications and the suggestions that we, as a faculty, make to this committee for your consideration. So, I thank you very much for your time.

Josh Morse: Thank you. The next scheduled speaker is Ralph Ermoian, and Dr. Ermoian has three minutes.

Ralph Ermoian: Great, thank you. Thank you for the opportunity to address your committee. My name is Ralph Ermoian. I am a radiation oncologist. My board certifications are in radiation oncology and general pediatrics. I practice at Seattle Children's Hospital, the University of Washington, and at the proton center and so, my, if I have a conflict of interest it is because part of my practice is up at the proton center.

I am going to briefly address the, some of the applications of proton radiation therapy in children and the particular benefits. Dr. Laramore nicely covered an example just like this in the patients who have medulloblastoma, essential nervous system disease, need radiation to their entire craniospinal axis. This is actually a Washington resident who I treated last summer, and compared on the left her, the treatment that she did receive versus if she had to receive photons, which she would have received, and one can see the dose distribution

is that the radiation stops in the targeted area with the proton plan and continues to go forward with a photon plan if she had to received, but I want to emphasize in growing children whose organs are not developed is that there is absolutely no therapeutic reason why a patient should receive radiation to her heart, to her ovaries, to her lungs, to her intestines in patients like this. The only reason the radiation continues to go there is because with conventional radiation we do not have a way of stopping it, but with protons we do, and there are good studies looking at dosimetric studies, as well as case series, supporting the benefit with respect to the heart, the ovaries, thyroid, lungs, and breasts, all of which I included in some of my submissions to the committee earlier this year.

There is also data supporting the cost benefit in children of craniospinal radiation. This fairly busy table is an important summary of looking at specific complications that children can experience after receiving craniospinal radiation, the probability of them receiving, of that risk and the difference in ultimate cost, if they were to have that complication versus considering the reduction of that risk with protons compared to photons, and there is a dramatic reduction in lifetime healthcare costs associated with patients who received proton radiation therapy for diseases, such as medulloblastoma.

The additional slides I have essentially summarize similar findings. The one that I want to highlight is this last one with craniopharyngioma tumor in the middle of the head. For a young, developing child, the greatest concern that I spend a lot of time talking to families about is longterm neurocognitive effects, and when we look at this chart that projects the longterm neurocognitive effects, there is a substantial difference between the neurocognitive effects of a child treated with protons versus with photons, and that is a separation in longterm IQ that will only widen over time that will have dramatic effects on quality of life, as well as longterm function of the patient over her lifetime. The last two things that I would mention, as a pediatric radiation oncologist, are one that before we had protons in the northwest, I sent my patients for protons and that often that meant having to travel to Texas, to Massachusetts General, other places because I believed in it so strongly.

The last thing I would say is that the children's oncology group is the main national organization for doing research and in all their trials, there are no randomizations between protons and photons. They basically say if you can receive protons, it is considered equivalent, and patients can receive it. Thank you.

Josh Morse: Thank you, Dr., I'm sorry, Dr. Ermoian. So, next is, next scheduled presenter is Eugen Hug, and if you could please state any conflicts and where you're from, thank you.

Eugen Hug: Yes, thank you, committee. My name is Dr. Eugen Hug. I am currently the chief medical officer of ProCure Therapy Centers, and as such, I am salaried by ProCure by a proton developing company, but I also speak to you on behalf of

the Particle Therapy Cooperative Group of North America whose president I am, and maybe more importantly, I speak to you as one of the longest serving radiation oncologists actually worldwide in particle therapy. I'm, I'm treating patients with protons for 21 years now. Next slide, please. Oh, I'm sorry. I guess we do those, sorry. Which one is it? Alright, thank you, I'm sorry.

OK, I guess we are all sort of trying to, trying to make sure we drive home the same points, as to where we are with protons and what a relief it can be if only we will have the continued support. That is really why we are here right now. So, we all, the central paradigm of radiation oncology always has been increase the dose to tumor and decrease the dose to normal organs. This has been pointed out by my previous speakers here, and the entire history of radiation oncology is really exactly that, going from two-dimensional treatment to three-dimensional treatment, now to four-dimensional treatment and as such, we have always accepted the technology that delivers less radiation to normal organs while focusing dose in the tumor is the superior technology. That's the paradigm of our subspecialty and one can actually stipulate that proton therapy is the next evolutionary step in this process. This does not mean that protons are the panacea in radiation oncology. No one has claimed that, but we do believe that it represents actually a very important next step and it is upon us, upon here the center, for example, at the University of Washington centered in Seattle, as well as worldwide, to now crystallize the subgroup of patients who will have the clinically-meaningful benefit from this new modality.

Here again, showing you, hopefully, the importance of actually preclinical dosimetric studies. On the left side a patient with breast cancer with a proton dosimetry plan, on the right side with conventional photons. The little dots there, the circles there, are the coronary arteries. As you see, there is the majority of coronary artery simply do not receive radiation dose. You cannot have a radiation injury if you do not deliver radiation dose. That again is, is very much a very clear paradigm. Now, what you can do is, you can subtract the, you can subtract protons from photons and then you get, all this is the unnecessary radiation delivered with conventional radiation.

In the remaining time, though, just to tell you, where do we all, where are we worldwide. We are worldwide at this exponential uptake of particle therapy. Many indications, we actually have only started very recently, but there is a bonafide tremendous effort, worldwide, of the entire particle therapy community, that I do not see paralleled in history, not the history of IMRT, not the history of brachytherapy, to truly evaluate our, to evaluate the efficacy, the safety, exactly what you, what the, the components that are your mandate with the clinical trials, and therefore, I believe that indeed with the proton community is doing a bonafide effort, but it only can do that with economical support and very importantly, begin to state that I do believe it is very difficult to say that you can, you can actually judge an emergent, emerging technology by the evidence of mature data, clinical data. That, in itself, I just do not see how that is possible, and I think this is very evident actually in some of the, in some of the documents. So, again, our plea is give us this time that we need

this next couple of years worldwide to gather the evidence, but as it has been pointed out, it cannot be gathered without support. Thank you, very much.

Josh Morse: Thank you, Dr. Hug. The next scheduled presenter is Robin Baird.

Robin Baird: Good morning. My name is Robin Baird, and I am here today as a person whose battling cancer. I am also here on behalf of thousands of others who will face this disease in the future. The recommendations made by this committee will have a significant impact on our lives and our access to cancer care. I was first diagnosed with Stage 2 breast cancer...

Craig Blackmore: Ms. Baird, I'm sorry to interrupt, I really am, but could you please share with us if you have any financial conflicts of interest?

Robin Baird: Oh, I'm sorry. I do not have any financial conflicts...

Craig Blackmore: Alright.

Robin Baird: ...of interest. I was first diagnosed with cancer in 2001, and after successfully treating my tumor with surgery, chemo, and photon radiation, I thought my journey was complete, but it wasn't. In 2003, 2005, 2007, and 2011 my cancer, breast cancer returned. Because of the many chemotherapies, surgeries, and two courses of photon radiation, my options were severely limited, and my body really couldn't take any more surgery or anymore photon radiation. Upon review, those things were ruled out as treatment and I only had, and I had already used all the chemo available. I was referred to Dr. Rengan for proton therapy as my only treatment option, and I'm personally thankful I was able to pursue proton therapy, and my insurance plans were able to cover most of the cost of my treatment. If not, I would have had to face a devastating choice, use all of my financial resources to pay for additional radiation or not receive radiation at all and allow my cancer to grow.

When people purchase insurance, they expect it will cover for most of the cost of treatment. I believe it is wrong for insurance companies to decide what form of treatment is right for any individual. That's at the doctor-patient decision. If the current Health Care Authority findings are used as guidance for insurance coverage policies, insurers will have reasons to die, deny proton therapy for cancer without considering each person's unique needs, and I am very concerned that the current written assessment on proton therapy would not support my future treatment plans.

Taking proton therapy was my only option, and it is very concerning to me that future cancer patients with similar or special circumstances will not have access to the care they need. The current assessment fails to recognize that proton therapy may be the only option for some patients because of their unique circumstances, prior treatments, and specific needs.

In closing, I ask that the Health Care Authority report recommend that each patient's unique circumstances be considered by the insurers and that they be directed to provide coverage for proton therapy when medically recommended. I am doing well today because I received this proton therapy as part of my care, and I hope by modifying your recommendations, you allow patients, like me, to have access to the care we need to battle this terrible disease.

Josh Morse: Thank you, Ms. Baird. We have one more scheduled comment, Norman Hubbard, and if you could please state where you are from and any conflicts of interest, thank you.

Norman Hubbard: Sure. Good morning, my name is Norman Hubbard. I am executive vice president of the Seattle Cancer Care Alliance. We are a 19% owner of the proton center up at Northwest Hospital. My perspective is not as a medical expert. You heard from the clinicians and the scientists, and from a patient about the importance of proton therapy. I respect the challenges of what you are doing. It is important socially to be looking at where we can begin to control healthcare costs and assimilate new technology. The difference in this instance is, protons is an emerging technology, as you heard. The SCCA is owned one-third by the Fred Hutchinson, University of Washington, Children's Hospital. We are the NCI cancer center for this region. Our job is to develop the evidence that you need to do your job well, and in the cases where the evidence does not exist, if we do not have the ability to treat patients, as you have heard, we cannot develop the evidence. So, there are many cases where a decision to say, gee, there is not a clinical trial that supports this would simply cause us not to be able to advance the research. So, in hematologic malignancies, two-thirds of our patients are on clinical trials, two-thirds, and many of those are Phase 1 and Phase 2 trials. So, if the standard is, gee, where is the randomized clinical trial, we would not be able to see patients or do that, and these are patients that are covered on Medicare and covered by insurance companies. So, we need them to have access to this care. It is not the case that all patients should receive proton therapy. Nobody is asserting that. It is clearly the case that some do now, and it is probably the case that some will need to more. That is changing so rapidly, I do not know how you can responsibly make a decision and have it stick for 18 months where you can come back and look. This is changing day by day and week by week in terms of what matters, and we are the ones who need to develop that evidence. If we do not have the ability for our patients to get access to the therapy, we will not be able to develop the evidence and it's, it's just (inaudible).

The one interesting that you have heard about the, reducing the dose of radiation therapy, we started looking at protons in 2006. We had experts from around the country come and talk about this. Trust me, there were different points of view around whether this made sense or not. We had experts from within the University of Washington and The Hutch, and Children's, all over the country. There were pros and cons to this, for sure, and we did not go into it lightly, understanding that, that this was something that had to be developed and understood over time. Fundamentally, our goal is to advance therapy and

make this available to patients responsibly and a cost-effective way. If you use the example of IMRT, which is the radiation therapy, which is pretty common practice. In the year 2000, IMRT did not exist. There was 3D conformal, which was felt to be pretty good. There are no randomized trials, still I think, actually, that proved that IMRT is better than 3D conformal. It is all volumetric, right? So, the standard for advancing cannot always be a clinical trial. I, we agree it is best, but it is not always going to be the case that a clinical trial is best. So, our plea is to look at the evidence, hold us accountable for being the people who develop the evidence, but to develop the evidence that you want and that you need, we need patients to have access to the therapy as it is being provided, and we will do that responsibly. I appreciate your consideration.

Josh Morse: Thank you. That concludes the scheduled comments. We do have a signup sheet. It is now in my hand. We will go to this sheet for people who signed up today. There is one signup. His name is David, is it Shepard?

David Shepard: (inaudible)

Josh Morse: OK. So, we will check the phone.

Craig Blackmore: Was, was there anyone who wanted to talk to the committee that did not? OK. OK, if you could please, again, tell us who you are, who you are representing, if anyone, if you have any financial conflicts of interest and we will have you sign in at the conclusion, just so we have that information.

Josh Morse: I apologize for...

Craig Blackmore: No, that's alright. We, it's a process, but, please.

Vivek Mehta: My name is Vivek Mehta. I am a radiation oncologist at Swedish Cancer Institute here in Seattle, Washington. I practice clinically. I am also the director for the Center of Advanced Targeted Radiotherapies at Swedish. I submitted that conflict of information form to Christine online. I work at Swedish. I have a research program, but we have no conflicts, as it relates to proton therapy.

As you know, the Swedish Cancer Institute is the oldest cancer institute west of the Mississippi. I don't know if you know, but we are 77 years old. We have a long track record for innovation in radiation oncology having done clinical trials, developed programs, doing clinical research. Years ago, we were approached to bring protons to the city of Seattle with Swedish, OK, the same organization that brought the protons to the University of Washington. It was a private investment group, and the proton project was in excess of 100 million dollars. When you look at the number of patients that needed to be treated, we could not find justification within our system to support that investment at that time. We are not anti-innovation, but we could not justify that based on patient numbers. We made the decision that we did not want to go into bed with financial people or investors who had a profit motive whose position was that we could market, we could do direct media advertising, we could draw business

in to treat patients. We wanted to treat them appropriately. So, we made the decision at that time not to move forward with protons. Today, as I fast forward, Swedish is now part of a 35-hospital system that spans from Anchorage down to Los Angeles over to Idaho and Montana. We are an enormous system. In the Northwest, I believe our market share is nearly one-third. We are taking a thoughtful approach to protons. We are interested in proceeding with a second generation proton technology that comes at a much lower price point, a price point that would allow us to treat just from our own patient population in Seattle, less than 10%, and still break even. We will only treat the patients that we have evidence to treat. We actually support the report that you have all read, that there are certain patients that are appropriate to treat and those are the patients that we intend to treat within our system. I want you to know that where I sit, we want to treat patients appropriately and we are seeing patients. We are treating cancer patients, and we have a strategy that we think is thoughtful for where protons fit in.

That is sort of my background. So, I am both one, sitting in a group of people who decided not to do protons initially but an incredible advocate in our own system for this next generation technology that will allow us to do it at a lower cost and an advocate for evidence-based medicine. One of the things that you heard is that it is important to do clinical trials. One of the things that you heard is that sometimes when you do clinical trials, you find results you did not anticipate. We anticipated that higher doses of radiation in lung cancer would have improved outcomes. Unfortunately, that did not occur. Before we embark on marketing to patients or treating patients, we need to do the data that actually shows us what works and what does not work. I totally support randomized clinical trials. We run a large clinical trial program at Swedish. What's important is, that we do the randomized trials that allow us to prove that benefit. So, we support that, as well. Thank you, for your time.

Josh Morse: So, we will check the phone. If there are no other commenters here. So, we are in the public comment period for the proton beam therapy topic. Is there anyone on the phone who would like to provide comment? Thank you.

Craig Blackmore: Alright, that closes the public comment period, and will move on with the next item on the agenda, which is the Washington State Agency Utilization and Outcome.

Dan Lessler: Thank you. My name is Dan Lessler. I am the chief medical officer at Washington State Healthcare Authority, and I am going to be presenting on behalf of the agency medical directors.

So, I think actually a lot of the background I have has already been, been well covered by people who are, are much more expert than I am in, in radiation therapy to be sure, but I think, you know, really what this slide sort of does is, is summarize, I think, the intent of, of trying to deliver higher doses of radiation to the tumor with less dose to surrounding tissues and certainly that, that has been the quest, I think, of people in the field and now proton beam therapy is

being considered because of its theoretical advantages and these have been well described, as well, that protons deliver most of their radiation to the tissue of interest and the potential that normal tissue surrounding a tumor is, will not receive radiation and hence have the benefit of fewer side effects. This is, I think the committee is going to see this again and again and again, 'cause I know it will come up in the ICER, the ICER Report. This is just sort of, again, underscoring the theoretical considerations of proton beam.

I think, I think it is also important to point out, as the last speaker was alluding to, that while there are certainly theoretical reasons that proton beam can and should benefit, there are also a number of uncertainties, and these are, these are well called out in ICER Report, and, for example, there is uncertainty around the end of the dose range when you are talking about deep-seated tumors. There is possible concern around lateral spread, and the fact that protons are sensitive to tissue heterogeneity, as they move through tissues.

There are also concerns around production of neutrons and what effect they might have, although this is debated and the relative biological effectiveness of protons in relation to photons. So, I think this really underscores the importance of what everybody has been talking about here today, which is the need to develop real clinical evidence around effectiveness and safety, and also I think it points out that one needs to be careful when, sort of deciding purely on the basis of theoretical considerations.

The key questions that were addressed to ICER, which the committee asked to be answered, are here. The comparative impact of proton beam with curative intent on survival, disease progression, health-related quality of life, and other pertinent outcomes versus radiation therapy alternatives and other cancer-specific treatment options. The comparative impact of salvage treatment with proton beam versus other major alternatives on survival, disease progression, health-related quality of life, and so forth, and then likewise comparative harms, as described here.

Further key questions included the differential effectiveness and safety of proton beam according to factors, such as age, sex, race/ethnicity, and cost effectiveness of proton beam.

The cancers that were reviewed are listed here, well known to the committee, and then there were several noncancerous conditions that were reviewed, as well.

The agency medical directors' concerns going into this were related to safety, were medium but again, because of the potential theoretical advantages of proton beam, really concerned as to whether or not these translate into actual clinical benefit. With respect to efficacy, a high level of concern, and with respect to cost, a high level of concern, as the costs of proton beam is up to two times the cost of standard treatments that are currently available.

So, in terms of the ICER report, sort of high level, there was insufficient evidence for eight cancers to evaluate the net health benefit versus comparators. Those were breast, esophageal, GI, gynecologic, lymphomas, sarcomas, seminomas, and thymomas, and for pediatric cancers, there was one poor quality study and really the other information or data that was presented were all based on decision analytical modeling techniques.

With respect to cancers that appear to have a potential benefit, ocular cancer, there was a moderate strength of evidence that there was improved outcome with comparable rates of harm, and for brain, spinal, and paraspinal tumors, there was a low strength of evidence. We concluded that there was equal outcome with possibly less harm. Then, with cancers with comparable treatment outcomes included bone, head/neck, liver, lung, and prostate.

With respect to noncancerous conditions, there was insufficient evidence with respect to AVMs and other benign tumors and comparable treatment outcome with respect to hemangiomas. The current state agency policies with respect to coverage of proton beam are shown here. Across the agencies, this is on prior authorization, and it is essentially this is considered on a case by case basis at this point.

This is in the public, for the PEB, the public employee's benefits, numbers that have had proton beam treatments over the last four years, and you can see the total number here is 20 and you can see the attendant costs, as well, and this, actually, is an interesting slide. It is somewhat busy but I think what it, it is just describing the types of cancers that are being, that have been treated over the last four years and the relative numbers, and you can see that actually the largest numbers have been in prostate and, and then the smaller numbers in terms of eye, brain, and so forth.

Until relatively recently, as has been mentioned, as well, PEB has sent those who have received proton beam therapy out of state to receive this therapy at various institutions across the country, and this is a description of where those patients have been sent. Obviously, this is changing now that there is the center here in Seattle.

So, in summary, as we look at it, the available literature that looks at the comparative effectiveness and safety of proton beam is limited and generally of fair to poor quality. The available evidence suggests that proton and photon treatments are either equivalent or the benefits of proton therapy are uncertain, and any theoretical advantage comes at double the cost of available covered alternatives, so, quite expensive. Evidence for proton beam is possibly superior is best for ocular tumors and studies of proton beam in pediatric populations with cancer are especially lacking.

This is just a sampling of coverage, as provided by a number of different commercial payers, and I think this is best summarized as saying that it tends to be, as is often the case, in my experience, where there is limited evidence, it

tends to be quite variable across all the different payers with respect to a sampling of some different cancers.

With respect to CMS, there is no national coverage decision on proton beam. There is a local coverage determination that covers proton beam in the following circumstances; for those with life expectancy greater than two years, unresectable benign or malignant tumors of the central nervous system including glioblastoma, acoustic neuroma, and AVMs, intraocular melanomas, pituitary neoplasms, advanced unresectable tumors to the head and neck, malignant tumors of the paranasal and other accessory sinuses, unresectable retroperitoneal sarcoma and solid tumors in children. I think I just, so with respect, as we look at this and what our recommendation would be as the agency medical directors, we would cover for ocular tumors. We also would recommend covering in pediatric populations, undergoing treatment in the context of evidence collection. I would say I think that, obviously as has been discussed, the pediatric population is particularly complicated in terms of, at least in our conversations, about making a decision. I think that there is, obviously, a strong consensus in the medical community that ICER points to that pediatric population should be covered, and I think one could argue that the theoretical considerations that are present really across patient populations are most salient in this population, as others have already spoken to.

With respect to the, well, excuse me? This is the wrong, it is not the, it is not the right presentation. The, what I can, the essence of our recommendation is that for the remainder of the tumors, we would, our recommendation is not covered, that there is not adequate evidence, and we are very sensitive to the fact that, and I think we all would like to see better treatments for people with very serious illnesses, but as we look at the available evidence, and as we look particularly at the extraordinary cost relative to existing available treatments, we come down on a decision or a recommendation that these be noncovered.

If the decision of the committee is to cover under, for one or other or a number of conditions, our recommendation would be to cover it in the context of evidence collection. I think one other comment that, in our conversations along this line, along these lines that came up is just who should pay. Really, I think part of the question comes down to here, for your decision making, is who should pay for the evidence collection. Who should pay to have this work done, and I think we would just, we would just point out that there is quite a bit of investment that goes into constructing these centers and it would seem to us, as we look at it and we consider how to pay for the needed clinical trials, that one would also want to look towards the money that goes into investing and building these centers and how it might, or some capital might be used to help finance the necessary studies of effectiveness. So, we just, we just would want to make that point. So, with that, I will stop and see if there are any questions.

Craig Blackmore: Questions for Dr. Lessler from the committee?

- Richard Phillips: I had a question for Dan. The, you have only had a few patients who have been in, paid for by the state. Have those been part of investigational studies or?
- Dan Lessler: Rich, you know, I know the ones, what I can say is, the cases that I have approved have all been in the context of registries. I cannot speak to all of them.
- Chris Standaert: I had a question. So, I mean, I, in general this committee has always wanted evidence, and we have always been very supportive of the idea of people receiving technology we are discussing being part of studies and receiving that technology so we can get data at some level, but it always comes down to the idea that it, I mean, the agencies already have the prerogative to cover procedures in the setting of a clinical study regardless of what we say. Even if we choose not to cover, you still can cover under a clinical trial. I don't know if we have really mandated that you do so, because we assume that you can, and we heard a number of comments about this. Have you been approached by organizations within the city to cover patients under clinical trials?
- Dan Lessler: No. There's not, you know, not in any organized fashion.
- Chris Standaert: OK.
- Joann Elmore: I had a question about the utilization data. Looking at 2009 to 2012, you look at the average paid per patient, it's quite a variable amount there from 96 down to \$18,000 and as I look at the slide below, it looks like the usage of the procedures is fairly similar in 2009 to 2011. I'm just curious why that 2011 is so different, do you know?
- Dan Lessler: I would have to actually defer to Margaret. Do you?
- Joann Elmore: It is slide 17 I'm talking about.
- Margaret Dennis: We, we could speculate that might have something to do with the year Regence took over the PEB plan.
- Joann Elmore: We just reimbursed a lot less for the procedure, or?
- Margaret Dennis: Oh, and the number of treatments, because it is such a small data set, the number of treatments per patient is widely variant.
- Richard Phillips: Perhaps this is a question for Margaret. Did you have any idea of what the costs would be if you used IMRT versus proton therapy?
- Margaret Dennis: I don't. I believe it might have been addressed in the ICER report, though.
- Richard Phillips: Well, yes, I was wondering if the state had, if you had been able to determine that on your state data.

- Margaret Dennis: We actually provided the data to ICER.
- Richard Phillips: Oh, you did? Oh, OK. Good.
- Margaret Dennis: It's in the, it's in the report.
- Richard Phillips: Oh, yeah, you're right.
- Craig Blackmore: Well, thank you, Dan. We will obviously have more opportunity for discussion. It is 10:00. Let's take a 15-minute break and resume at 10:15.
- Alright, I am going to ask the committee members to take their seats, and we will resume our meeting. Alright, we are going to call the meeting back to order. Before we go on with the next presentation, excuse me, I want to take the opportunity to introduce our clinical expert. At the HTCC meetings we, because the committee members themselves may not all do or be involved in the technology under assessment, we always have a clinical expert who is here to advise us and to participate in the discussion and so I will introduce Dr. Lia, and I am going to struggle with pronunciation, how...
- Lia Halasz: It is Lia Halasz.
- Craig Blackmore: Halasz, OK, and if, if I could, I am going to have you introduce yourself, but, just to speak for a minute about the role of the clinical expert. Your presence here is incredibly valuable, because we, again, are not technical experts on this technology. We do not have a specific presentation that we ask you to make, but we will, throughout our discussion, have, I am certain, numerous questions about the different technical aspects. So, we will call on you at periods of time during our, during our deliberation. So, thank you for being here, and if you could give us just a little snapshot about yourself and also, again, if there is any conflict of interest that we should be aware of.
- Lia Halasz: Sure. My name is Lia Halasz. I am an assistant professor at the University of Washington and the department of radiation oncology and also neurological surgery. I have been on faculty there for three years and prior to that, I did my training at Massachusetts General Hospital. So, I have had experience with protons for the past eight years. Oh, and I do treat about 20 to 25% of my patients, depending on the condition, at the proton center here in Seattle.
- Craig Blackmore: And no, no financial conflicts?
- Lia Halasz: No financial conflicts.
- Craig Blackmore: Thank you, and then Dan, we will turn to you.
- Daniel Ollendorf: OK. I suppose I should make a disclosure myself. So, I work at the Institute for Clinical and Economic Review, which is under contract with the Washington

Healthcare Authority to produce evidence reviews, and so we were tasked to produce the evidence review for this topic. I have no other conflicts to disclose.

So, just to provide a brief overview of what I will be talking about, we will go over the scope of this review, the comparators of interest, the outcomes of interest. We will talk about our findings from our systematic review of the published evidence. We will talk about published evidence on comparative value, as well as the straightforward budget impact model that was alluded to earlier. We will provide our view on the ratings of the evidence and then summarize what authoritative clinical guideline statements have said and payer coverage policies, and then wrap it all up.

So, here is that “Bragg Peak” again. So, protons have actually been in clinical use for more than 60 years, and we have already heard a lot of detail about the clinically-appealing physical attributes of the use of protons in comparison to traditional photon beams. So, I am not going to belabor the point, but essentially the focus of attention has been on that lower radiation dose at body entry or at shallow tissue depths, as well as the lack of an exit dose due to the “Bragg Peak” phenomenon.

So, because of this, there was widespread and early adoption of proton beam therapy in pediatric cancers because, as you heard, kids are more sensitive to radiation at low or high doses, in fact. The issue of secondary malignancy is particularly poignant with children, because they are treated so early in their life, and they have potentially longer life expectancy, and for those latent effects and they are also the potential impacts on neurocognitive and other development. There was also adoption in relatively rare cancers that were located adjacent to or on very critical anatomic structures, brainstem, the eye, the spinal cord, because again, this concern about treating effectively in terms of tumor control while sparing those critical anatomic structures from nonessential radiation.

So, because of that relative rarity of those cancers, even pediatric cancers, I believe the total incidence of solid tumors in children is less than 10 per 100,000, for a very long time there were just a few facilities in the U.S. So, as little as ten years ago there were fewer than five that were treating patients. Really, only two that were treating patients at any significant volume that would have been the Harvard/Mass General facility in Loma Linda, but there has been more recent use in more prevalent cancers, as you have heard a bit about, and so there are now fourteen facilities online, eleven under construction nationwide, and even more in development. So, things have grown exponentially.

So, there is a lot of clinical enthusiasm, but again, as you have heard, chiefly through Dan’s presentation, there is some uncertainty around the use of proton beam therapy. So, what happens at the end of that dose range is a little uncertain, especially for deep-seated tumors like the prostate. There is a ‘penumbra’ or a blurring of the beam edge that forms at the end of the beam

range, as well, and its effects on normal tissue is uncertain. There is debate about whether the neutrons produced by proton beams have a deleterious effect, as well, and the lack of precision and estimates of relative biological effectiveness, so, essentially the ratio of tumor control with one form of radiation over another. There aren't very many estimates, because there is a lack of comparative data, as we are going to talk about ad nauseam over the next few minutes.

So, that is really where that comes from and, in fact, proton therapy has continued to evolve, as well, across this time period. So, as you heard, there is 3D conformal radiation that was replaced by IMRT, so increased precision and less radiation to normal tissue with photon therapy, as well, and so how proton beam compares to the latest standard of care with photon therapy may be uncertain in some areas, as well, but we explored that. And then concerns about cost. Certainly, an increasing issue with all kinds of technology, and this is no exception.

So, this image is a picture of a treatment gantry at a proton facility. So, in terms of what patients can expect when they undergo proton beam therapy, there is an initial treatment planning and simulation session to try to understand how the dose will be delivered for a particular patient. Patients receive treatment in daily fractions. So, every weekday they will go into the facility and be treated. The treatment duration can be 15 to 60 minutes per session, depending on the tumor type, and patients can be treated for up to eight weeks. The risks of proton beam therapy include systemic side effects, nausea, fatigue, side effects specific to the anatomy being treated, and secondary malignancy. I should note that this is not just a series of risks for proton beam therapy, it is a risk for any form of radiation therapy.

So, this just lists the chief radiation alternatives that came up in the evidence review that we conducted, and there is a column with the approximate cost based on Medicare reimbursement levels for these technologies. IMRT and 3D-CRT we already spoke about. Brachytherapy, which is used for certain tumors, is an actual procedure that involves implantation of radioactive seeds. Stereotactic radiosurgery is a slightly different form of external beam therapy that involves computer modeling and simulation to deliver radiation typically in a smaller number of fractions than other external beam modalities. It goes by trade names like Gamma Knife for brain cancer, CyberKnife for prostate cancer, etc., and then proton beam.

So, you have actually already seen these key questions. I don't know if I need to go through them in any further detail. We focused on treatment with curative intent. So, primary treatment in key question one. We focused on salvage treatment, treatment for recurrence that would have included any comparative studies involving re-irradiation, which was alluded to in earlier comments, in comparison to other alternatives. We focused on comparative harms, and we will go through some details on how we categorized those harms in a bit. A subgroup question that we were always asked to consider whether there is any

evidence on differential effectiveness and/or safety of proton beam according to certain factors. These included traditional demographic factors in the presence of comorbidities, as well as tumor characteristics, such as tumor volume and treatment protocol, the dosage of radiation received, the duration of treatment, etc., and then finally, evidence on the cost and cost-effectiveness of proton beam relative to alternatives.

So, our scope, and again you saw the list of conditions before, so we do not need to go through that again, but these were candidates for external beam radiation therapy who had one of sixteen types of cancer or three noncancerous conditions, treatment of primary cancer for curative intent or recurrent cancer. We did exclude palliative treatment from consideration, and we got clinical input when we drafted our key questions, suggesting this was a very infrequent use of proton beam therapy. So, we did not include it, and obviously because pediatrics were included in the scope, we looked at both adults and children.

So, we compared proton beam therapy alone and in combination with other treatments. You will note, as we go through the evidence, that in certain studies, protons and photons are combined in certain treatment approaches. So, that is one combination, but there may have been others, chemotherapy and other therapeutic approaches, as well, surgery. Primary comparators were other forms of radiation therapy, but other disease-specific comparators were included if they were found.

So, there's the list again. Clinical outcomes included disease free and/or overall survival and conversely disease-related and/or all-cause mortality, measures of regression of the tumor and control of the tumor, incidence of metastasis, tumor recurrence, which would have included intermediate measures, such as biochemical recurrence that is a measure used in prostate cancer, has several different definitions, but it involves essentially a rebounding or a change in levels of PSA after treatment, health-related quality of life, and whether subsequent therapy was required.

Potential harms, so here, just a little bit about how we categorized things. We did look at specific adverse events if they were noted that way. So, there are a couple of examples here, urinary retention in prostate cancer, pneumonitis in breast or lung cancer, but we also recorded information on categorized toxicity, as noted, according to some standardized measures. So, the Radiation Therapy Oncology Group, or RTOG in particular, has developed categorizations that group toxicities of like severity together. So, for example, gastrointestinal toxicity, which is often measured in prostate cancer, might include a combination of bowel incontinence, rectal bleeding, etc., and so these are clinician-graded toxicity levels and generally this is an example for radiation to brain. Zero would be equivalent to no toxicity, four would be equivalent to the most severe toxicities, in this case seizures, paralysis, or coma. Five is typically death. So, if this information was recorded in studies, we also abstracted that, and we split them between those considered to be acute toxicities or those occurring within 90 days of treatment, and those considered to be late, so 90

days or later after treatment. Secondary malignancy, because it is of keen interest, was also looked at, and then it raises specific adverse events, as described.

Literature search, we went back a little farther than we typically would, because we expected a dearth of comparative studies, so we wanted to go back to the possible swath of comparative studies that we could include. So, we went all the way back to January, 1990 through February of 2014, and our focus was on comparative studies. So, we looked at RCTs and observational studies that would have included contemporaneous and non-contemporaneous comparisons, and we did abstract information from case series, but that is not a focus, that was not a primary focus of the report, nor is it a focus of my presentation today. We did not set any priori limits on sample size or duration of studies, because we recognized that especially when there were few centers in the U.S., there may have been studies with small numbers of patients, and we wanted not to make any exclusions off the bat there. We did not evaluate simulation or dosimetric comparisons. That was noted in earlier public comments. Our decision to do this was, again, based on those residual uncertainties with proton beam therapy. So, we felt that inclusion of simulation and dosimetric comparisons on something approaching the same plan as clinical studies would not be appropriate given that what we are really interested in, as an evidence review group, and what I think you are most interested in as a clinical committee, is the evidence on whether the simulation or dosimetric advantages translate into clinical benefit.

Quality and strength of evidence, so as we have done in the past, we used USPSTF criteria, which are specific to study design, but use a good, fair, and poor rating system focused on how comparable study arms appear to be whether controls are in place or confounding, either in design or in analysis or both, whether intent to treat analysis is used for RCTs, etc. There is further detail in the appendix of the report. There is also a slide at the end of this stack, if anyone wants to see it. Then, we also rated the overall strength of evidence. We used methods from the agency for healthcare and research and quality to assess the strength of evidence using these primary domains, risk of bias, the study design, and the quality of the studies, the consistency whether the direction and magnitude of findings were relatively consistent, whether the comparisons made were direct either in terms of direct comparisons of the interventions of interest and/or whether the outcomes of interest were directly measured or whether surrogates were relied on, and finally precision. So, it was the confidence interval around any sort of overall estimate of treatment effect, narrow or wide.

Then, we also looked at our judgments. This is what ICER has used in its own methods of overall net health benefit, so that really combines the information from all of the key questions together whether we consider one technology versus another to be superior and that there is consistent evidence of a moderate to large net health benefit, whether it is incremental, small to modest net health benefit, whether it is comparable, meaning that there are tradeoffs

in benefits and harms but that the therapies are reasonably equivalent, is there clear evidence that the technology of interest is inferior to existing alternatives and then insufficient, whether evidence is insufficient to really make a judgment about the presence and/or magnitude of any clinical benefit. We will be talking about insufficient in some detail.

So, this is the PRISMA Flowchart. We actually do not need to go through this in detail, but suffice it to say that we abstracted over 300 studies. Relatively few of these studies were actually truly comparative. About 37 studies had some sort of comparison involved, 6 RCTs and 29 comparative cohort studies, as well as 8 comparative cohort studies that we decided to term non-contemporaneous comparisons of case series, because they involved evaluation of outcomes at one setting and in one group of patients compared to outcomes from a completely different setting and completely different group of patients from a different time period in many cases.

So, to review our findings, of those six RCTs, only one involved an explicit comparison of proton beam therapy to an alternative treatment. The others were either comparisons of different doses of proton-based therapy or comparisons of combination therapy including protons to protons alone. So, that is a key thing to consider. Of the 37 comparative cohort studies, we judge none of them to be of good quality. So, another important consideration; 21 were fair quality, 16 were poor quality. On an overall basis, and I will return to this at the end, we consider the evidence base to be insufficient, completely or essentially absent of comparative data for 12 of the 19 conditions of interest. So, we are going to focus in this presentation on the remaining seven conditions, and I will further clarify that we will talk about individual studies really only for those conditions where we consider the level of evidence to be moderate.

So, key question one, proton beam therapy with curative intent. So, just to orient you to how we sort of summarized things graphically, we have some notations that indicate how we have viewed what the evidence is saying. So, a double-sided arrow indicates the evidence is mixed on whether there is a benefit. ND stands for no difference so no difference was either, no difference was identified in the results of these studies, and if information was absent, then there are dashes. So, this summary here focuses on survival and tumor control. Obviously, any other clinical outcomes are summarized in detail in the report in the executive summary.

So, for these conditions, we see that we have moderate strength of evidence for lung, ocular, and prostate cancer; low strength of evidence for these other conditions; and I will talk about the study details in a minute but obviously any cancer types that are not listed here have no comparative evidence available to us for this key question.

So, in terms of lung studies, we identified three fair-quality comparative cohorts. Two were retrospective comparisons of proton beam therapy to IMRT

or 3D-CRT at MD Anderson, relatively short followup. So, maybe that's one indication of why there were no differences in survival between groups. There was a measure of the diffusing capacity of the lung for carbon monoxide, something I would not be able to explain if you asked me, but the findings suggested that proton beam therapy was superior to older generation conformal radiation 3D-CRT. There are some comparisons to another heavy ion therapy known as carbon ion therapy. This is not something that is currently available clinically in the U.S., but we felt that these were important to include, nonetheless, as they represented part of the evidence base. No differences in tumor control, progression-free survival, or overall survival between proton and carbon ion therapy in the one study we identified.

Importantly, there was a study mentioned, I believe, in one of the public comments regarding a Phase 3 trial in lung cancer. Those results have not yet been published, so they were not included in our review. I think it might have been presented in abstract form a couple of years ago, but no publication was available to us.

Ocular studies, there was one RCT and three cohort studies, but these did not explicitly compare proton beam to an alternative. They are summarized in the report but not here. We based our conclusions on the three fair-quality retrospective cohort studies focused on uveal melanoma with surgical enucleation, that is removal of the eye, as a comparator, and essentially two of the three studies found statistically significant reductions in mortality, so improved survival with proton beam therapy versus surgical enucleation. There was one study that showed nominal survival benefit for proton beam therapy, but after statistical adjustment for differences between patients, there were no longer significant findings found.

In prostate cancer studies, this was the one RCT that I was referring to. It is an older RCT comparing a higher dose that featured proton beam therapy and photon therapy to photons alone in advanced prostate cancer. Median followup was five years, about 200 patients were treated between 1982 and 1992. So, this would not have been conformal therapy, such as IMRT, because it was earlier than when IMRT was introduced in about 2000. So, there were no differences in tumor control or survival in either the overall study cohort or those who completed the RCT, but there is better tumor control identified at eight years using actuarial methods in men with poorly-differentiated prostate tumors. There were also two fair-quality comparative cohorts in prostate cancer, one prospective evaluation of quality of life showed no differences in overall quality of life but some benefits of proton beam therapy versus surgery, photons, or watchful waiting, and individual quality of life domains. I believe emotional functioning and physical functioning on the SF36 were some of those domains where there were advantages against certain comparators. There was also a retrospective and matched comparison to a cohort or brachytherapy recipients for prostate cancer, and no differences in survival, metastases, or biochemical failure were identified.

So, here is the list, we will not go through it in detail, of no or insufficient study, comparative study, for key question one, and additionally no comparative studies, clinical comparative studies for key question one in pediatric populations. So, again, this is coming from that early widespread adoption and use in pediatric patients with focus on the dosimetric results and a belief in the clinical community that further, or any comparative study, is unethical based on that acknowledged increased sensitivity of radiation in kids and the modeled benefits of proton beam therapy. So, so the reasons behind this, and we do not need to talk in any more detail about whether there will be any more comparative studies coming down the line, but that essentially is what we have found from our review of the literature, as to why there are none.

So, let's move to key question two. Here, we are looking at proton beam therapy for recurring outcomes, recurrent conditions and the impact on patient outcomes. So, here we found very little evidence from a comparative standpoint in liver cancer only and ocular cancer. No differences found in liver cancer, and in ocular cancer with one study we did see benefits in terms of survival and tumor control. That study was a fair-quality retrospective cohort of 73 patients who had recurrent uveal melanoma after an initial course of proton beam therapy. This was done at Mass General. These were treated with a second course of proton beam or had surgical enucleation at Mass General, and were followed between five and seven years. Both overall and metastasis-free survival were significantly, found to be significantly in favor of proton beam therapy both on an unadjusted basis and after adjustment for differences between groups.

Again, you have the list of other conditions and again, the statement that we found no comparative studies for key question two in pediatrics.

So, in terms of potential harms, and you heard before that this really the other side of the coin for radiation therapy, that the goal is to adequately treat the tumor while reducing the level of harm to the patient. So, it is not surprising that we found a fair amount of evidence in this regard, specifically focused on harms, or studies that were focused only on harms rather than on clinical outcomes, clinical benefits. So, here you see, again, that relatively few of the populations had information that we considered a moderate strength of evidence, so I will talk about lung cancer and prostate cancer, but there are some other conditions, as well. Brain and spinal tumors, for example, there is some indication that there is reduced toxicity and disease-specific harms in a couple of retrospective cohort studies. The same is for esophageal cancer, as well. There is mixed evidence, in fact, in terms of the types of harms that were seen.

So, some of these studies I have already spoken about, because they looked at both clinical benefits and harms, but three fair-quality cohort studies for lung, relatively consistent results showing lower rates of severe acute esophagitis for proton beam relative to IMRT, but in one study a higher rate of severe dermatitis with proton beam versus IMRT. Pneumonitis, as well, in one study,

appeared to be reduced with proton beam relative to IMRT. Again, another comparative study versus carbon ion, which showed no differences.

In terms of prostate cancer, the RCT that was listed also did look at harms, as well, found significantly higher rates of mild to moderate rectal bleeding in the proton beam therapy plus photon group, 32% versus 12%. Again, this is a patient group that received a higher dose of radiation, but there were no differences seen in severe grade 3, essentially, or higher toxicities, as well as in rates of other harms, hematuria, urethral stricture, incontinence, loss of potency. There had been a fair number, especially in recent years, of retrospective database comparisons looking at relative rates of harm with proton beam versus IMRT and other technologies in prostate cancer. There was an analysis of about 30,000 men in the Medicare-SEER database, so this is linked healthcare claims and clinical data that found that regression-adjusted rates of gastrointestinal morbidity were two to fourteen times higher for proton beam versus alternatives, and higher GI toxicity was also seen in another Medicare-SEER study that compared proton beam specifically to IMRT, but no differences seen in other key harms for prostate cancer, urinary morbidity, erectile dysfunction, hip fracture or the need for additional cancer therapy. In a little bit of a contrast here, so this is leading to our conclusion of mixed evidence, a matched study using another database that is maintained by CMS, known as the Chronic Conditions Warehouse, found that there was lower urinary morbidity for proton beam therapy versus IMRT at the six-month time point, but that statistical difference went away at 12 months.

So, secondary malignancy is obviously a key issue of interest, and we found two studies that focused on this specifically, one was a relatively recent study, again, another study using the Medicare-SEER database with a median followup of 6.4 years. These patients were matched on a number of variables. There was a pediatric subgroup included, as well, and there were no second cancers detected in either the proton beam or the photon treated pediatric cases. There were no statistical differences between groups in an unadjusted comparison of the rate of secondary malignancy was about 5% with proton beam and was a little over 7% for photon treatment, but after a Cox proportional hazards adjustment for age, sex, the site of the tumor, the year of the diagnosis, and other factors there was found to be a significantly-reduced rate of secondary malignancy with proton beam therapy. There were a couple of caveats. There is an editorial accompanying this article that describes some of these caveats. One is that an analysis done by the authors of this editorial looking at solid tumors occurring within five years of treatment, of initial treatment, the difference in favor of proton beam therapy went away and there are a fair number of epidemiologic studies suggesting that a second malignancy occurring within five years of the initial radiation treatment is not necessarily attributable to that initial treatment. So, that was the point of discussion. The other was that this comparison, again, was primarily made to older generation photon therapy, not IMRT.

A second study focused exclusively on pediatrics. So, this was a study of patients who were initially treated as infants for retinoblastoma and were followed for seven to thirteen years, and there was a comparison of proton beam to photon therapy. A relatively small proportion of the photon treated patients got more state of the art approaches to treatment. There was a numeric, but nonsignificant difference in the overall rate of secondary malignancy in favor of proton beam therapy, 5 versus 14%, but when these malignancies were restricted to those occurring in the initial field of radiation or were thought by clinicians to be radiation induced them there was a significant difference in favor of proton beam therapy. One important consideration, though, is that these groups did have some imbalance in terms of their baseline characteristics, and there was no adjustment made in the study for these differences, only for differential followup, not for clinical differences or demographic differences.

Again, we have our list of no or insufficient comparative study and that single study I just described for pediatrics.

Moving on to key patient subgroups. So, relatively limited information available to us from these studies that focused on specific subgroups of patients. In terms of demographics, there was evidence from two fair quality retrospective cohort studies that suggested persistent benefits of proton beam therapy in terms of reduced rates of metastasis and secondary malignancy with, in patients of advanced age, but there was another study that also looked at age, also in uveal melanoma that found no differences between treatments in terms of different subgroups according to age. Clinical characteristics, there were reduced rates of secondary malignancy in infants with a hereditary form of retinoblastoma for proton beam therapy relative to photons. In terms of tumor characteristics, I already described in that prostate RCT that those men with poorly-differentiated prostate tumors seem to have a tumor control benefit with proton beam therapy relative to photons, but no differences were seen in three other fair-quality cohort studies comparing proton beam to IMRT or 3D-CRT in lung cancer, enucleation on uveal melanoma, or brachytherapy in prostate cancer.

Finally, in terms of treatment protocol, so I mentioned at the beginning of the evidence section that there were some RCTs that focused exclusively on different dosage levels of proton-based therapy, and there were four RCTs, in fact, that looked at different dose levels, two in prostate cancer, one in ocular melanomas, and one in chordomas and skull-based tumors. So, in one of the prostate RCTs, there was improved disease control with higher-dose proton beam therapy versus photon, essentially 79 versus 70 Gy, but also a slightly-greater severe acute GI toxicity and greater moderate GI toxicity with that higher dose. There were no major or statistical differences seen in either effectiveness or harms in the other three RCTs.

Economic impact, so this, I think, there was an allusion to this in Dan's presentation, as well. This is particularly difficult because in many cases, we

were talking about decision-analytic models. So, simulation models that were based on clinical stimulations, so we did not have clinical data driving many of these models, because the results were derived, in many cases, from dosimetric findings or assumed clinical benefits of proton beam therapy. So, we found three modeling studies in breast cancer and there were assumed rates of underlying risks of cardiac disease and assumed effects of proton beam therapy versus photons that were driving the results of those models. In terms of head/neck cancers, there was an assumption of lower mortality with proton beam therapy in these two studies that was based on a potentially higher curative dose, again from dosimetric studies. In lung cancer, two modeling studies, proton beam therapy was found to be superior to conventional radiation but clinically inferior to and more expensive than either carbon ion or stereotactic radiation in inoperable, nonsmall cell lung cancer. This was based on clinical data that were derived from meta-analyses, that these meta-analyses of case series not of comparative studies. So, there were case series data used for each technology.

Pediatric cancer suggesting, model results suggested lifetime costs of proton beam therapy were lower in patients with medulloblastoma and proton beam therapy being more effective than photon radiation. Again, this is based on the dosimetric studies that were performed, used in pediatrics. Prostate cancer results are sensitive to a number of assumptions that were made regarding reductions in cancer recurrence, which have not really been shown in any clinical study, save for the single RCT in the subgroup of men with poorly-differentiated tumors, as well as benefits for urinary and GI toxicity and, as I just described, there was mixed evidence from the clinical studies that we found. There were also four studies that really were not clinically focused but focused on the, I guess, likelihood of solvency in developing proton beam therapy facilities, that the larger, sort of traditional three to four gantry facilities that have construction costs between 100 and 150 million all would require treatment of prevalent cancers and relatively noncomplex cases to really fully be able to, be able to fully service their debt. So, that was really the focus of those studies.

So, as we, as was described before, we did do a relatively straightforward budget impact analysis. We did not do our own decision analysis here because obviously with the sheer number of clinical conditions to work with and some of the challenges with comparative clinical study available to us, we did not think that would be very helpful, but we did look, based on data that the state provided, a 2012 radiation therapy volume for lung and prostate cancer in 2012 and we estimated that replacing brachytherapy, IMRT, and radiosurgery with proton beam therapy would raise treatment costs by about 75% from 2 million to about 3.5 million. We got some comments on the draft report suggesting that because of some of the variability in payment rates that the state data showed, maybe we should use sort of more national standardized rates, and so we found a Medicare source to do an alternative analysis. In that case, we focused exclusively on prostate cancer, but we found that using Medicare

reimbursement rates for brachytherapy, IMRT, and proton beam therapy yielded a similar increase in terms of percentage, about 75%.

This is the per-payment rate using a mix of standard treatments in the 2012 public employee's volume and correlating that with what the rates would be on a per-patient basis for proton.

So, moving into clinical practice guidelines. So, we obtained information on guidelines for treatment using data from the National Comprehensive Cancer Network, American Society of Radiation Oncology, and the American College of Radiology, and our summary, all the details are available in the report, but our summary is that practice guidelines do not recommend proton beam therapy for routine use in prostate cancer outside of a clinical trial or a registry setting. This is actually one of ASTRO's Choosing Wisely topics, as well. It is appropriate for ocular tumors, may be appropriate for some CNS lesions, appropriate in some of these guidelines for nonsmall cell lung cancer, as well as unresectable chondrosarcomas of the skull base and axial skeleton, and it may be appropriate for certain lymphomas and soft tissue sarcomas pending longterm studies of benefits and harms.

Moving over to payer coverage, so you saw this slide in Dan's presentation, but there is a second list of covered indications in the local coverage determination that covers Washington State, and this is focused on patients who are enrolled in a clinical trial or registry who have unresectable lung cancers, upper abdominal cancers, and left breast tumors, advanced unresectable pelvic tumors, pancreatic and adrenal tumors, skin cancer with nerve innervation of the skull base, unresectable lesions of the liver, biliary tract, anal canal, and rectum, and nonmetastatic prostate cancer with documented clinical staging and demonstration of the clinical necessity of proton beam therapy. So, this is a separate list from the prior list, which is the, which only has the condition of the life expectancy greater than two years.

In terms of private payers, we found that there is relatively consistent and uniform coverage, both regionally and nationally for uveal melanoma, chordomas and chondrosarcomas, and pediatric cancers, although some payers do limit coverage of pediatric cancers to CNS lesions and retinoblastoma. Coverage by some payers for CNS tumors close to vital structures in adults, AVMs, and pituitary tumors. I think, as mentioned in Dan's presentation, most of the private payers consider proton beam therapy for lung cancer investigational and/or experimental, and finally for prostate cancer, it is a slightly different conclusion. Coverage is not uniformly provided, not necessarily due to an investigational consideration but that it is felt that while potentially clinically comparable, there is no evidence suggesting that it is more effective than other radiation alternatives in prostate cancer.

So, again, you have already heard about some of these, but there is a fair amount of ongoing study of proton beam therapy. So, we looked on clinicaltrials.gov and focused on studies that were enrolling more than 50

patients and found 11 RCTs that are ongoing for proton beam therapy. We also looked to see if we could find some notable registries that had publicly available information, and we found that several of these, I should point out that there is a pediatric-specific registry that was initiated in 2012 that is looking at information from five sites. There is also a comparative registry at the bottom that is being done at MD Anderson that is looking at patients who are receiving thoracic re-irradiation with either proton beam therapy or IMRT, and then there are other registries focused on collecting more detailed clinical data for proton beam recipients, and I believe that the Seattle site is participating in at least one of these.

So, this table exists in the report, as well. What we tried to do was to provide information on our assessment of overall net health benefit, the direction of that net health benefit and whether it represented increased benefits and reduced harms or equivalent benefits and reduced harms or what have you. Our review and assessment of the strength, overall strength of evidence across all of these key questions and then for further in, what guideline recommendations are saying in terms of their universality and coverage policies, as well.

So, you see again that for 12 of these 19 we found the net health benefit insufficient. There is not a lot of information beyond that that is provided. In terms of those where we found superior net health benefit that really was relegated just to ocular tumors. We are rating the evidence, or the net health benefit for pediatric, as incremental despite the lack of comparative clinical information. Again, it is based on the acceptance of the use of proton beam therapy for pediatric tumors rather than a clear review of the evidence. We also found a number of situations in which we deemed the evidence to represent a comparable net health benefit, liver, lung, prostate, and hemangiomas, but we found a low strength of evidence for some of these.

So, we have our summary and conclusions. We talked about the ocular conclusion already, moderate evidence of a superior net health benefit, judgment of incremental benefit for brain and spinal tumors, but there was a low strength of evidence there, the acceptance issue for pediatric cancers, and then there were situations where we deemed the evidence to suggest comparable clinical outcomes and harms, but the strength of evidence was either low or moderate for these. So, obviously, there is a lot of comparative work that is ongoing and so that may provide an opportunity to revisit the evidence base, as it emerges, but that essentially summarizes my presentation.

Craig Blackmore: Thank you.

Daniel Ollendorf: I guess I'll take questions (inaudible).

Craig Blackmore: OK. So, questions from the committee for Dr. Ollendorf?

Richard Phillips: I had a question, but I am not sure if it is for you or for, or maybe also for Dan, and that was the issue of the local coverage decision. I, I think that local coverage decision was made by Noridian here, and I am wondering what parties are involved in that? Does that state have any participation, Medicaid, any of those, and I am trying to figure out, did that come just from Noridian, or where, did it come from the committee, does anybody know anything about that?

Daniel Ollendorf: Well, we found the information, so Medicare has a coverage database, and so you are allowed to search for national and local coverage documents. There has been no national coverage determination on proton beam and so, in that situation, then the jurisdiction is left up to the individual regional contractors. All the contractors published their local coverage determinations, as well, and so this was a published document that we reviewed.

Richard Phillips: Thank you.

Chris Standaert: I had a question. We had some comments in other notes previously about patients who had had prior irradiation or had essentially reached their radiation dose limits for various tissues now being considered for proton therapy, and I did not hear anything about that in here. Were they, and I imagine studies like that are hard to find, because you cannot really randomize them, because you are not, you know, they sort of, I guess the chemo or some other treatment used but, did you go looking for studies on that particular subgroup? Can we be able to comment on that subgroup of people with, who essentially are contraindicated for further photon therapy?

Daniel Ollendorf: Right, and so, so this was brought up in the public comments. I can be wrong, and I could be corrected on this, but I am assuming that in our search for studies in the recurrent key question, there was a study comparing proton beam therapy to some non-radiation alternative for those patients that it would have ended up in our search. So, I think that the, the studies that were cited in the comments were not comparative studies. I think these were case series and maybe we can...

Chris Standaert: So, you would have looked for that, sorry, just one second, you would have looked for that in the setting of the recurrence tumor...

Daniel Ollendorf: Right.

Chris Standaert: ...category.

Daniel Ollendorf: Right.

Chris Standaert: OK.

Craig Blackmore: So, that, that's key question two, right?

Daniel Ollendorf: Yes.

- Craig Blackmore: What is the comparative impact of salvage treatment including treatment for recurrent disease with proton beam therapy versus major alternative? That's...
- Margaret Dennis: In my recollection of looking at the literature, there were some (inaudible) but I do not think there were any concerns.
- Chris Standaert: Alright.
- Margaret Dennis: And the case series were included, you know, in the end but not as far as being in the report.
- Craig Blackmore: So that was part of...
- Chris Standaert: So, there are...
- Craig Blackmore: ...the material presented.
- Chris Standaert: ...so there are case series in the appendix on the...
- Daniel Ollendorf: They're in the, the case series are in the appendix and there are, there is some description in the full report of the findings from the case series, but the primary write-up was focused on the comparative studies.
- Chris Standaert: OK, yeah, because my only concern is that they're hard to, comparative studies in that population can be very difficult to do, and so you may exclude a, if you just tried to find only comparative, you may exclude a population, because they are very difficult to study, although I get it. Thank you.
- Daniel Ollendorf: There were some studies published that were comparing populations at separate institutions at different times in the body of the report. You could have done the same kind of approach for the question you're talking about.
- Chris Standaert: Yeah. Yeah, no, nothing is impossible.
- Daniel Ollendorf: Right.
- Chris Standaert: Yeah, and certainly compared to, if you compare it to surgery, they can compare it to other types of therapy, not to, not to other forms of radiation, because they can't have their (inaudible) compared to the other alternatives, chemo or surgery.
- Richard Phillips: I have a question about cost. This, I think the cost of these is much higher than other forms, maybe you can embellish that a little, but one of my concerns was, is there a possibility that the costs will be pushed down with increasing volume, that is not being used? That is number one, number two, are these, is the facility, there's only 15 I guess in the country, are they being utilized to the maximum, as they are right now? You know I'm trying to figure this out

whether or not the, the cost issue is a fixed issue or whether or not there is a possibility that the costs will go down over time either because of new generations of machines or whether or not this is really a major impediment to, to healthcare expense.

Daniel Ollendorf: There are a lot of issues wrapped up in that question. I think that, so the slide that I presented used Medicare Reimbursement rates and so, Medicare reimbursement for proton relative to IMRT for prostate cancer, for example, is somewhere between one and a half and two times the level. The rates that private payers pay will vary substantially according to the payer themselves, as well as their contracts with individual employers, and the notion of reimbursement versus institutional costs is a very different thing. I think that the, one of the comments related to the use of relatively new smaller facilities with just one single treatment gantry and the cost to construct those is much lower than what has been quoted previously for bigger facilities. It is about 25 to 30 million, as opposed to 100 to 150 million. I think that is what the gentleman from Swedish was talking about, but I cannot answer the question of whether the facilities that exist are treating to capacity or not. I don't know if you have any thoughts on that yourself.

Lia Halasz: Well, I know that our center has been a ramp-up period, so we have been open for the last year. So, we have had more and more patients, as we open up more and more rooms. So, we are certainly adding every, every month, but probably not at the, quite the capacity yet. We have three out of four rooms open. I think it is very different now when, with the fact that there is a lot of, you know, treatment centers opened in the last few years. So, I am not sure how much the patient population has really caught up to that. Before that, when there was only a few treatment centers including MGH and Penn, they certainly were turning a lot, away a lot of patients and patients who would be presented from many places, but I think that is probably a very, changing very quickly now.

Craig Blackmore: So, maybe we can turn that also to the agencies. How do you determine how much you pay for proton therapy whether it is locally or Mass General or some other distant site?

Daniel Ollendorf: You know and actually there are folks here that get more involved in, in the contract. What I can, and actually my experience has been more on the Medicaid side and in that case, it's like with other payers. I mean, we, we, you know, there is a negotiation and a contracted, you know, a contracted price.

Lia Halasz: I think also to point out that the cost of each treatment is very individual. So, the cost really depends, number one, on the complexity of the treatment. So, a treatment for a prostate may be very different from a treatment for craniospinal, for medulloblastoma. So, that's one part. The other part is that treatment really is based off of treatment length. So, whereas the prostate takes eight week for treatment, many brain tumors may take five weeks, and I know at our center and in our department, we are also interested in hypo-

fractionation schedules where treatment is given in much shorter amount of periods, and that also changes the cost for this treatment.

Richard Phillips: I have a question for the, maybe it is for the medical expert. It has to do with the, one, one of the slides that was in the presentation, it brought up the issue of in the pediatric population, the ethics involved for an individual physician who is looking at one of these and then they base that on dosimetric kind of stuff, which is not covered in our analysis. I wonder if you could make a comment about that. Is it, I mean, I know this is a new technology and it is sort of silly to say we have new technology and it is unethical not to use it. Nobody is going to say that, but on the other hand, I think if there is a safety factor involved here, you know, how much do we give, how much do we weigh that as we make a decision and, I would certainly appreciate your perspective.

Lia Halasz: Yeah, well as a treating physician, you know, I think my job is to make the possible radiation plan, and I think, you know, our field is sort of a hard field, sometimes, to look at some of these issues because we do make technological advancement. So, for instance, it was brought up the 3D conformal going to IMRT was a technological advancement. It didn't use a different particle, but it was able to improve our dose conformity around our target, and so it was approved for that sort of thing. Protons, and especially with children, is the most extreme example, so it is the easiest to see. When there is no dose to a certain structure, like the heart or the ovary, then there is no risk of late effects, and so that is the very issue with our children. We know that we could cure a lot of our children but at 10, 20 years after they are cured, then they are at most risk for treatment complications, and they end up dying of that instead of their disease. So, I think what is hard is, as a physician, it is true. I look for the best possible plan for my patient, and we know that protons allows me not to get that low dose to important parts of the brain, the rest of pediatrics, and that is where we do think proton therapy has a role in a lot of the places where we are. So, it is very tough, as a physician. I treat mostly brain tumors, and being able to avoid hippocampus or avoid the optic structures just means that I do not have that risk of a very likely treatment effect later on.

Richard Phillips: Is there ever a time that it would be unethical not to provide proton therapy if it were available?

Lia Halasz: Well, it would be unethical...

Richard Phillips: Yeah, medically?

Lia Halasz: ...well I think that's where, there has been a lot of debate in our societies, and that is where the pediatric comes up. So, even though there is not comparative evidence, there has been quite a bit of, you know, adoption of protons for pediatrics, because they feel that the clinical sequelae of those treatment is very important. So, I think that is the easiest way to put it. With the rest of the conditions, I mean, I think that is where we really look at it, you know, we have to argue what is ethical risk, etc. and how big that risk is.

- Kevin Walsh: I would, I, I would like to point out that if proton beam therapy has been around for 60 years, there has been adequate time to follow people who were children over time to see if the assumptions upon which this is based were proven to be true or not. They haven't been done. So, we are continuing to make some hypothetical assumptions and use those as the basis for ethics. I, I'm not sure about the validity of that.
- Richard Phillips: Well, I, I'm really responding to the fact that one of the presenters actually used the term of ethics, and it was also brought up in the, in the, one of the terms in one of the slides and that is why it sort of caught my eye as to whether or not it is really something we should even put in the, and I respect what you are saying here, but what I am saying, I just want to make sure it is not something we need to deliberate on.
- Lia Halasz: I think pediatric patients have been followed, and there have been recordings of what delayed effects of the treatments were. Where I think that the literature in looking at this big body of literature, is that a lot of those did not compare to a photon group, because I think it was sort of knowledge within the community about this is the percentage of late effects that you would have.
- Craig Blackmore: So, let's...
- Lia Halasz: So, there, there are those published studies that are in the (inaudible).
- Craig Blackmore: Let's turn that, if we are talking about questions of evidence, we should go to our evidence source. So, Dan, can you refresh us on what is out there in terms of the pediatric population specifically, longterm sequelae, second malignancy, registry versus comparative studies.
- Daniel Ollendorf: So, in terms of the comparative studies, we identified the two studies of secondary malignancy. One had a pediatric subgroup. One was focused exclusively on pediatrics. We identified no other comparative studies during our timeframe; however, there are a number of case series that do look at the longterm sequelae; so, those are, again, briefly summarized in the report and available in the evidence tables, as well.
- Craig Blackmore: And so which slide would we be looking at? You can, maybe we can all...
- Daniel Ollendorf: So, the, so key questions one and two, we found no comparative studies on clinical benefit, but when we look for the...
- Craig Blackmore: So, I think we are at slide 36 and 37, does that sound right?
- Daniel Ollendorf: On harms, yeah.
- Craig Blackmore: Yeah.

- Daniel Ollendorf: That sounds about right.
- Chris Standaert: Well, I would go back to Kevin's question about the, so, nobody has done a study that is looking at comparative historical controls of photon therapy of some sort. I mean, there is data on this, but nobody has actually done a direct comparative study looking at historical controls with the same diagnosis trying to match a matched cohort so a study with historical controls so we get...
- Craig Blackmore: Well, that...
- Chris Standaert: ...some idea of whether...
- Craig Blackmore: ...that's what this is.
- Daniel Ollendorf: In these pediatric studies, these are the two, these are the two comparative studies.
- Kevin Walsh: But it was mentioned earlier that the same thing is true for IMRT. It's never been proven that it's better. It was just accepted and they moved on.
- Craig Blackmore: So, this, this is the evidence that we have, right? This is retrospective, cohort, comparative cohort studies of pediatrics, as you said in one, and relatively longterm followup, I guess, maybe not long enough to get to the point of secondary malignancies, or all secondary malignancies, so, slides 36 and 37. So, does this get at the issue, or?
- Chris Standaert: So, the, so the pediatric question, this would be our, they have 88 pediatric cases there in this cohort series, that is how I'm reading this, and a data you're giving us there for the whole population, not pediatric?
- Daniel Ollendorf: Right, because there were no second cancers detected in any of the pediatric...
- Chris Standaert: Any of their...
- Craig Blackmore: And then there ...
- Daniel Ollendorf: ...in that study. There is a second study on the next slide.
- Craig Blackmore: Slide 37, there is another small.
- Daniel Ollendorf: Oh, wait. There we go.
- Craig Blackmore: So, a very small study, 86 infants.
- Joann Elmore: Hmm, well there was a trend.

- Craig Blackmore: So, again, we are dealing with rare disease, we are dealing with rare outcome, and we are dealing with a small study. So, you know, we are not really probably powered to show much here.
- Carson Odegard: I have a question for our clinical expert. On the volume, or not the volume, but the percentage of pediatric population in your center, how does it compare? I know you say it has only been a year, but.
- Lia Halasz: Yeah, well, I could be wrong on this, but I think we have about 30 patients on treatment right now, and about five or six of them are pediatric patients, and that has been about how, how it has been. There were probably more pediatric patients in the beginning, as, you know, that was sort of some place that we felt like starting and had the rooms available.
- Carson Odegard: OK, thank you.
- Seth Schwartz: I have a question for our evidence vendor, again, regarding, we heard some stuff from one of the public comments about cardiac toxicity for breast cancer treatment, and then I have not heard anything about that even mentioned as a side effect of therapy. Was there any data on cardiac side effects in the breast population?
- Daniel Ollendorf: We did not find any comparative studies in breast cancer.
- Seth Schwartz: Were there any case series or anything?
- Daniel Ollendorf: I will check right now.
- Michael Souter: Just to add to the list of questions while you've got an answer for Seth, do you have an answer for him?
- Daniel Ollendorf: Yeah, I do. Yeah.
- Michael Souter: Oh, OK, go for it.
- Daniel Ollendorf: In terms of harms, there were two case series identified. They were focused on grade 3 or higher cardiotoxicities and found 0% in one case series and 8% in another, and these were acute. No late effects were observed.
- Craig Blackmore: So, so these are case series of what now, of?
- Daniel Ollendorf: Proton beam and breast cancer.
- Craig Blackmore: Is it, individuals who had proton beam, this is the rate of cardiac toxicity.
- Daniel Ollendorf: Correct.

- Seth Schwartz: Do we know what the historical rate is for IMRT or for traditional photon therapy?
- Michael Souter: So, I'm interested in this question, again, of the followup period of times that are available. Just, I am struck by the previous slide showing that the kind of median followup there was (inaudible).
- Daniel Ollendorf: Yeah.
- Michael Souter: You know, a median is a median, and I am kind of interested in where the bulk of the population, rather, you know, what, what's kind of the modal followup in terms of the populations that were studied. I realize that will obviously differ across all the different, you know, studies that are mentioned there, but can you give us any sense as to the range of modes of followup. I am trying to get a sense of, you know, how much bulk the data there is in terms of following up for these complications.
- Daniel Ollendorf: I have that study, I have the publication itself here. So, let me take a look while we move on to the next question.
- Michael Souter: And then while you are looking up that, I have a question for the clinical expert, which is that, you know, the, we are all consumers of technology and, you know, whenever I am buying any technology, somebody is always trying to impress me with the statistic as to how, you know, good this is and how good that is ranging from the number of pixels on my computer screen, etc. to, you know, the, the bytes per second I might hear in a speaker. I suppose my question is that, um, can you give any kind of parameter, as to the meaningful clinical difference with regards to how tightly the volume is controlled with the proton beam therapy, as opposed to the photon beam therapy?
- Lia Halasz: So, if I understand your question right, you are asking about whether protons and photons have a difference in terms of how they control a tumor?
- Michael Souter: Yes, I mean, I suppose in terms of, you know, the great play here, the most significant obvious difference as a non-practitioner in this field is that you can more tightly control, you know, the targeted effect...
- Lia Halasz: Right.
- Michael Souter: ...of the protons. Yeah...
- Lia Halasz: So...
- Michael Souter: ...to what degree does that translate to a, you know, a clinical difference in terms of biological damage to the tissues.
- Lia Halasz: I see. I see. So, protons and photons, we think how we use them have the same tumor control when you give dose per dose. There is some question about

whether proton has a slightly higher radiological-biological effect on the tumor, but we tend to account for that in our calculations. So, overall, what we think is that it has the same control on the tumor. The difference is really the bystander tissues, so the tissue that we have to treat in order to get there. So, the idea is that a photon is an x-ray, comes in, and you get bystander tissue coming in, you get the target, and then you get bystander tissue coming out. The idea with protons is you come in, you get bystander tissue as you are coming in, and then you treat the tumor. So, much of what protons is suggesting and what makes it favorable is the fact that your bystander tissues do not get the treatment, thus you do not have the risk of normal tissue toxicities. That also plays into, so where people talk about better control is that, that may also allow you to increase the dose to the tumor, because you have not given the normal tissue as much dose as you are limited by. We are always limited in radiation oncology by normal tissue. We would like to give as much dose as possible to control the tumor but obviously are really limited in that based on radiation effect on normal tissues.

Michael Souter: OK. So, what I'm, you've helped me kind of think about the question, are we the one to ask I suppose, is to what degree of, is there a, is there a dose limit beyond with any theoretic improved targeting that you have is actually lost?

Lia Halasz: So, there is, you know, a theoretical dose limit in terms of the tumor and how much we can give, although we have not reached that because in radiation oncology, we cannot always reach the doses we want, mostly because of the normal tissues, and that changes depending on the area of the body. So, the brain can take a certain amount of radiation versus the heart versus the lungs. It also has to do not only with dose, but also volume that receives it. So, if you think about many different organs, obviously the volume of the lung receiving a certain amount of radiation is very important, as well as the dose, and so larger volumes receiving lower doses of radiation account to, you know, sort of similar risks, higher volumes with higher, and so a lot of our field is really also based on historical, you know, how much can we give to certain amounts of tissues, and that is what we take into account to our everyday planning. I am constantly sort of taking into account, you know, what the normal tissue toxicity is, how much dose it gets, and I try to limit it, but also know where those thresholds are.

Daniel Ollendorf: I have some details from that study on followup. The only other statistic provided was the intercourse high-low range, which was 7.4 years, but there is also a statement that second malignancies were found up to 23 years after initial treatment. So, the latest followup, I guess, was 23 years.

Craig Blackmore: OK, so it is the chair's prerogative to rearrange the schedule because it is always awkward to break up our discussion in the middle to have lunch. So, we have moved lunch up and it is just about ready. We will do lunch now, and then resume and at that point we can have the open deliberation among the committee and works towards a decision, and then we will move on the agenda beyond that. So, it is now 11:30. It looks like we are almost ready for lunch.

That's great. So, why don't we take, why don't we take a half an hour and reconvene at noon, and we will have our discussion, thank you.

OK, we are going to, we are going to call the meeting back to order. So, the next item on the agenda is where we get to the committee discussion and decision-making process, and so this is our opportunity to debate among ourselves or to dig further into the evidence, and we still have the agency directors and our clinical expert and our research evidence vendor to provide us with input, as necessary, and we will follow through to make a decision, but I thought I might make a few comments before we started that process because I think particularly in light of a lot of what we heard from the, from the public from some of the presenters this morning is worth making a few comments, and so it is useful, I think, to review briefly the charge of the HTCC, and that is that our job is to determine if technology is safe, effective, and cost effective, and if we determine that they are based on the best available evidence, then we are to have them funded or covered. This sounds very simple, but it turns out to be very difficult. I think every one of these meetings that we come to is different and each is challenging in its own way. That is why we have this lengthy process with the evidence vendors with multiple opportunities for public input.

Also, it is worth pointing out that this process is innovative. The traditional model for paying for medical procedures is to pay based not necessarily on the evidence of effectiveness but really on potential for effectiveness or potential for benefit. So, the prior model before this committee might be to pay based on some pathophysiologic model that would suggest something would help and in this case we might think about dosimetry as an example of that. It does not mean that it works. It means that it might work. It means that it has potential to work, and in the past that potential has been sufficient for technology to be covered. Of course, the consequences of that we are all aware of. We live in a system where costs are twice as much as most others or more, as most other developed nations in the world and their outcomes are simply no better and often worse. So, the legislature and the governor, back in 2007, established this program to change the way in which we fund technologies, and the program, this committee, is to make decisions based on evidence, evidence of effectiveness, evidence of safety, and evidence of cost effectiveness. Again, we are, we are novel. There are still very few programs in the country and even in the world that explicitly require evidence of all three of those components before they will cover. So, really, our job is to draw lines, draw a line in the sand and say we will not cover or we will cover based on some set of conditions, and again, that line is drawn not based on the potential for benefit, but what the evidence really tells us about what the benefit is. It is important, as a committee, that we not be seduced by technology. Everything that we see before us is some innovative technology. It might be new. It might be old. It has potential for benefit. So, our job is to be critical and to dig down into the evidence and to determine if that benefit really exists and to use that evidence to make our determination, and that is explicit in the legislation that defines this committee and that defines this program.

Now, why am I talking about all this? The committee is familiar with that. They are all looking at me like, why are you reminding us, and I am because it is always useful to be reminded, because that is why we are here, and also because by understanding what we are charged with doing and what is specifically in the legislation that establishes this committee also allows us to see what we are not charged with doing, and that I think becomes relevant today. Specifically, it is not within our mandate to establish research priorities for the State of Washington. I am very impressed with the presentations we saw today and the need for research in this area and the desire and the plan and some of the ongoing research, but again, this committee is not a committee designed to set research priorities. Our charge is not to say this is something that we should do research on. This is something we should fund research on. If the legislature had intended us to do that, it would have been within the legislation, and it is not. Furthermore, I would not suspect if we wished to design a committee to help allocate research funding within the State of Washington it would look exactly like this. The information that is given to this committee does not, is not the information you would need to prioritize. We do not know what conflicting demands there are for research money. We do not know what trade-offs there are if we designate that a specific research agenda should be funded, what are the impacts of that in terms of other research, and what are the impacts of that in terms of healthcare. It's a set pool of money that the agency's work with. So, though we may desire research, and though we may feel that this is worthy research, it is not within our charge to make those determinations. Our charge is simply to determine if there is evidence of effectiveness, safety, and cost effectiveness, and if so, to order, if you will, or to tell the agencies that they will pay for it.

The other thing that is explicitly not within our charge is to determine payment for procedures. We determine if they are paid for, but it is specifically excluded from our charge to determine how much they get paid. So, we cannot say we will allow coverage for this procedure under a specific set of payment or amount of payment or criteria, we can do criteria, but we cannot determine what that dollar number looks like. We can only say yes, the evidence is there that it is effective, safe, and cost-effective, and so we should pay for it. So, I think there is a lot of potential in this topic to go off in directions that are not where we live. They are not why we are here, and even though we might have opinions, and we might even wish to go into those areas, that is not why we exist. That being said, let's go with the discussion.

Marie Brown: Are you actually referring to the article that we read from the Journal of Clinical Oncology about, they were suggesting referenced pricing with evidence development and that is what you are meaning about it is not our job to determine...

Craig Blackmore: We are not allowed to determine pricing.

Marie Brown: Right, right.

- Craig Blackmore: It is not our job to determine research priorities. We are actually non-empowered to determine those things. That is, that power, that responsibility is within other areas of the government specifically.
- Marie Brown: Right.
- Carson Odegard: So, if there is a subset of patients that are undergoing treatment within a trial, we can make a determination on that subset or not?
- Craig Blackmore: We, we, our charge with making determinations about all subsets, either collectively or individually whether or not they're involved in trials. We can make a recommendation to the agencies that it should be paid for if it is within the context of the trial, but I am telling you that that is not what we are asked to do. We have the power to do that, I believe, but we are not charged with doing that and, and realistically, we are not given the tools to do that, because that is prioritizing research. That is saying, this is important, spend the research money here and do not spend it on, you know, I don't know what else, you know, diabetes, public health. I have no idea what other priorities there might be for research because that is not what we are asked to do. That is not the information that is provided to us. We are simply asked to make a judgment about the technology that is before us.
- Michael Souter: Just to phrase Carson's question slightly differently, perhaps, if we do make a coverage decision, we can specifically say that this will only be covered in the context of a patient being entered in a trial or a...
- Craig Blackmore: We could say that.
- Michael Souter: ...registry, yes.
- Craig Blackmore: Yep.
- Marie Brown: We have done that before.
- Craig Blackmore: Yeah. However...
- Chris Standaert: We have done that, but it always gets tricky doing that. I mean, I, I like what Craig said. I thought that was very well put, and I think our charge is not again to decide which topics are appropriate for research funding, which research studies are better than others, what a good study is in this state, what, what research studies are beneficial to the citizens of the State of Washington. That is not our, that is their job more than our job, and so, at the moment they are free to do that. Whatever our concerns are, we can say we cover or we do not cover. They are always free to do that. Somebody can go to them with a study and say, I have a study and I would like the state to pay for the treatment for their subjects, their partic-, their insurance for participants in our study, and they can propose that to the state regardless of what we say. They can always do that, but that is not us to tell them that they have to, they should, and to

define the parameters about which they find the study appropriate. I, I personally do not see that as our role.

Michael Souter: Unless we cover it without conditions, that is...

Chris Standaert: Right, right, right. Yeah, then we are...

Craig Blackmore: Then they have to cover.

Chris Standaert: Then they have to cover, yeah. That would be our...

Michael Souter: Yeah.

Craig Blackmore: So, so at this point, the way we usually proceed is for a member, several members of the committee to give us a starting place without saying cover or not cover but sort of summarizing where they think we are and we sort of use that to start us off.

Kevin Walsh: Could I, could I ask a process question, first? There are 16 different kinds of cancers that were proposed.

Craig Blackmore: Yes.

Kevin Walsh: So, are we going to do this by anatomic type, location, etc., or are you asking for a generic discussion, because we need to frame this a bit.

Craig Blackmore: Yeah, so, in the planning for this meeting, the assumption was that we would look at each of those individually. I would propose, and, you know, tell me if this does not work, I would propose we do that but we start with the ones where maybe there might be more evidence, and we might get to a point where we decide to lump several of them that we think the evidence basis is similar, if that makes sense, but I do think we need to deal with at least some of them on a sort of cancer/organ specific level rather than global. Now, we can do that one of two ways. We can have separate decisions, or we can say cover with conditions and the conditions are these types of cancers, these populations, whatever they are, and I think we can do either after we get a feel for where the committee is. Does that, do you want to comment?

Joann Elmore: Yeah, I will comment. I will propose that there are three conditions that we should discuss, and I will name them, and then I am going to propose that all of the other types of cancers that they not be covered. The three that we should discuss would be ocular, pediatric groups, and then the brain/paraspinal, that we discuss those in more depth, but I am going to start off by just asking the committee members if they agree for a noncoverage for all of the others, and I will point out one additional thing. I, I appreciated Craig's comment about how we as a committee, it is not within our mandate to evaluate whether something should be paid in a research setting. I sit on NIH grant review committees, American Cancer Society, it is a very different protocol and committee makeup

and, and so that is not our mandate. If members of the community want to try to get a patient treated, they can speak with the state staff members, and the state have, within their purview, the ability to approve or disprove. So, I think we as a committee, while we all support research endeavors, it is not within our mandate for our committee. So, I appreciated you saying that, and I wanted to add in the caveat that just by voting a noncoverage for all of these other cancers, we are not excluding them from the possibility of research involvement. They just have to, in the future, go directly to the state folks.

Craig Blackmore: Yeah, I, I think that is, I think that is very important, and our intent is not to limit research, it is simply outside of our scope and there are other pathways that exist appropriately to allow for funding of individuals who are engaged in research studies and that, the agencies have their processes for dealing with that, which is simply that we are not a part of that process, but we are not blocking that in any way. Richard?

Richard Phillips: Question of schematics or clarification and that would be that if we, as you say, there is no evidence that this works and yet, at the same time, we say that this is something that perhaps could be done under research with approval by the state. Is that something that we would put in there in say coverage with conditions, i.e. conditions where the state accepts it, or do we just say no coverage and it is up to you to work something out with the state. In other words, I am trying to figure out what we can do to facilitate this so that it is, you know, they know how to deal with the process.

Kevin Walsh: I think what has been said a couple times is that we do not have to do that because the state has the ability to do that separate from this committee.

Richard Phillips: In a noncoverage situation, at least that is what you are saying.

Kevin Walsh: Right.

Richard Phillips: That is what I am trying to clarify. If that is the case, then...

Kevin Walsh: We do not have to...

Richard Phillips: ...I think we are...

Kevin Walsh: ...we do not have to put in that...

Richard Phillips: Well that's where, that's...

Kevin Walsh: ...study in...

Richard Phillips: ...really what I wanted to clarify...

Kevin Walsh: ...a clinical trial caveat. I think that is...

- Craig Blackmore: That is correct, and, and we can confirm from the agency directors that even if we say no coverage you are still empowered to pay for, at your discretion, pay for, you know, procedures, technologies, within the context of an investigation.
- Daniel Ollendorf: You know, what I would say is, I know for L&I that is true and I know for Medicaid in law that is true and, but I, I actually at this moment cannot speak for, for PEB with absolute certainty and, you know, I don't know, it, Suzanne, do, do you know whether we, I mean, in the, in the other two cases, I think, actually, it is, it is in statute for the, for you and for, for Medicaid.
- Suzanne: (inaudible)
- Josh Morse: Suzanne, can you please use the microphone?
- Suzanne: You got it.
- Chris Standaert: I guess the question would be can not should, right. Yeah, so can this, does it have the ability to cover a clinical trial for things which it does not normally provide coverage...
- Suzanne: Right, right.
- Chris Standaert: ...the other patients.
- Suzanne: It would require specific coverage approval through the plan. It would be a special case scenario rather than a routine case scenario. It is not explicitly included in the certificate of coverage between PEB and the members that we would cover a clinical trial.
- Chris Standaert: Right.
- Suzanne: It is something that, as Josh had mentioned, we could make choices to do but we have not to date.
- Daniel Ollendorf: So I just, I want to, I just want to clarify, because I know this is an important point and with, with Josh, I mean the, the, just in terms of with L&I and with Medicaid there is, there is, from my understanding, actual, actual statute which, you know, in some sense, would trump, that is the one situation in which the decision of the Health Technology Assessment might be, you know, it might be trumped so to speak, and, and so could we just, I'm wondering, so the question really is, if, if the committee decided noncoverage and given that, you know, assuming that, that works its way through the process and that is the final decision, it is a noncoverage decision, does PEB have that same latitude in the face of an Health Technology Assessment decision that is noncoverage if, if there is no other, you know, no other stipulations, such as, you know, covered with, developed as a condition.
- Josh Morse: Are you asking me if PEB has the ability?

- Daniel Ollendorf: Right, I am, I am just, you know, I am, what I am aware of, yeah, I am. That is the question. The question is, if the Health Technology Assessment makes a noncoverage decision whether, whether because we are bound by that decision.
- Josh Morse: So, the Health Technology Assessment law was specifically written to, and I am looking at the, the legislation for the committee, that even if this committee says something is noncovered, it specifically says that reimbursement provided under an agency policy regarding experimental or investigational treatment services under a clinical investigation improved by an institutional review board or health technologies that have a human device exemption from the FDA, those are specifically the out for the agency.
- Daniel Ollendorf: There, OK, so there is that, that, OK.
- Josh Morse: OK.
- Marie Brown: So, they can't do it.
- Chris Standaert: No, they can.
- Craig Blackmore: No.
- Marie Brown: They can.
- Chris Standaert: It means they can, yes. Yeah.
- Marie Brown: Can, C-A-N-.
- Richard Phillips: They may, yes.
- Chris Standaert: C-A-N-, and, and we do not have to specify that they can because the legislation, our legislation says they can.
- Michael Souter: So, can I just ask that (inaudible) proposal.
- Michelle Simon: Yeah, I think we all heard that. I think the strongest argument (inaudible).
- Marie Brown: Do you have your microphone on?
- Michelle Simon: I'll speak up. So, the only evidence, really, in support of (inaudible) seems to be the strongest evidence, anyway, is in the two conditions of brain and spinal and ocular, and even those are low quality of evidence. If you look at the Medicare tier database with over 30,000 patients with regards to prostate cancer (inaudible) that there is a two to fourteen time higher GI morbidity. So, even I n safety, I would say this, this is not the strongest technology. So, I think we really need to look at (inaudible).

Seth Schwartz: The one caveat I saw was in terms of the prostate cancer. There was one fair quality RCT that called out the subpopulation with poorly-differentiated cancers and, so it looked that group did substantially better. I mean, they had 85% with tumor control at eight years versus 40% and that was just (inaudible). So, I think we should at least look at that one subset.

Joann Elmore: Well, I question that study, because they had multiple comparisons. They had at least ten other comparisons. They looked at 5-year, 8-year. They looked at intention to treat. They looked at all others. They looked at three other outcomes, and so I wondered how many different comparisons did they look at in order to come up with something statistically-significant.

Seth Schwartz: Could we maybe get a little more, well, I mean, in the context of this discussion, I mean, I, I tend to agree with your statement about, with ocular situation. I think we see clearly that there is, it seems to be an improvement and disease control is a vital benefit. Also, regarding safety issues I would agree in terms of the brain and spinal cord safety issues are pretty significant, and then the pediatric population is one, I think, that we see some, some meaningful evidence on secondary malignancies, and we saw some evidence on potential cost-effectiveness benefiting that population, which I think is reasonable to call out. I tend to agree with you that most of the other stuff I, we haven't seen any evidence that would really support its use other than that one scenario. So, I think, I'd like to look at that study in a little more detail.

Chris Standaert: And regarding this study you're talking about also is from '95. It is well before IMRT. It is on patients between 82 and 92, and so, that is not even compared to sort of modern standards for care for prostate cancer. So, there is no brachytherapy. There is no IMRT. There is no, so I, that is one I would personally love to get, pop, that same number pop up again in a study in the last ten years, then I would be more confident of it, but that is a limitation, too, I would think.

Daniel Ollendorf: Just a comment about the study report, there is not a clear description of how the study was powered, but it seems as though the primary outcome was local failure, as determined by PSA levels. So, there were comparisons on the specific survival, overall survival, those tend to be in these studies, but they are often felt to be too short-term to actually use those as primary endpoint, so this is based on local failure. Lots of other outcomes reported. Lots of other comparisons and subgroups, as well.

Seth Schwartz: And the one other sort of category that I wanted to pull out a little bit, I'm not sure if we need to, but what I would like to at least discuss it, we did not really see a lot of data on it, but in terms of salvage scenarios, based on the toxicities of the surrounding tissues. We know that some patients are, may have failed other treatments. They no longer have the opportunity for other treatments, and this, and based on the safety criteria that at least we have heard about through protons, that may be a possibility in some of those sort of really

extensive salvage situations, and I do not know if we want to call that out or at least have a discussion about it. We did not really see any data on its effectiveness in that scenario, and I do not know if that is part of our charge to talk about today, but that was one of the sort of...

Kevin Walsh: Or, or data on the proven safety.

Craig Blackmore: So, I am, I am worried that we are going to get talking about too many different things at once. So, I, I think I am hearing, I am going to have people turn, if you could, to page 29 of the ICER report, slide 58. There is a list of the numerous potential uses and it sounds like we have converged on a number of these as being without sufficient evidence for coverage, and so, let's get rid of the easy ones first and, and then we will have to have some more discussion about some of these others, but then we can focus on one at a time. So, so which ones can we probably...

Joann Elmore: I propose the 13 ones, the cancers with the exclusion, there is 16 listed, and I figure that as a group we would need to discuss brain and spinal, we would need to discuss ocular, and we would need to discuss pediatric, but I thought the remaining 13 would be something that I propose that we as a group get off the table right now. I also propose we get off the table the noncancerous...

Craig Blackmore: OK, so...

Joann Elmore: ...and again...

Craig Blackmore: ...you are faster than I am. You said brain and spinal, ocular, and pediatric?

Joann Elmore: Those were the only three that I think...

Craig Blackmore: OK.

Joann Elmore: ...we need to discuss further.

Craig Blackmore: And we are going to discuss prostate further, because we heard that.

Joann Elmore: OK.

Craig Blackmore: And then discuss, just discuss, and then is there any, any sort of, does anybody believe there is evidence for these others that we should consider them, as well? So, bone, breast, esophagus, GI, gynecology, head/neck, liver, lung, lymphoma, sarcoma, seminal thymoma, and noncancerous. Are we prepared to move on from those as noncovered or are there any others in that group that we need to discuss further?

Kevin Walsh: The only thing I would say about the noncancerous is, I think that some of those were CNS lesions, and so if we are talking about brain and spinal, that we might want to consider those in the same category, so.

- Craig Blackmore: OK. So, we will take those off until they get into an organ.
- Marie Brown: Well, and ocular is the one that has superior evidence, so.
- Craig Blackmore: Yeah, ocular is...
- Marie Brown: Right, I mean, that is the only one. So, that...
- Craig Blackmore: OK.
- Marie Brown: ...one would be easiest.
- Craig Blackmore: OK. So, I have got four, four that we are considering plus the noncancerous depending on location. Of the other 12, is there any other concern here?
- Michael Souter: Other than the treatment failure, which Seth alluded to, we can talk about that as a separate. It is not all in that group, but it is, it was a key question, itself.
- Craig Blackmore: Yeah. So we will, we will...
- Michael Souter: So, I think it warrants discussion again.
- Craig Blackmore: Yeah, OK. OK. So, so let's go through these one at a time, and let's start with the ocular, because again, I think from our evidence vendor that seems to be one where there was a little, at least moderate strength of evidence. So, discussion on ocular.
- Joann Elmore: I propose coverage with conditions, but I still want to see more data gathered.
- Craig Blackmore: OK.
- Joann Elmore: I would like to see them at least in a registry.
- Craig Blackmore: Thoughts?
- Joann Elmore: I do not know if that is overstepping my bounds. Remember when I first joined this committee a few years ago, I was very naive and I wanted everything coverage with research condition, because there is such poor data out there.
- Chris Standaert: Again, I, I personally do not think mandating registries are, you know, I, I just, I...
- Joann Elmore: You guys pointed out that a registry could be gathering the blood pressure, and that is data gathering.
- Chris Standaert: ...it, it, it just for us to get into that oversteps. If we think it should be covered, we think it should be covered, and...

Joann Elmore: OK.

Chris Standaert: ...that's why, there are a lot of other things where, if you really think that you need more data before you say yes, you should say, I guess we should say no to, you know.

Joann Elmore: OK.

Chris Standaert: So, the, the ocular stuff we actually have an RCT, which is unusual for these things, and it showed benefit.

Joann Elmore: Mm-hmm.

Chris Standaert: At least for up to two years.

Richard Phillips: Let me ask you a question about that. Is it not true that almost all of these studies, or I mean, all of these things that we would be recommending coverage for are going to be part of a randomized control trial? I mean, they are in some kind of trial right now?

Daniel Ollendorf: No.

Richard Phillips: Oh, they are not investigational then.

Chris Standaert: No, they are, they, I mean, payer coverages, payers cover the very same three that Joann mentioned, the payers largely cover. They are covered by most payers as routine medical care.

Richard Phillips: OK.

Chris Standaert: Yeah. So, I assume they are not all in, all in remotely in clinical trials.

Richard Phillips: OK.

Chris Standaert: People may be tracking their data doing other things. They mentioned a bunch of registries are being built around the country, but I do not know that, I would highly doubt they are all being tracked.

Craig Blackmore: Other thoughts on ocular? OK, I am hearing enthusiasm for ocular. Maybe enthusiasm is not the right word, support.

Chris Standaert: Yeah, you have some...

Craig Blackmore: I mean, we are not voting, right? This is just (inaudible).

Chris Standaert: Yeah, some improved benefit and some decreased harm, although the level is not phenomenal, it is there.

- Craig Blackmore: How about pediatrics? Does somebody want to summarize pediatric?
- Seth Schwartz: I think we are kind of falling into an X-category with pediatric. I mean, you get the sense from what is going on the community that the studies are not likely to happen. We certainly did not see a lot of inclusive evidence or really any evidence at all that it... that it is superior to the same treatments, but clearly the concept is that the side effect profile is less in the longterm. Consequences are less and the cost effectiveness data, for what it is worth, is...
- Kevin Walsh: But none of that stuff is proven.
- Seth Schwartz: Well, it depends, I, I do not completely, I disagree with you a bit. I think...
- Kevin Walsh: I mean, I think we are all, I think there is, there is, there is several hypotheses that are kind of a priori in this, in this situation, and we can accept them. We can make kind of a religious decision to accept them or not, but there is not...
- Seth Schwartz: But I disagree on that, Kevin.
- Kevin Walsh: ...safety...
- Seth Schwartz: I, I do not think it is a religious decision to say that, that, that decreased, that, I think there is some evidence to say that decreased risk of secondary malignancies is significantly different in these populations.
- Kevin Walsh: Can you show me the, the study?
- Seth Schwartz: Yeah, what was that?
- Craig Blackmore: Slide 36 and 37.
- Seth Schwartz: I am hearing slide 36 and 37. Yeah, I mean, the Sethi Study of 2013 has infield malignancies 14% with 0%. Again, you know, they are fairly small numbers, but that is, invariably these are going to be small numbers. These are rare cancers on a fairly recently treated, you know, form of treatment. So, we are not going to get better numbers than this is sort of what it comes down to, but this is highly suggestive, and this is a known consequence. I mean, treating children with cancer, with radiation therapy, secondary malignancy is a known consequence that people worried about for ages. The data is not fantastic here, but, but in my opinion compelling enough for this type of a risk assessment. So, I see that. I did not see a lot in terms of immediate side effect differences between the two. Really, I did not see a lot of that. I mean, there is certainly some suggestion of that based on what we have seen, but I, I agree with you that this is limited in terms of, you know, immediate toxicities, at least the data that we are seeing, but in terms of the late effects, I, I am convinced by what I am seeing here.
- Craig Blackmore: Other comments?

- Marie Brown: One, one piece of information that I obtained from the clinical expert that was helpful for me in looking at this was I was asking, so what is the data, how well have they studied the surrounding tissue to ensure that what they are saying is, there is no radiation there. How well documented is that, just as basic, and your explanation was that there is reasonable (inaudible).
- Kevin Walsh: But, but it does not translate data. They have not, they have not provided any information that that translates into difference in disease over time.
- Marie Brown: Radiation versus...
- Kevin Walsh: So, these are, these are...
- Marie Brown: ...no radiation?
- Kevin Walsh: But that is not what we are talking about.
- Chris Standaert: That is not what we are talking about.
- Kevin Walsh: We are talking about photon versus proton.
- Chris Standaert: And it is not broken down all by cancer type. This is a huge category so it is, you would think they are sort of (inaudible). It is a theoretical thing and they, the, the ethical question can be a bit of a trap at times and avoid you from finding, avoid people from finding the truth, and I think...
- Marie Brown: But I think...
- Chris Standaert: ...it is a problem that there is no data. It puts us in a difficult situation if there is none in the pipeline. So, it is, you know...
- Lia Halasz: But I think what we are discussing is, it is not theoretical where radiation is deposited and where it is not. We know that there is radiation to a certain body part or we know that it is not there. So, it is more of a technique, kind of like in surgery when you know where you are cutting. That is our job. We know where the radiation is, and whether that translates to clinical benefit is definitely a good question, but if you are not, if you are not giving radiation to an organ, then you are not giving radiation there, and that is not theoretical. We know that then there is no risk to that tissue, because you have not touched it.
- Kevin Walsh: But we are asking for evidence of benefit or lack of benefit, not risk.
- Chris Standaert: Well and lots, and lots of theories that do not seem to, lots of things sound good at the time.

- Michelle Simon: I have a question about the later effect of radiation. If we were looking to find out if exposure to radiation causes cancer down the road, how many years and what timeframe are we looking at? Is five years sufficient? Is it too little, too much, or what are we looking at?
- Lia Halasz: Generally, we, we look at ten years and above. There are different definitions, but in general, radiation-induced cancers are thought of as ten years and later. So, they are late effects.
- Michelle Simon: OK, so none of these studies relay then the pediatric population, encompass that timeframe, is that correct?
- Michael Souter: They, they do.
- Seth Schwartz: The Sethi Study goes up to 13 years.
- Craig Blackmore: They start, they start to. They do not, they start to.
- Michael Souter: But, but there are some, that, that is what I was kind of getting at earlier on. There is some of the population in whom they do not actually, you know, fit into that category, and we heard some of that in the evidence report that, you know, that there was some confounding there when you stripped out patients who were, in fact, developed their problems earlier than that. We all read about that kind of five-year period, but I think that, you know, given the fact there is some patients go out to, you know, 24 years, and, and right about that time that they were seeing some of that population. I was just trying to get at how many, you know, how much of the population actually goes out that long so as to be able to kind of strip out that, you know, confidence that there is a secondary effect from the radiation.
- Craig Blackmore: I, I hate the argument that we are never going to be able to study that. We cannot do research on it. The reality is, if you are looking at 20 to 30-year followup, you are looking technology from 20 or 30 years ago, and so, it, it really is not possible to know what is going on now, and we do not know what is, what it is going to look like in 20 or 30 years.
- Chris Standaert: There was this, question for the vendor. There was no data on the pediatric population broken down by tumor. So, there is no, so, like a spinal cord tumor versus, you know, a, an osteogenic sarcoma versus a lymphoma. These are very different diseases and, you know, if we talk brain as brain, we may not have the same brain from kid to adult, so, but this, but we, pediatric is a lump which I found sort of odd that it was not broken down any other way. Is there a reason for that, or?
- Daniel Ollendorf: In terms of a comparative study for the clinical benefit questions, there were none, and for the one harms study that was medulloblastoma alone.
- Chris Standaert: So, blastoma?

Daniel Ollendorf: Yeah, medulloblastoma.

Chris Standaert: So, brain?

Daniel Ollendorf: Yeah.

Chris Standaert: Yeah.

Daniel Ollendorf: I think, again, in terms of comparative study, that, that was all we had to work with anyway. There is obviously case series data that would have been broken down by tumor type, but that was not our major focus. I guess one other point I think, Craig, I think you alluded to this already is that in part the lack of comparative study is because there was this early clinical acceptance of the use in these relatively rare pediatric cancers. There was really not, no longer anything to compare these patients to. I may be overstepping my bounds by saying that but I, I do not, I do not know that there is any prospect for future comparative study or even any benefit in looking at older generation technology that would have been used before proton became acceptable for this particular cancer type.

Craig Blackmore: And we, we do know, from several different sources, that children are more radiosensitive, so the same radiation dose is somewhere between two and four or even eight times more likely to cause cancer in a child than in an adult, and that is established from, you know, the data from Hiroshima and data from various other radiology studies even at low doses. So, so it is not, so there is that, and then there is also the fact that children with many of these tumors that can actually be cured are likely to live through their whole latent period, and they have a life expectancy of more than 10 or 20 or more years, and so they can get a secondary malignancy. So, where a secondary malignancy in a 7-year-old with prostate cancer is theoretical construct that may be less clinically relevant for most of those individuals, in these children, it is potentially very relevant. So, it is not, the risk is real. We have not necessarily seen data that that risk is decreased because of difference in technique, but it does make sense that more careful fractionation or more careful cloning of the field would be of more value in a pediatric population than in an older population.

So, just in terms of process, we have been sort of going through casually, but I wonder if maybe we do need to jump ahead a little bit and, and actually vote on each of these conditions separately so we do not have to keep going back and forth. I am looking for nods of heads. OK, so, so why don't we, it will not be a formal vote with cards, but it will at least be a show of hands that we are going to include. So, so from the process standpoint, we are going to either vote cover, no cover, or cover with conditions. So, we are now in the exercise of determining what the conditions would look like if we chose to cover with conditions. So, I am going to go by show of hand votes if each of these should be included as our, one of our draft conditions. You guys understand where I am going with this, right?

So, the first is how many people think ocular, just to be complete, would be among our covered conditions. I want a show of hands, OK? So, if I can get a (inaudible) of this. We do not need all the text, just a list of where we are. OK, so now let's look at pediatrics. So, again, should we include pediatric as one of the conditions under which we will cover, and if I can get a show of hands for that. So, we have got most. So, put that on the list. Next, I want to go to brain and spinal, and ask somebody on the committee to give me a, ground us on brain and spinal. Tell us where they think we are. Slide 33 is harms. Slide 23 is...

Kevin Walsh: So, there were, I think there were two studies. There was a poor-quality retrospective study of 40 patients who received proton beam therapy or photon therapy after surgery for medulloblastoma. At two years, there was no difference in overall or progression-free survival. There was another retrospective study with 32 patients, 24-month followup controlled for age, tumor, pathology, and treatment modality and proton therapy was associated with a significantly increased mortality risk.

Craig Blackmore: So, where are you?

Chris Standaert: It is 36 of the report, it is there.

Craig Blackmore: Page 36 of the report.

Chris Standaert: And actually, that is where the, even the second study is tricky, 'cause it is, the adults, they got IMRT with the mean age of 40, and the mean age of the pediatric group was 14. So, there, they compared them, but these are, I mean, these are, again, probably different. Are they giving, it may be the same tumor but different, they may be ventricular gliomas, but they took very different populations, but actually proton beam therapy looks like it did worse. The, the crude mortality was lower for proton beam therapy, but when controlled for age, tumor pathology, and treatment modality, you start to see an increased mortality risk at a ratio of 40.

Daniel Ollendorf: And we saw that to be a counterintuitive finding. We attempted to contact the first author and never got a response.

Chris Standaert: What do you mean by that? Why do you find it counterintuitive?

Daniel Ollendorf: Well, usually when a crude mortality rate is lower, even after adjustment, you would not necessarily see a flip in mortality risk that is that dramatic, 40 times increased risk of mortality. I do not know if this is driven entirely by the big age difference or what have you. It just seems strange.

Chris Standaert: But they also may be, again, very different diseases and if you had it at age 14 it may be much, your longterm survival may be a lot less regardless of what you

do. I do not know, I do not know if that is the case, but it would not be an unreasonable supposition.

Kevin Walsh: Together, I was not impressed that there was proven benefit.

Chris Standaert: No. It again falls in the theoretical thing that neural structures are particularly sensitive and often, maybe the clinical expert can help me, but they are often sort of rate limiting in the toxicity of the neural structures.

Lia Halasz: Yeah, and that is a big issue with brain.

Chris Standaert: Yeah.

Lia Halasz: Because the whole interval...

Chris Standaert: Theoretical.

Lia Halasz: ...dose to the brain is always decreased and then depending on exactly where it is, then you can limit to for neural cognition and eyes and...

Chris Standaert: So, theoretically on proton beam therapy, do you do, do you deliver a higher dose to the tumor in proton beam therapy than in IMRT in a brain lesion because you do not have all the surrounding limitations?

Lia Halasz: Data has been done in some trials and actually one of the new RTOG trial for glioblastoma plans to do just that, but generally right now it allows us to have better plans in terms of sparing normal tissues. So, it...

Chris Standaert: OK.

Lia Halasz: ...most often, accepting more for patients who have, you know, a good prognosis, as was pointed out here, benign...

Chris Standaert: Mm-hmm.

Lia Halasz: ...lesion and lower grade brain tumors, but there is a cooperative group looking at increasing dose, which MGH has also done in the past.

Chris Standaert: OK.

Craig Blackmore: So, I mean, there are two issues, right? There, is proton beam more effective, meaning mortalities change or is it safer meaning mortality is the same but we are getting less toxicity to the adjacent brain. So, I do not know what to make of the mortality data. It is counterintuitive, but it is hard to be convinced these patients are doing any better, but then there is the issue of, are we really sparing toxicity to the adjacent brain parenchyma, which looks like slide 33, I believe. So, what does that data look like with more granularity? So, it looks

like there is one, the one study of 40 adults. Proton beam had lower rates of weight loss and esophagitis.

Seth Schwartz: Well, Craig, on slide 33, I am not sure where the summary comes from, but they, they, the summary slide was that there is decreased toxicity and decreased to significant harms in brain and spinal cancers.

Craig Blackmore: Yeah.

Kevin Walsh: Right, but we are looking at, we are looking at the actual studies.

Craig Blackmore: And I am trying to drill down on that, and page 49 of the report, which I...

Kevin Walsh: Right, well...

Craig Blackmore: ...think...

Kevin Walsh: I think Craig is saying, so what exactly is the decreased toxicity?

Seth Schwartz: Got it.

Craig Blackmore: I am trying to understand and then, so, if there is one study of 40 adults and there is a second poor quality study comparing ten pediatric patients to 22 adults. I am not sure I want to deal with that too much, and then there are two case series, 39 patients with glioblastoma, but there is no comparison. So, it is hard to know what to do with that. So, mostly we are relying on 40 adults treated for medulloblastoma and statistically significant lower rates of weight loss, esophagitis, nausea, and vomiting, which I guess I was more concerned about neurocognitive decline and some of these other things.

Group: Right.

Chris Standaert: That is the thing. We have that theoretical issue of, you know, cognitive decline and the data we saw on the data graph, so, IQ declining, pediatrics depending on when they were dosed. Like, it brings me back to pediatric was brain, neuro, as well as the whole issue of the theoretical neurocognitive stuff and the theory versus the proof.

Craig Blackmore: And, and there is, there is also the issue of adult versus pediatric. I mean, if we are...

Chris Standaert: Yeah.

Craig Blackmore: ...already allowing the pediatric, is any of what we are looking at in brain and spine really in adults or is that all data on pediatrics. That was my question. Do we have adult data on the spine? Or is it all?

Kevin Walsh: Well, isn't the Brown, is the Brown study pediatric or adult?

Chris Standaert: Brown study is adult.

Daniel Ollendorf: The Brown study is the only one.

Craig Blackmore: It is adult.

Daniel Ollendorf: That is the adult one.

Craig Blackmore: Yeah, and that is giving us some systemic...

Chris Standaert: Yeah, and they seem to do, tolerate the treatment better substantially.

Craig Blackmore: Yeah, the esophagitis is (inaudible). We need more data.

Chris Standaert: Mm-hmm.

Craig Blackmore: OK, I mean, what, what do you guys think? Where are we in brain and spine? Theoretical benefits. There is a not a lot of data. I mean, we can vote, but I would rather make sure we had a chance to talk it through.

Richard Phillips: On the brain and spine?

Craig Blackmore: Yeah, yeah.

Richard Phillips: OK. One other thing was that the guideline recommendations is that it was universally recommended in all the guidelines, so, not that that necessarily...

Chris Standaert: Mm-hmm.

Richard Phillips: ...reflects our evidence, but it is, I think, an important factor.

Seth Schwartz: Universally (inaudible).

Craig Blackmore: Anybody we have not heard from that wants to comment? Alright. So, I will just go with a show of hands again on brain and spine. So, including that as a condition, let's just have your hands. That is more than half. We are not voting officially. Alright, next on the list is prostate.

Chris Standaert: (inaudible) Oh, we did pediatric, OK.

Craig Blackmore: So, prostate, we heard a little bit. Seth, do you want to reiterate? There was one particular study?

Seth Schwartz: Yeah, well I think some points were brought up that were good points about it. It was just, it was an older study from '95 that had that one subgroup of patients with poorly-differentiated cancers that did about twice as well with protons

versus IMRT and I would just would love to hear a little more detail about that study.

Daniel Ollendorf: Not IMRT.

Seth Schwartz: Sorry...

Daniel Ollendorf: It, it was older with degeneration photon.

Seth Schwartz: It was, and we said it did significant, that it did really well. What was shown was that local controlled tumor was better.

Craig Blackmore: Well, it is even more than that. So, it was an RCT of 202 patients, and there was no difference, but when they did a subanalysis on the poorly-differentiated tumor, so post-hoc, grades 4 and 5, local controlled eight years was significantly better.

Seth Schwartz: Right.

Craig Blackmore: But not survival...

Kevin Walsh: So, my quest-, my, my point is...

Craig Blackmore: Yeah.

Kevin Walsh: ...does local control linearly translate into better outcome?

Craig Blackmore: And what is the value of the secondary analysis of the subpopulation in an RCT that was not your...

Kevin Walsh: Well, I was not even going to go there.

Craig Blackmore: Yeah, but...

Kevin Walsh: I, I am just, I am just asking, I mean, I, I understand. It is, local control is better, but does that translate into anything?

Seth Schwartz: Well, I mean, one of the other more recent studies also showed there was, there was, at least on some, some scales on the quality of life assessments, there was an improvement in the, or that the patients with, who had protons did better, as well. So, again, on the overall quality of life, it was not real clear.

Craig Blackmore: Which study?

Seth Schwartz: That, that was the two fair quality comparative cohorts, the Galbraith from 2001, and the overall differences, here it is.

- Richard Phillips: But I think this is also, with prostate cancer one of the big issues is, is entering into adjacent tissue as being a critical thing, and I do not think there was a lot of difference statistically, and that is the reason I was very much up in the air about prostate. I do not, I did not see that the proton therapy was overwhelmingly better than other forms of therapy.
- Chris Standaert: No, I did not see it either.
- Richard Phillips: Even, you know, even though what you mention is true.
- Chris Standaert: It is not without complications, either. It actually came out worse on a number of the safety, the side effects when compared to IMRT.
- Richard Phillips: Yes.
- Chris Standaert: Yeah, compared to the better.
- Richard Phillips: And did not, and maybe even, we did not get any comparison with brachytherapy, but.
- Craig Blackmore: Yeah.
- Daniel Ollendorf: There was one study comparing proton to brachytherapy, but it was focused on clinical benefits not on harms.
- Richard Phillips: Oh, OK.
- Daniel Ollendorf: But they were, and there were no differences between the two groups.
- Richard Phillips: Yeah.
- Chris Standaert: So, I mean, that one, there actually are data that, we have that theoretical issue with the brain that maybe it does things that work, and we have the same theoretical concerns as the prostate, but we actually have many more patients being followed after radiation of prostate and then they are not panning out very well. That, that is that neural complication that are not significantly reduced at all, particularly longterm. They (inaudible) six-month (inaudible) and other complications are higher. So, it is, you cannot even rest on the theory there. It is not really panning out by the data that is published to date.
- Craig Blackmore: Yeah, I think we had, I think they are higher.
- Richard Phillips: Can our clinical expert weigh in on this, since, do you see much difference between, is there one form of therapy that clearly is better from a safety standpoint or from a treatment standpoint?
- Lia Halasz: Yeah, honestly, I think that is what is still being debated, you know, in the trials that you see and then that is why also we are doing a randomized controlled

trial now to kind of look. You know, each of these studies has their, I do not know if this is overstepping bounds today, but usually these studies have their pluses and minuses, and as you guys all know through Medicare there is also question about how that kind of data comes as a randomized trial, which were often dose escalation and so looked at it like that, but I think you know, actually ICER did a good job of presenting everything that is out there. I do not know the other data, except for data that is going to come up and be published.

Richard Phillips: Yeah.

Craig Blackmore: So, on slide 35, looking at the safety of the prostate cancer, there was one study that had worse complications of rectal bleeding in the proton group, and the retrospective databases, GI morbidity was higher in proton in one study, in two studies, and then the third one it was lower, or urinary was lower, but GI was higher in the others. So, I mean, I think it is...

Joann Elmore: (inaudible) it did not pan out if you look (inaudible).

Craig Blackmore: (inaudible) a year later. So, I think there is, if there is evidence of differential safety, it would, it is not great, but it would lean against the proton based on what we know, but it may actually have more complications.

Chris Standaert: Right, then again, there is more evidence than we have for some other things that the benefit is not really there that it is not substantially better.

Michael Souter: I am just very struck by, you know, the semi-familiar, when we were discussing the IMRT question previously in our meetings that we were going around this, this similar question about, you know, the, the safety of those, because I see a less role for, for proton beam therapy there and one could guess that doctor vendor was for IMRT.

Craig Blackmore: OK. So, so how many, I want hands if you think we should include prostate as a condition of coverage. Raise them now if you wish to. OK, so get rid of that. OK, that leaves us with the treatment failure group.

Seth Schwartz: The benign conditions, yeah. Are we just going to lump that in with the brain and spinal?

Craig Blackmore: Um...

Seth Schwartz: Which is what I would propose. I am just...

Craig Blackmore: Right, I mean, I, I thought that is what we were going to do.

Seth Schwartz: OK, that is fine.

Craig Blackmore: Is that, is that what?

Michelle Simon: That is what we did.

Craig Blackmore: Yeah, OK. OK. OK, so, so salvage. So, this is, I am trying to find the right page. So, key question two, recurrent conditions. Let's skip the ocular.

Marie Brown: What are other, cover, other (inaudible) coverage decisions on, on salvage?

Craig Blackmore: I do not know. Let's look at that.

Marie Brown: Other insurers, I guess.

Craig Blackmore: Yep. I do not know. CNS local, I do not see it. Private payers, well I am not seeing anything in the summary. It could be down more. Practice guidelines.

Chris Standaert: Where is the report of the Chung Study in the, in the report? Where is the discussion of that? I am trying to figure out...

Daniel Ollendorf: Secondary malignancy study?

Chris Standaert: Yeah.

Daniel Ollendorf: In the harms. It is the first couple of paragraphs.

Marie Brown: So, that would be page what?

Daniel Ollendorf: I am looking now.

Craig Blackmore: It takes you to, it looks like page 44.

Chris Standaert: 44, yeah.

Craig Blackmore: It is the, on key question two, recurrent cancer.

Marie Brown: OK.

Chris Standaert: So, I guess I was asking this question before and I maybe did not ask it quite correctly. So, it, there is an issue with, there are almost two issues here. There is the issue of sort of dealing with recurrent disease with prior failed treatment where you try the treatment and it did not work, the disease comes back. You want to do something. You probably should not do the same thing, because it did not work the first time, so you have to rethink your, your algorithm or whatever you are trying to do clinically versus people who either have recurrent disease or even a new disease in the setting of prior radiation treatment where they have late, reached their toxicity limits where you cannot irradiate them with photon beam again and whether it is, it may not be a recurrent tumor. It may be a new tumor. It may be something else. It may be a tumor 20 years later, as a consequence of the first chemotherapy, and no you have to reradiate them and they are 35 years old and I was trying to get a good data on that. I

was, that is what I was sort of looking for and then people were really, you just cannot, and whether this is salvage or treatment as a last resort, or whether this is, you would like to use the radiation therapy treatment but toxicity limits every other radiation approach, and so in that setting, is there data that sort of looks at those, at that population? You seem to understand the population I am describing.

Lia Halasz: Yeah, no. I think, I think that is a very good way to kind of look at it. I think that the report looked at the first...

Chris Standaert: Yeah.

Lia Halasz: ...scenario that you are talking about. So, recurrent disease does not necessarily mean that it was gone through radiation before.

Chris Standaert: Right.

Lia Halasz: It could have, but it could not have. What I think was brought up with public comment and...

Chris Standaert: Right.

Craig Blackmore: So, I...

Lia Halasz: ...we were talking about...

Craig Blackmore: ...sorry, I, I...

Lia Halasz: ...reirradiation, so.

Craig Blackmore: ...I do not mean to interrupt, but actually I do. Did, what did the report say? I mean, you are, did, did the evidence review attempt to encompass people who had recurrence or new disease and are already radiated field and the comparison of using, of, the clinical scenario of using proton beam in that already radiated field either with or without comparison to some other treatment.

Daniel Ollendorf: So...

Craig Blackmore: I am not sure that it did, and I want to know if it really did.

Daniel Ollendorf: We looked at use or proton beam in a setting of recurrent disease. It could have been recurrent disease in the prior radiation field. It could have been recurrent disease based on treatment with something else beforehand. So...

Craig Blackmore: So, if it was there...

- Daniel Ollendorf: If there was recurrent disease and there was proton beam used in a comparative study, then we would have captured it. So, one example of reirradiation is the ocular study that is in they key quest, summarized in this key question, Marucci and colleagues. So, these are patients who had a first course of proton beam therapy who had recurrent uveal melanoma and then were treated with a second course of proton beam or surgical enucleation.
- Joann Elmore: And because there are no data on the topic of salvage treatment of last resort, I favor noncoverage with the understanding that we have already discussed in the context of a clinical trial individual clinicians can contact the state offices.
- Craig Blackmore: Comments? Does anybody want to present a different perspective?
- Chris Standaert: This is tricky because there is a huge data gap, and it is not a big population, and I guess I could forsee patients who just do not have other therapeutic options where you are, where salvage is, palliation is, whatever, and it is a theoretical thing, and you are trying to limit dose and all these sorts of things and, but it is not going to be in a study because you have one patient who fits no, they are going to be, they are going to be so sporadic that I, I assume those people can apply to the agencies for coverage and say we have a sole situation. I assume you get this all the time. Even if something is not covered somebody says, no, I really have a problem here. There is nothing else I can do. Can you please reconsider? I assume you do this regularly. So, us saying, us not including that does not mean those people cannot appeal to the state and the providers do not have any way through the state.
- Daniel Ollendorf: Correct.
- Marie Brown: Right.
- Chris Standaert: Is that correct?
- Daniel Ollendorf: Correct.
- Chris Standaert: Am I correct or incorrect?
- Gary Franklin: I mean that, that does happen, but again, Josh, I would, I would ask so this in the context of...
- Josh Morse: So, if it is no cover...
- Gary Franklin: ...noncoverage.
- Josh Morse: ...it is no cover.
- Gary Franklin: It is not covered.

- Josh Morse: If it, the request comes and it is in the context of a clinical trial, then there is the option for coverage.
- Seth Schwartz: OK, I am struggling with this, too. I mean, it is almost like a humane use type of situation, because I, I...
- Chris Standaert: Right.
- Seth Schwartz: ...I do not think we are ever going to be able to study these patients. There is not going to be a study...
- Chris Standaert: Right.
- Seth Schwartz: ...for patients who have been radiated twice before and have this persistent disease and whatever else. You know, it may be that this is a decision that, that, the better choice may be not to do anything, but we do not know that, I mean, that is, and that is, these are these very one-on-one situations that if we say no cover and they cannot appeal, then it is no cover period, and so that is why I am just, I find that one situation a little bit problematic, because this is a technology that while, well, there are a lot of questions about benefit and harms and things like that. They can create a dosimetry spectrum where they can treat it, potentially treat a tumor without toxic effect to the surrounding tissues that you cannot do otherwise. At least that is what I am hearing from the, from the expert. Is that true?
- Lia Halasz: Yes, it is. There is a certain dose limit that you just cannot go over a lifetime.
- Seth Schwartz: And, and currently would, could you use protons in that situation or are you using protons in this.
- Lia Halasz: We are using protons in that situation, and as you point out, it was, it started as a very much case-by-case basis, because it depends on what you receive it for, and generally we also look at our different modalities and see which one comes out the best in terms of the, you know, the toxicities, and I think, you know, that is part of the anatomic, you know, planning of radiation is really a very individualized treatment plan.
- Seth Schwartz: So, what is challenging here is, I do not want to simply say, well if you cannot give other radiation fields, you should, you can go ahead and get protons, but at the same time, if there is scenario where...
- Chris Standaert: Right.
- Seth Schwartz: ...really there are no other options and you have a patient who (inaudible).
- Chris Standaert: Page 83 is totally nebulous. I mean, I do not like being nebulous in these things, and I, and I get the evidence thing, but I agree with you. There is almost this humanitarian thing and if our not including it wipes that out, could we say

something like, patients with significant radiation dose or safety concerns could be treated at the agency's discretion where it has to be on that basis or something like that. I don't know. I am try, just off the top of my head we have said something like that before in one of these things.

Carson Odegard: Well, I think we have got...

Chris Standaert: Because that is the population you are after.

Marie Brown: Right.

Carson Odegard: We have run into this before with other technologies, and I think it is one of these situations where there is just so few patients that it is basically at the clinical judgment of the professionals that know when this is appropriate and when it is not. I do not think we are running into a situation where you are going to have a lot of patients that are going to fall in this category.

Chris Standaert: No.

Craig Blackmore: How, I do not know how often this comes up. How often does this come up in practice?

Lia Halasz: Um, well, to be honest, at, at a referral center it comes up more, because you get sent patients from all over, also...

Craig Blackmore: But all for the time . . .

Lia Halasz: ...hmm?

Craig Blackmore: ...it is all, for the time being, centers are referral centers, right?

Lia Halasz: Exactly, exactly, but you know, especially for our University of Washington population, we do see quite a few. I think the other thing is, this is becoming more common, as well, as patients get a better systemic therapy, so, which means that they live longer and so you have more locally recurrent disease.

Craig Blackmore: Yeah.

Lia Halasz: You know, so it used to, if advanced disease, it used to be sort of a non-issue because you did not have these people running around with three times recurrence and doing well. So, it, it does happen, you know, quite often in our practice. Also, because the techniques have just gotten better over time, then I think that, you know, that the toxicity is possible to be able to do that.

Craig Blackmore: So, it is possible to do it, but we do not know if it helps. We do not know if it is better than other options, but the other options are pretty limited. There may not be any other options, except to do nothing, but of course, we do not know if going that way is not better.

Marie Brown: Yes, right.

Craig Blackmore: Other thoughts?

Seth Schwartz: It is always hard to lay conditions when we do not have data to base the conditions off, and, and it seems that we have handled situations like this before by being very restrictive but not explicitly saying no coverage. So, you know, saying your patient has to have, there has to be a previously-radiated field, exhausted all other potential treatment options, then it can be done on a case-by-case basis or something like that. I mean, I, I, I guess I would favor some highly-restrictive situation that could be evaluated on a case-by-case basis so the physician and the, and the patient could look at it all and say well, look there is nothing else to do, and if they decide still that it is better to do that than to do nothing, that they can at least...

Richard Phillips: Yeah.

Seth Schwartz: ...apply to the agency for, for...

Richard Phillips: So, this would be a cover with conditions, as far as that goes.

Chris Standaert: So, if they say...

Seth Schwartz: Yeah, and then, and then...

Chris Standaert: ...those prior radiation with significant concerns about toxicity on a case-by-case basis, but it has to be people who have been irradiated previously, not...

Seth Schwartz: Yeah, I, I...

Chris Standaert: ...only...

Seth Schwartz: ...we are only talking about previously-radiated sites.

Chris Standaert: Right.

Seth Schwartz: Yeah.

Craig Blackmore: Yeah, I guess my framework on this whole issue is that we have a new technology that is more expensive and we have to show that it is better than existing alternatives if we want it to be covered, but now we are talking about a situation where we do not have an existing alternative in effect. So, I think that, that, the framework is different.

Michael Souter: Well, if you do not have an alternative...

Craig Blackmore: We still do not know if it works, but I do not have the alternative.

- Michael Souter: But if you do not have an alternative, I mean, it's (inaudible) to some extent but...
- Richard Phillips: It, yeah...
- Michael Souter: ...nonetheless.
- Richard Phillips: ...becomes an overwhelming safety issue.
- Craig Blackmore: Yeah. Well, I mean, you still do not know if it works, right?
- Seth Schwartz: Right.
- Richard Phillips: Yeah.
- Craig Blackmore: That is, there is, the alternative is always to do nothing, which might be the answer. We do not know.
- Chris Standaert: Yeah, something is not always better than nothing.
- Seth Schwartz: Well, and, you know, and, and just in clinical practice, thinking about the way this often works, you have a patient with previous radiation to an area and you cannot reradiate them because you are worried about surrounding toxicities. You end up doing either nothing or oftentimes a radical surgery, which can be pretty bad in its own right, and yet you may, we do that frequently. It may or may not be the right thing to do, but, you know, it happens, and so if this is an existing alternative, and again, we are talking about extreme situations, and I do not know how best to frame it, but I am, I am uncomfortable totally excluding the use of this in these...
- Chris Standaert: Right.
- Seth Schwartz: ...extreme situations.
- Chris Standaert: Something like, in patients with prior radiation therapy who are contraindicated for other forms of radiation therapy.
- Craig Blackmore: Well that is, that is a given. It has to be contraindicated, for me, it has to be, you cannot get any more...
- Chris Standaert: Yeah, but that, that is what I am trying to say, but I mean, let's explicitly say that.
- Craig Blackmore: Prior radiation (inaudible).
- Chris Standaert: Prior radiation with contraindication to any, to other forms of, say to other forms of photon radiation, photon-based radiation therapy.

- Michelle Simon: I understand what we are trying to do. I, really, but I still think we are guessing whether it is the right thing to do.
- Chris Standaert: If...
- Michelle Simon: We are talking about a, quite expensive technology and if you think about the cost of the treatment, \$35,000, how many screening colonoscopies can you cover for that with the state, you know? Simple things that could be covered. We only have a set amount of money that we have and we are, we are choosing to use it in the, a technology that is, in my mind, yet unproven. (inaudible).
- Chris Standaert: No, good consideration.
- Seth Schwartz: I like the statement, inability to use other forms of photon therapy, because, I mean, there are things like stereotactic radiosurgery, which may reduce doses to those focal areas and so, and that is what I am talking about and that, that is currently covered. So, that would be an alternative, but if that is not even an alternative.
- Chris Standaert: Right.
- Craig Blackmore: It is tough for me to spend most of our resources in the last six months of life and a lot of it is on treatment that is futile and...
- Marie Brown: That is right.
- Craig Blackmore: ...we do not know, necessarily, in advance or we would not do it maybe, but we do not know if this is another example of that or not, and...
- Marie Brown: Right.
- Craig Blackmore: ...the data is not going to help us understand that, and it is tough. It is challenging.
- Seth Schwartz: Well, do, do you want to take just a, a straw poll of whether we think we should try to structure a condition for this or...
- Craig Blackmore: Yeah.
- Seth Schwartz: ...because if people say we do not even need to worry about this, people say do not cover anyway, then we do not need to go...
- Craig Blackmore: I think that...
- Seth Schwartz: ...into discussion and try to frame what it sounds like.

- Craig Blackmore: ...that is exactly what we should do. I was just trying to make up my own mind before I do that.
- Joann Elmore: Can I make one request?
- Craig Blackmore: Yeah.
- Joann Elmore: That at a, a future meeting that we spend 15 to 30 minutes having you go over what are the ground rules and current legal issues within the state for things that we vote to not cover if someone wants to make a request. I am a little unclear. I, I had thought that some of these groups, if it within the context of gathering data, I mean, a clinical trial, does it have to be a clinical trial? In other words, I would assume that we could vote noncoverage and yet they could contact you if it is in the guise of a, a clinical study, registry, or compassionate use on an individual basis, they still have leeway, and so, that is what I heard half an hour ago, and then I heard ten minutes ago, no. If we vote no for this salvage...
- Seth Schwartz: For the study scenario, we heard yes. We have not talked about compassionate use at all.
- Chris Standaert: Right.
- Seth Schwartz: So, that is...
- Joann Elmore: No...
- Seth Schwartz: ...what we are talking about here, and I, I propose that we do that at the retreat. That might be a good place for it.
- Joann Elmore: OK.
- Josh Morse: So, the law is very clear on medical necessity questions, that those are not a consideration if you say no cover and I guess that is a question for our, our state attorney about compassionate use versus medical necessity.
- Joann Elmore: So, if we say no cover, even if they say it is in the guise of a clinical study, it is still no cover.
- Josh Morse: No, that is a different... that is a different situation.
- Chris Standaert: That, that is really (inaudible).
- Joann Elmore: OK, well see, I mean, how do you, OK, as an investigator how does one define a clinical study. You can say a clinical study is a, is a case of, you know, two people.
- Chris Standaert: They have to decide, I mean...

Joann Elmore: Yeah, and they can decide...

Chris Standaert: ...if, they can decide.

Joann Elmore: ...they can have two people that have this or one person.

Chris Standaert: But maybe that is all they need.

Joann Elmore: Maybe that is all that needs.

Seth Schwartz: But I do not think that is what we are talking about. I mean, we are not talking about patients that they are going to be studying here. I guess, I guess, you know, as Chris and I were saying before, I do not think this is a patient population that is ever really going to be amenable to study, because it is going to be, right now I could be wrong about that. Maybe, maybe there will be some study on these patients or whatever, but I, the scenario that I am thinking about as I, and I kind of brought this up, was not in the context of a trial. It was in the context of essentially compassionate use, and it would be hard to make an argument to the state, but, you know, that, o well, we are going to study this one patient, you know?

Joann Elmore: Mm-hmm.

Seth Schwartz: It is disingenuous to do that. I think that either there is a compassionate use exception or there is not, and if there is not, then I am debating whether we should create one.

Chris Standaert: I am not sure that is the right word, though, I mean, compassionate, in part, implies that there is some other treatment that they know would benefit that they cannot have, I mean, we do not know, like Craig said. So, is it actually better or worse than doing nothing? We do not know.

Marie Brown: We do not know.

Chris Standaert: We do not know, and so, yeah, I, I do not know if, I would not use the word...

Seth Schwartz: But there are several...

Chris Standaert: ...compassionate there, I mean...

Seth Schwartz: ...situations there. I mean, one could be, I think that is, compassionate use is probably the wrong word, but...

Chris Standaert: Right.

Seth Schwartz: ...it could be a secondary malignancy in a field that is previously irradiated. So that...

- Chris Standaert: Yeah, no, no (inaudible).
- Seth Schwartz: ...and that is not a situation where you say, OK, well we are, well we just should not do anything about that because it is a new tumor, but they may not have other options.
- Craig Blackmore: OK, so I guess we will follow Seth's recommendation that we have a straw vote about whether it is time to figure out wording on, I mean, I think we all know what we are dealing with now. We are dealing with individuals who have exhausted their options for photon radiation therapy. Should we word a condition around the use of protons for those individuals. Again, we can work on wording, but can I get a straw vote about who would, among the committee, would feel it is appropriate to have that be one of our conditions, and I, and I will just take a show of hands, please. What is that, four?
- Chris Standaert: Five. It depends if we can make it really tight.
- Craig Blackmore: Alright, we will work on wording and see if, see if that helps. OK. So, so prior radiation with contradiction, contraindication to other forms of radiation therapy. That I think is fair. Does that make sense?
- Joann Elmore: I think someone else said at the opinion, or discretion, of the medical directors. In other words, let them decide.
- Chris Standaert: Expectation of clinical improvement or something maybe?
- Craig Blackmore: That is their job.
- Chris Standaert: But maybe, it is not futility if you really think...
- Marie Brown: I think I would not have the salvage treatment of (inaudible)...
- Chris Standaert: No, that was, that part needs to go away, yeah.
- Marie Brown: (inaudible)
- Chris Standaert: That is the category we are talking about.
- Michelle Simon: One of the guidelines talked about, I think it said more than two years, less than two years of symptoms.
- Craig Blackmore: Well, that is a good point. Yeah, we will, if we could get that wording.
- Seth Schwartz: Wasn't it Medicare?
- Michelle Simon: Yeah, it was Medicare, right.

Joann Elmore: In other words, we do not recommend this in someone with severe comorbid congestive heart failure and is (inaudible).

Seth Schwartz: Yeah, and, and not necessarily a total hail Mary, but that, I think that is a great (inaudible).

Chris Standaert: That is right, and it cannot be a (inaudible).

Craig Blackmore: (inaudible)

Marie Brown: And why, why did that set, pick that two years?

Richard Phillips: It is a local coverage.

Marie Brown: Why did the pick that?

Richard Phillips: (inaudible)

Chris Standaert: Boy, us throwing that line and knowing how hard it is to make that prediction and I am not sure I want, you know, one year, one and a half year, 20 months, two years, I mean, gee.

Marie Brown: Right.

Chris Standaert: I think something about leaving it to the discretion or with, with the expectation of, or with, with potential for, for responsiveness of tumor to further local treat, to further local risk, something to tell you that there is some reason to think that this will help.

Craig Blackmore: He would not recommend it if he did not think it had potential for (inaudible).

Chris Standaert: Right.

Marie Brown: Although he might, he might just to do something.

Chris Standaert: Yeah, he might just to do something.

Marie Brown: Yeah.

Michael Souter: I mean, if you are asking for somebody to predict the future, they are just going to do it and then they say, whoop, I got it wrong, whoops.

Chris Standaert: Right, exactly. I would put at agency's discretion, I suppose on a case by case basis.

Richard Phillips: It is good the way it stands.

Michael Souter: Well, then that is just, for (inaudible) I think (inaudible). That is effectively us saying we cannot make a decision.

Joann Elmore: Yeah, we cannot. We do not have the data, but we realize...

Craig Blackmore: But if we do not have the data, then we are obligated to say no.

Joann Elmore: ...no. That is just it.

Seth Schwartz: That should be contraindication to all other forms.

Marie Brown: All other forms of therapy?

Michael Souter: Mm-hmm.

Richard Phillips: Yeah, to other forms of intervention, radiation or intervention therapy.

Craig Blackmore: I think we put radiation in.

Chris Standaert: So, I mean, in cases, contraindication to surgery?

Seth Schwartz: All other forms of radiation therapy.

Chris Standaert: I, I would keep radiation. I mean, that is the whole context.

Joann Elmore: Before therapy, I mean before surgery.

Craig Blackmore: OK, I, I mean I am not hearing that we can come up with any other reasonable way of restricting this to the target population. Are there other suggestions for how we might do that, or not?

Chris Standaert: I mean, I would put the radiation back in...

Craig Blackmore: (inaudible) radiation.

Chris Standaert: ...of radiation therapy. We are not talking about (inaudible).

Carson Odegard: You almost have to have radiation therapy.

Group: Yeah.

Chris Standaert: You can take out the, the parenthesis. That is the punctuation I was looking for.

Craig Blackmore: Prior radiation. So, it should specify that it is prior radiation to that target, not just he got radiated somewhere, although maybe that applies.

Michael Souter: Up to that area.

- Chris Standaert: Prior radiation...
- Michael Souter: (inaudible) might be adjacent.
- Craig Blackmore: Right. Prior radiated tissue.
- Michael Souter: Mm-hmm.
- Craig Blackmore: Yeah, I mean, I think we know what we are trying to say here. I am just not sure we are being as concrete.
- Chris Standaert: Prior radiation in the expected treatment field with contraindication to all other forms of radiation therapy.
- Michael Souter: Mm-hmm, something like that.
- Chris Standaert: Prior radiation within the expected treatment field but prior radi-, but radiation at the end of the sentence there, prior rad-, prior radiation.
- Craig Blackmore: What were the other coverage decisions on this one we were trying not to conflict with?
- Marie Brown: I think there was no mention of the, anything.
- Daniel Ollendorf: Sorry. I am not sure we found anything specific.
- Craig Blackmore: No other, other, when we do this we are saying every case of prostate cancer or every case of any other kind of cancer that has already gotten radiated and recurs is eligible for proton beam.
- Chris Standaert: If they cannot proceed with any other type of radiation.
- Craig Blackmore: Well, I mean, they got the radiation. The tumor came back. We are going to give them all proton beam. Is that our goal?
- Chris Standaert: Can you not re-, I mean, assuming they are, only if they are at their toxicity limit from IMRT or whatever you gave them the first time.
- Craig Blackmore: Yeah, so that is, you know, everybody gets their radiation, that standard treatment for all these cancers, and if they all, if they recur, which some of them do, we are saying they are now all eligible for proton beam. Is that our intent? Are we (inaudible).
- Joann Elmore: I am not supportive of this, but (inaudible) second radiation word needs to come out because what about aren't, he could be eligible for surgery, you know, or something else. It might be a proven benefit as opposed to just theoretical, and I can see where (inaudible) word.

- Richard Phillips: The way I would look at that is if that is what the managing radiation therapist say, I would support it. It is not what I would do, because I do not know any better, and I am going to try to do that, but I am just saying that, if that is what they say, who am I to argue with them?
- Craig Blackmore: Well, if we just leave it up to radiation therapy, you do not actually need this committee.
- Richard Phillips: Leave it up to the, I am sorry?
- Chris Standaert: I just...
- Craig Blackmore: I mean, our, our job is to look at the evidence and make a decision and we cannot just...
- Richard Phillips: Well, you know, there is all forms of evidence, too, and it is pretty weak, here. There is no doubt about it.
- Chris Standaert: Yeah.
- Richard Phillips: But the issue is, you know, I mean, we did not even consider the dosimetry and a lot of, underlying a lot of these decisions is the safety issues related to the, the relative dosimetry advantage that, you know, we are not even considering that except, you know, it is hard for me to separate that, you know, and I know that, if I know the tissue is not going to get treated, I, theoretically there is an advantage there, and it is totally theoretical. We do not have any data to substantiate it.
- Seth Schwartz: That is true.
- Craig Blackmore: So, do we include the second word radiation? Joann was suggesting we do not need that second word radiation. It should be prior radiation in the expected treatment field with contraindication to all other forms of therapy.
- Joann Elmore: Another word, they could have surgery or chemo or something else.
- Chris Standaert: Yeah, it is more, it is more restrictive. (inaudible)
- Craig Blackmore: Let me ask a question of our clinical expert. I mean, how, I think lots of people get radiation to their, for their cancers. How common is it that they would still be eligible for proton? So, if I get, if I get a standard dose of, you know, the breast or the prostate, you know, whatever, whatever the standard is, would most of those people still be eligible for proton in the sort of the same site?
- Lia Halasz: Right, so, again, it, it really depends on where...
- Craig Blackmore: Yeah.

- Lia Halasz: ...anatomy wise the treatment is, and it also depends on time interval, um, and there has been increasing study, not with necessarily protons but photons and protons about reirradiation, because I think especially with old techniques, you know, our dose limits were a lot more restrictive, and that has, with improvements in technology, sort of increased over time. So, I know for brain tumors, glioblastoma, there are very active protocols about reirradiation in that setting, which never would have happened before staying with other cancers, as well. So, in most cases when these patients live long enough, then they are candidates for more reirradiation. The hard thing is really the specific areas of the body if you have already reached those limits, and that is where the protons can, not always, but can have dosimetric improvements because of just their physical properties and where you can stop the dose.
- Craig Blackmore: Yeah, but, but would you say that that is usually the case or it is, you know?
- Lia Halasz: I think it is a...
- Craig Blackmore: Is that, is that...
- Lia Halasz: ...I think it is the minority of the cases.
- Craig Blackmore: ...minority.
- Lia Halasz: You know, it really is a small minority of the cases we (inaudible), but again, I think it really has been more of a newer trend and, like I said, because one, because people are living longer with...
- Craig Blackmore: Yeah.
- Lia Halasz: ...the diseases with a better quality of life, and two, with our better techniques, this allowed us to give more dose and so that is, protons is one of the ideas. Stereotactic was also brought up. That is also a way we reradiate and generally in these special cases, we do look at different forms and try to figure out which one is the best and which one is possible.
- Michael Souter: What would be the minimum period of treatment that would be required to see? I, I know that is a hugely, there is a huge range there depending on the cancer on the side, but what would be the minimum period. I mean, is there, you know, can you do it in any less than six weeks, for example, or three months. I mean, I, I just do not know.
- Lia Halasz: Right, right. So, that is a good question. There are some scenarios, like sarcoma for instance, that you would do a special what we call boost radiation that would be after surgery, you know, three to six weeks after, but I think of that time period as part of sort of the initial plan. I know in glioblastomas, the recent RTOG randomized trial looking at reirradiation had a period of six months. You know, I think it is different depending on people's, on the tissues and depending on people's comfort zone, because we know, for instance in CNS that there is

regeneration of tissues. So, that is where six months is felt to be, you know, a comfortable place where you could reradiate, but I would have to say that there is probably difference of opinion about that across the board, but, you know, that is one reirradiation protocol where kind of six months was established.

Michael Souter: I just wonder whether that might be the basis of, you know, seeing that life expectancy beyond that period. In other words, they got to live long enough to actually have the completed course of therapy.

Craig Blackmore: The challenge is, nobody knows how long you are going to live.

Michael Souter: Well, I, I, but, well, if somebody is clearly, you know, in their last...

Craig Blackmore: Right.

Michael Souter: ...last legs, I mean, then, they are likely to survive, you know, two months and maybe that is something that we should not be going on.

Craig Blackmore: Is there a lot of research right now about reirradiation, a lot of trials? You mentioned one.

Lia Halasz: Yeah, I think there is more and more. I am trying to think of the RTOG trials. I know for sure brain, which is where my specialty is. There has been more interest, as well, and a lot of case series published on breast and their... for local reoccurrence. Again, a very rare occurrence.

Craig Blackmore: Yeah.

Lia Halasz: Prostate, as well, in terms of reirradiation, but sometimes they do brachytherapy or, you know, other types of treatment.

Craig Blackmore: So, people are working on trials? You mentioned the RTOG.

Lia Halasz: Yes, no. I think, you know, it is an active look, and those are very disease specific. There also are some trials, I think UPenn has a trial where they are collecting data on everything we irradiated. I know that our center is putting through the IRB now to a trial to look at putting kind of dose limits on the reirradiation and then collecting that data, but of course, it is going to be, as we all discussed, kind of earlier, too. The, the problem is, is that each case is very individual, so sometimes it is a little hard to glean from each of those, but there is definitely a lot of effort in that, as it is becoming more common.

Seth Schwartz: We are, you know, I am not sure what the right terminology is, but I think what we are talking about is with therapeutic intent. I mean, not, we are not talking about salvage here, or we are not talking about palliation. We are talking about with intent to actually treat whatever it is that is there. So, that also, I think, should be in this statement.

- Richard Phillips: I mean, you are not treating to cure, you are reradiating?
- Lia Halasz: Well, since I, I mean, if, if it is still localized then, you know, that is where I feel like cancer has really changed over the years. If it is still localized and it is not the usual, usually it met, met, you know, mets out and then you are not in the mode of curing, but there are cases where it can still be localizing. Patients can go for a second round.
- Craig Blackmore: So, do we include that?
- Seth Schwartz: I mean, because I am thinking with curative intent, I mean, then you are ruling out the people who have metastatic disease and we are not just throwing it at all these people who have no, no chance. But if you have someone where you actually are trying to treat with curative intent, maybe that is, I mean, does that come into down, I am just trying to figure out...
- Kevin Walsh: Yeah.
- Seth Schwartz: What we are trying to do is cone this down, I think, to who, people who we think it is actually reasonable.
- Craig Blackmore: So, this is nonmetastatic? I mean, is that, is that what we intend here? Prior radiation to the expected field of treatment, contraindications to all other forms of therapy for patients with nonmetastatic cancer?
- Chris Standaert: With curative intent?
- Richard Phillips: Yeah, with nonmetastatic recurrence.
- Craig Blackmore: Local recurrence and no evidence of metastatic disease.
- Josh Morse: May I ask a clarifying question?
- Chris Standaert: You had local recurrence.
- Marie Brown: It is going to take a lot of money to answer that part.
- Richard Phillips: (inaudible).
- Josh Morse: Craig, may I ask a clarifying question?
- Craig Blackmore: Yes.
- Josh Morse: Is this, starting at other, so this is other cancers other than the top three because those top three, you have already covered. Those were the primary or?
- Craig Blackmore: Right, those are covered.

Chris Standaert: Those are covered.

Josh Morse: Any, any form of treatment.

Craig Blackmore: This would be other, other cancers.

Josh Morse: OK.

Chris Standaert: So, recurrent brain is not (inaudible).

Craig Blackmore: (inaudible) votes.

Chris Standaert: Recurrent glioblastoma is already, we have already said...

Craig Blackmore: Well, this is...

Chris Standaert: ...you can pay for glioblastoma, you can pay for recurrent glioblastoma.

Craig Blackmore: Plus prostate, lung, and the others.

Chris Standaert: Right.

Marie Brown: There is a reason why nobody else is trying coverage decisions on this particular issue, because it is, I mean, it looks like we are going to be the, if we do it, if we are, we are the only one.

Seth Schwartz: No, that is not true. I mean, there is, there is, there is a national coverage determination on this situation.

Marie Brown: Oh, there is?

Seth Schwartz: Yeah. Local coverage determine, oh sorry, local. Local coverage for the following if life expectancy is greater than two years, and it is pituitary tumors, unresectable tumors of the head and neck, paranasal sinuses, intracranial sarcomas.

Chris Standaert: Only if it is recurrent, if it is recurrent.

Seth Schwartz: No, they have not gone to that.

Craig Blackmore: No, no, but we do for some of these others.

Marie Brown: Yeah.

Craig Blackmore: We do for the brain.

Chris Standaert: We are more restricted than this, actually.

Seth Schwartz: Yeah, I mean, that is why, I mean, this is a wider, this is an even wider net than we are talking about now.

Craig Blackmore: Alright, how do we feel about those other nonmetastatic cancers, so prior radiation (inaudible) contraindication to other vehicles of therapy? More likely, do you have six yes votes for this (inaudible)?

Chris Standaert: Yes.

Michael Souter: Are you asking for a show of hands?

Chris Standaert: It is more restrictive.

Seth Schwartz: Unless the people (inaudible)...

Marie Brown: A lot of it is...

Seth Schwartz: ...less restrictive vote yes.

Craig Blackmore: Alright. Any other suggestions?

Seth Schwartz: You could still put with curative intent and then that narrows it down even more.

Marie Brown: That is just going to make...

Chris Standaert: Yeah, just...

Marie Brown: ...it more subjective.

Chris Standaert: ...yeah.

Marie Brown: I, I think, and more controversial.

Josh Morse: (inaudible)

Marie Brown: Yeah, right.

Craig Blackmore: OK, well. So, let's have a show of hands on this other nonmetastatic cancers, prior radiation in the expected treatment field with contraindications to other forms of therapy. So, including this as a condition I would like a show of hands.

Josh Morse: So, we have got seven.

Craig Blackmore: So, that takes care of that. Alright, have we covered all our bases, and are there any considerations anybody has that we have not talked about?

Gary Franklin: I have a question.

Craig Blackmore: Yes.

Gary Franklin: Yeah, just on a, just as a point of clarification on spinal we wanted to be clear, and it would help us, I think, agency medical directors to, to say is that spinal cord as opposed to vertebra, spine/vertebra? I mean, it just says spinal and, and so I just, I would just ask that we be as clear as we can in either.

Chris Standaert: We do not have any data on either one of those. We do not have spinal cord tumors and we do not have vertebral tumors.

Michael Souter: This is, I mean, we are talking, we are talking about, spine, bone, bone you can take away.

Chris Standaert: Right.

Michael Souter: With spinal cord you cannot. So, I mean, I think we have got, I think it is reasonable to put cord in there.

Chris Standaert: OK. Brain or spinal cord?

Group: Yeah.

Chris Standaert: Yeah, and get rid of CNS, that is brain and spinal cord.

Craig Blackmore: But what does that, what does that do for your CP angle, CP angle tumor. It is not, would not technically be...

Seth Schwartz: They are considered brain tumors. They are considered brain tumors.

Craig Blackmore: OK.

Craig Blackmore: The pituitary, pituitary tumor (inaudible).

Michael Souter: It just said central nervous system.

Seth Schwartz: Yeah, I mean, I, yeah, I think it includes CNS is the same, is worth having in there.

Craig Blackmore: It is worth having in there.

Seth Schwartz: I think it is worth having in there, because we are talking about those tumors and . . .

Craig Blackmore: Right.

Seth Schwartz: ...and that gets rid of the question.

Michael Souter: Do you need brain and spinal cord if you have CNS tumors?

Craig Blackmore: I was going to say, it is being a little redundant.

Michael Souter: Just say CNS tumors.

Craig Blackmore: There you go. You said CNS tumors, would that be clearer?

Gary Franklin: I, I think CNS tumors would be clear, yeah.

Group: Yeah.

Gary Franklin: Thank you.

Chris Standaert: We can get rid of brain, too.

Craig Blackmore: Yeah. OK.

Chris Standaert: That is CNS.

Craig Blackmore: Any other, any other comments from the agency directors who will be charged with implementing what we do?

Gary Franklin: I am sorry, just, another question.

Craig Blackmore: Yeah, yeah.

Gary Franklin: Which was, I am sorry.

Craig Blackmore: This is your last chance to comment about this, so. We are trying to give you something. We want to know if it is clear enough to be implemented or if we need to clarify any further. That is our, that is our question.

Gary Franklin: What I would say is that it is clear enough to be, it is clear enough to be implemented, so that, you know, in terms of that specific question, it is clear enough to be implemented. I do not know if I, you know, I, I, I just, I think, I think we just, more generally, just concerns around the, the frequency with which this, this might occur and, and I just wonder even when, when we were looking at the key questions whether, whether you even, as a committee need to, need to comment on this or whether, whether it is possible to, to, you know, when, when you look at the key questions it, you know, it is around, sort of, comparative salvage therapy, as opposed to, you know, therapy of last resort. So, I just, my, my only comment would be whether or not it is possible to, to just remain moot on this point, but, but to the specific question of, if this is the decision of, of the committee, then yeah, that would be clear enough.

- Chris Standaert: So, I guess, my understanding was, that if we did not say this and somebody had a recurrent tumor with a lot of prior radiation and could no longer have radiation, had a recurrent tumor with a decent (inaudible) otherwise, they could not even come to you and ask to try this. So, if that is not the case, then I would be fine not having that myself, but my understanding was that if we do not, I mean, we are not explicitly saying you cannot cover it. So, we are not saying no coverage for this, but we are saying, we are not mentioning under our coverage rubric, and so if we do not say it and people can still come to you outside the box and say, we are looking for an exception because this person had radiation for lymphoma when they were a child to their whole chest, and now they have a breast cancer, and if we do this, we are going to kill their spinal cord, and we cannot do it. So, we need to do, our only choice is this.
- Gary Franklin: Your point is well taken.
- Chris Standaert: So, but, but which way, which is it?
- Gary Franklin: Well, I...
- Chris Standaert: Do we need to say it, or is it, does that exist if we do not say it?
- Joann Elmore: Can they come to you to get coverage?
- Gary Franklin: That last thing is a condition, then we would have to cover it. It would not just be a medical necessity decision. If you did not say anything about it and somebody came to us, it would be a medical necessity decision.
- Chris Standaert: No, it would be a noncoverage.
- Josh Morse: It has to be covered. If it is not covered, it is not covered.
- Chris Standaert: In other words, we have to say (inaudible).
- Gary Franklin: Right, I think, I think the point, right, the point was, it is, is if you are silent on this. So, so you are saying there are a whole bunch, there are a number that you might say noncover, and there are others that you are saying cover or, you know, cover with conditions. If, if you, if you are, if you do not speak to this one way or another, it would, it would mean that then we would have, we would have the, the latitude.
- Michael Souter: But a lot of the tumors that we are saying that we would not cover may actually fall into this category.
- Chris Standaert: So we may say do not cover breast but then that becomes a concern because of prior radiation...
- Gary Franklin: Right, right.

Chris Standaert: ...to this...

Gary Franklin: You are right, OK. OK.

Craig Blackmore: We will not say do not cover breast, we will say only cover under these defined conditions.

Josh Morse: I think you could say at agency discretion, and that would remove the limitation of a noncoverage decision and then the agencies, when asked, would be able to evaluate the medical necessity and make a determination.

Chris Standaert: And add that to this?

Josh Morse: Yes, yes.

Chris Standaert: So, other forms of therapy at agency discretion. So, they do not have to cover it. They can decide.

Michael Souter: We give them the choice?

Seth Schwartz: But I think...

Marie Brown: We are doing a lot of evaluation...

Seth Schwartz: ...that was the point. That is why...

Marie Brown: ...of the statement for breast cancer.

Seth Schwartz: ...this came up. I think that is why this came up. We did not, we are not saying we want them to be able to use it for all these patients. We want, we just do not want to say that they absolutely cannot be covered in that situation, and that is why this came up, and so I have no problem saying just, with agency discretion.

Chris Standaert: Yes.

Seth Schwartz: I mean, so that they then could have a medical necessity review on those patients. That is, I think, the restriction that we are really trying to capture here.

Marie Brown: Right.

Chris Standaert: Very rare circumstance.

Seth Schwartz: Because I mean currently, the, currently they are reviewing every patient that comes through and we are saying you are going to cover for these three. You are not going to cover for everybody else, but in this context, then they can do a review. I am cool with that.

Chris Standaert: Yeah, OK.

Richard Phillips: I agree.

Marie Brown: OK.

Craig Blackmore: OK, any other, any other issues we have not brought in? OK, we will turn to the decision tool and go through the formal decision-making process with the analytic tool, which is the last section of your folders. This is the tool we use to help lead us through the decision-making process. It is familiar to the committee members, details the process and the strength of evidence with considerations that we will make. There is also, included in the tool, other coverage decisions made by other organizations. In the page 7 of the form, the various outcomes that we are considering in our decision-making are listed, and the staff has prepopulated this page with outcomes they have defined that may be of importance. We should look at these outcomes under safety, efficacy, and cost and determine if there are other outcomes used in our decision making that are not already listed on here. Safety outcomes, and I think the inclusion of both acute and late radiation-induced toxicity would encompass most of the safety outcomes that we are thinking of. Effectiveness outcomes, mortality, progression, presurvivor tumor control, metastases, local success, survival. OK, any other thoughts on that?

So, we will move on to our first voting question, which is, these are nonbinding votes, but they are recorded, and that is whether there is sufficient evidence under some or all situations that the technology is safe, effective, and cost effective. We start with effective. If you believe that this technology is more effective under any circumstance, you should vote more, and if you believe it is less effective under all circumstances, you should vote less, and then of course unproven equivalent. So, is this technology effective, more or less, under some or all situations?

Josh Morse: OK, nine more, one equivalent.

Craig Blackmore: Similar for safety.

Josh Morse: Four more, please hold your signs up, one equivalent, four unproven, and one less.

Craig Blackmore: And then finally cost effective.

Josh Morse: Alright, we have one more, one less, eight unproven.

Craig Blackmore: OK. So, based on that, so now we are to the point where we will make, well, any other discussion. I do not want to cut things off prematurely. So, we move to our pink cards, and these are the, the binding coverage decisions and there are three choices. No cover would mean that the technology is not covered

under any circumstance. Cover would mean that the technology is covered without further question, and then cover with conditions and we have three determined conditions, and that would be that we would allow coverage for cancers that are ocular, pediatric, CNS, or other nonmetastatic cancers where there is prior radiation in the expected treatment field with contraindications to all other forms of therapy at agency discretion. So, questions?

Michelle Simon: I have one question.

Craig Blackmore: Yes.

Michelle Simon: Did we define what pediatric is? (inaudible)

Craig Blackmore: We did not define what pediatric was?

Michelle Simon: Do we need to?

Craig Blackmore: Do we need to define what pediatric is?

Chris Standaert: Less than 18.

Michelle Simon: There are two. (inaudible) less than 21 and less than 18.

Craig Blackmore: As written, we have left that to the discretion of the agencies.

Michelle Simon: OK.

Craig Blackmore: We do not have to do that. OK.

Josh Morse: Ten cover with conditions.

Craig Blackmore: OK, so part of our charge is to compare the decision that we have made with local and national coverage decisions and if there are differences, we should define why those differences exist. We have considered the local and national coverage decisions in the course of our deliberation process, and we did identify that there were some areas of difference, for example, life expectancy and we did not try to operationalize that, except for a little bit under nonmetastatic cancers and we are largely in agreement though there were some other areas identified by CMS that we did not feel there was sufficient evidence to support coverage and there was also a lot of inconsistency among the other payers, which we support some and not support others. Have we delineated our decision-making process sufficiently for the record, or do you need...

Josh Morse: No, I believe you have. Thank you. With regards to CMS, you referred to expert guidelines, as well.

Craig Blackmore: And we, and we have heard expert guidelines, as well, and through the course of our decision-making and again, differences are because of where we felt there was sufficient evidence of at least moderate quality.

OK, we move on. The next item on the agenda is draft key questions for the next two topics, and we can either take a five-minute break and get a coffee...

Gary Franklin: Did you guys make a decision about the other cancers?

Group: Noncovered.

Craig Blackmore: We, we said you would cover under only those conditions. So, whatever is not listed there is not covered.

Joann Elmore: Both cancer and noncancerous.

Gary Franklin: (inaudible) made a decision.

Chris Standaert: Not covered.

Gary Franklin: But these other cancers are covered.

Group: Right.

Craig Blackmore: The only covered conditions are the ones that we just defined.

Gary Franklin: OK.

Marie Brown: I say yes to a five-minute bathroom break.

Craig Blackmore: Five-minute break? OK. I am hearing enthusiasm. So, we will make it ten minutes, and we will start at 2:00.

We are back in session. So, how, how are we starting? Do we have slides on, on this?

Josh Morse: I do not believe that we have slides on this.

Craig Blackmore: Do we have handouts?

Josh Morse: You do in your binders. You should have handouts, I believe in the back.

Marie Brown: We do.

Craig Blackmore: Alright. Did you get that committee members? There are handouts in the back of your binders with the draft key questions.

Michael Souter: We did look, and we are ready.

Craig Blackmore: Awesome. OK, so let's start with functional neuroimaging, and I will just take a minute, everybody, to look through this. I know I need to. We are starting with neuroimaging for dementia.

So, we will do like we do in school when you finish and you are ready to discuss, put your paper down.

So, the context here is mild cognitive impairment is common in older populations, and one can do a variety of imaging tests to aid in the diagnosis of, of, for either the mild cognitive impairment or, as predictive of evolution of the mild cognitive impairment into some more advanced form of dementia-like Parkinson's or one of these other, and so I think, if I understand this correctly, the, the question is should one, or what, what imaging sort of studies should be performed, if any, and how does one sort of quantify the value of that imaging study in the care of that individual. So, ultimately one would hope that doing the imaging study would lead to better outcomes. There are several...

Male: There is no treatment, so...

Craig Blackmore: ...no, there is treatment. Is there treatment for?

Richard Phillips: Yeah, they put you on this committee.

Craig Blackmore: That is a different question that is handled by a different committee. That is the, the pharmacy and therapeutic committee.

Male: (Inaudible)

Craig Blackmore: Mild cognitive impairment is a clinically-diagnosed...

Michael Souter: I cannot hear what you are saying. Can you adjust the mic?

Chris Standaert: Oh, sorry. No, I just, so...

Craig Blackmore: Mild, mild cognitive impairment is a clinical diagnosis based on, you know, some simple tests. Remember these words and go through these tests, and then mild cognitive impairment in a substantial proportion of patients progresses into one of these other diagnoses, meaning that it probably was actually just an early form of it and the early form, you cannot clinically differentiate between them and, you know, I do not treat people but my understanding is that there are some medications that people are using...

Marie Brown: Right.

Craig Blackmore: ...and the... I do not know how good the data is on the effectiveness of these medications, but...

- Joann Elmore: Technically significant improvement whether it is clinically relevant is yet another issue.
- Craig Blackmore: OK, so, but we do not, we do not do drugs here, right? That is the therapeutic committee.
- Kevin Walsh: No, but that is the, but I am sorry, the question that we could ask was, does the neuroimaging lead to better outcome?
- Craig Blackmore: Well, ultimately, you know, that is the ideal world, right? So, I do not know if we are even going to try to address that. When I am trying to frame things her, that is now how it is worded, but ultimately you do this test because you think somebody is going to, it is going to help somebody, right, and...
- Kevin Walsh: Even they (inaudible) when they say...
- Craig Blackmore: Right.
- Kevin Walsh: ...(inaudible).
- Michael Souter: OK, so, you, you can actually argue that you can, you can choose benefit by actually limiting some of the decision-making. For example, advising of the instability of the rest of their family of the decision-making. Telling somebody it is time to retire, you know? All those things can be construed of as benefits and outcome benefits. Public safety could even be effected, as the most extreme.
- Seth Schwartz: I see what you are saying, but that is not what we are asked, being asked to look at.
- Michael Souter: Yeah.
- Seth Schwartz: We are simply being asked to look at, is this testing...
- Marie Brown: Reliable.
- Seth Schwartz: ...reliable...
- Michael Souter: Yeah, I am just answering Kevin's question abo U-turn the fact that this is (inaudible).
- Richard Phillips: In, in that regard, are we going to, it seems to me the study should have a, a baseline of what, of comparators. So, that would be the testing, and I thought that the neurocognitive testing was fairly sophisticated and could be fairly extensive in order to establish the diagnosis of dementia. I am, I am maybe wrong about that, but I always thought that was the goal.
- Michael Souter: It, it is a continuum. I mean, the more progressed you are along that continuum of dementia, then the more likely you are to be able to make a faster and easier

diagnosis, but this is about the mild cognitive impairment, whereupon there, you know, there is a lot more variability about, you know, being able to make an accurate diagnosis.

Craig Blackmore: In other words, what we are...

Michael Souter: So, this is about making the accuracy...

Richard Phillips: Making a diagnosis based on the scan.

Craig Blackmore: Yes. It, it is predict, it does, this, can we predict this person is going to worse down one of these pathways because they progress in different ways? So, a certain portion of the people with mild cognitive impairment will progress to frank dementia at, you know, one year, five years, whatever it is, and so I think the reason, I mean, I do this, so the reason we are going imaging is to predict their cognitive decline, prognostic, and it may affect treatment, because they may be put on the medications. Whether the medications help or not, you know, would be another issue, and potentially one assigns them to one of these different categories of dementia that has different prognostic implications.

Richard Phillips: So, is this going to be mostly, like, sensitivity, specificity kind of information?

Craig Blackmore: I think you can frame it as an accuracy study or you can frame it the way they have done here, as, does it change treatment, which would be presumably, if you put them on medication or not.

Joann Elmore: Yeah, right now key question two is the accuracy one and key question three is the wishy-washy sort of benefit utility. Can, can I ask a question about key question one. What is meant by reliability? That is sort of a vague term. It is often meant, you, you, when you do the same tests day to day or clinician to clinician you get the same results. Are, is that what they are looking for in key question one in regards to reliability? Like, it should narrow 20 times due to get the same location?

Chris Standaert: I think...

Joann Elmore: Because, because that is different than accuracy. Accuracy is compared with a gold standard, so...

Chris Standaert: ...I think, this is my confusion here, too. So, these things have to be distinct diagnoses that you can tell apart in some way, and they are asking then, in, in sensitivity/specificity they are asking...

Joann Elmore: Well, that is number two...

Chris Standaert: ...I do not really get it.

Joann Elmore: ...number two is accuracy. Accuracy is sensitivity/specificity, positive predictive value/negative predictive value, those things whereas key question one is how reliable is it that you get the same result day to day...

Michael Souter: (inaudible) observer (inaudible).

Joann Elmore: ...interpreted because it can be highly reliable and always get the same result but inaccurate. So, there are two different measures of test performance, and I think that is what they are looking for, but I just wanted to make certain that...

Chris Standaert: It cannot be accurate and unreliable?

Marie Brown: In research...

Joann Elmore: Oh, it can be. It can be. It can very reliably giving you every single time the same answer. That answer could be wrong, but it is a very reliable answer.

Chris Standaert: No, no. I am thinking the other way around, unreliable but accurate does not make much sense then, right?

Michael Souter: Oh, yeah. No, if only one clinician in ten manages to actually interpret it correctly.

Chris Standaert: Right.

Michael Souter: But you have still got somebody like Craig there looking at the results of the scan saying OK, this is right or not.

Seth Schwartz: They are right at least one out of ten times.

Michael Souter: What is that?

Seth Schwartz: Craig is usually right one...

Craig Blackmore: I work with Seth...

Seth Schwartz: ...out of ten times.

Craig Blackmore: ...so he knows.

Michael Souter: That is good to know.

Marie Brown: Well, in standard research language, it is either test, retest reliability, which is the multiple comparisons, or it is internal consistency, which is across different, different testers.

- Chris Standaert: So, I guess, so they are trying to say, can you make a diagnosis, which of these tests is best for which diagnosis and does making that diagnosis by using these tests make any difference? Is that sort of what they are after?
- Joann Elmore: The benefit difference is key question three, and I am still trying to...
- Chris Standaert: Right.
- Joann Elmore: ...deal with key questions one...
- Chris Standaert: OK.
- Joann Elmore: ...and two to make certain, and Gary looks like he is patiently...
- Gary Franklin: Yeah, technology assessments, you know, go through these stages. So, assessment, the very first step is, does it measure what you think it measures.
- Chris Standaert: Right.
- Gary Franklin: And, so reliability interrater, intrarater, and even validity to some extent...
- Chris Standaert: Right.
- Gary Franklin: ...are part of technical capacity. So, the next stage, if you decided that it does do what you think it is supposed to do, then you want to know, you know, is it accurate, you know, what is the sense of specificity predictive values, and the third stage is utility. If you, if it is accurate...
- Joann Elmore: OK.
- Gary Franklin: ...then what is the impact of it. So, we have got, those three questions just kind of went in that, that order.
- Marie Brown: Well, I think you mean validity then in key question one. You do not mean reliability in terms of interrater reliability or test/retest. You mean validity, how accurate is it in making the diagnosis. Am I?
- Joann Elmore: No. Key question two...
- Chris Standaert: That is the (inaudible)...
- Gary Franklin: Key question two is...
- Joann Elmore: ...is the accuracy.
- Gary Franklin: ...the accuracy.

- Seth Schwartz: I think, what is it, is it valid? Does it tell you what you think it tells you? If you read dementia, does the patient have dementia?
- Joann Elmore: That is key question two.
- Chris Standaert: That is key question two.
- Joann Elmore: That is why I wanted to make sense as a group...
- Marie Brown: That is why I keep saying it is reliability...
- Joann Elmore: There is a difference between reliability and accuracy.
- Craig Blackmore: There is basically no value to key question one, because if you are accurate, you are valid.
- Joann Elmore: And hopefully, the studies have accuracy, have looked at intra and inter-observer variability.
- Chris Standaert: Yeah, and it is intrinsic on some level.
- Joann Elmore: Not always. Maybe we should add that...
- Chris Standaert: Some (inaudible).
- Joann Elmore: ...to key question two.
- Chris Standaert: But your, your question one is superseded by question two.
- Joann Elmore: So, I am hearing to delete question one. I would still want to, in keeping key question two on accuracy, which is now going to be number one, to make certain that the review looks at intra and inter-observer variability, because the interpretation of these can be highly subjective.
- Gary Franklin: Well, this stuff should all be looked at. The question is whether you should have it in the background and not be a key question or do not put it in the background and have it more formally looked at as a key question. So, that was the only thing.
- Chris Standaert: What you said is key question one. That is what the question is. So, we can delete it and put it into question two, but it is the same thing. If you say, you know, the whole, again, the validity, the, the interrater reliability of it. That is key question one.
- Kevin Walsh: But we do not, we do not, am I correct at historically we have not often seen question one in our reports? I cannot remember seeing question one in our...
- Michael Souter: We, we have not had that many diagnostic tests to evaluate. Most of the time...

Joann Elmore: And it is very important...

Michael Souter: ...it has been therapies.

Joann Elmore: ...intra and inter-observer variability and diagnostic tests that have subjective review and interpretation by the human. You definitely need to include it.

Marie Brown: Well...

Chris Standaert: Yes, but we do not...

Marie Brown: ...usually when we talk about...

Chris Standaert: ...have (inaudible).

Marie Brown: ...diagnostic tests, we talk about sensitivity and specificity, and that is what, the terms you use for testing, but in research if you are looking at reliability it is a different kind of question. I mean, that, that is usually looking at the studies that were done.

Chris Standaert: Do we have...

Marie Brown: The term reliability.

Chris Standaert: ...so I do not treat this stuff. Do we have gold standards for these diagnoses or are they imaging based?

Richard Phillips: That is the (inaudible).

Michael Souter: (inaudible) biopsy.

Seth Schwartz: (inaudible) answer the question, does this, does the imaging reflect with neurocognitive testing (inaudible).

Joann Elmore: Well, the comparators have gold standards. It is just a pathological...

Chris Standaert: Yeah.

Joann Elmore: ...combination.

Kevin Walsh: Right.

Joann Elmore: Or a clinical diagnosis.

Kevin Walsh: Right.

Richard Phillips: You could support, they have a gold standard, one or two gold standards, at least, so that we can compare...

Michael Souter: Clinical diagnosis...

Richard Phillips: ...and we know what we are talking about.

Michael Souter: ...is much further down the road.

Chris Standaert: I mean, biopsy or autop-, I mean, that kind of a biopsy, many people, when they are, I mean, I guess maybe you retrospectively go say what did the MRI show after they died and see if the MRI showed what you thought it showed. Is that...

Joann Elmore: And they would be...

Chris Standaert: ...is that what you are talking about?

Joann Elmore: ...there would be no studies out.

Chris Standaert: OK.

Craig Blackmore: Yeah.

Chris Standaert: Autopsy is the gold standard diagnostic test (inaudible).

Kevin Walsh: But we need to cover this so they can continue to do the studies.

Chris Standaert: Yep, you are good.

Seth Schwartz: So, is it (inaudible). Is it specific to the diagnostic community...?

Marie Brown: Right.

Seth Schwartz: ...to the conditions they are looking at. Those are really the questions that we want to know.

Chris Standaert: Right.

Seth Schwartz: Obviously, we want to know whether the tests (inaudible) reliability but I mean, patients, essentially, it is a, (inaudible) and it is specific to that condition, then it should have...

Marie Brown: Right.

Seth Schwartz: ...(inaudible).

Marie Brown: Not necessarily. I do not think we care about, as much about the, I mean, the reliability. I mean, we are really looking at sensitivity and specificity.

Michael Souter: No, they are, they are different things.

Marie Brown: I mean, we care about it.

Michael Souter: They are different things. You can have a couple of expert people being, you know, making very good delineation between sensitivity and specificity, but if that is not actually reproducible across the range of clinicians, then that throws the sensitivity and specificity out the window.

Joann Elmore: Right. So, they are both important.

Craig Blackmore: So, we leave them?

Joann Elmore: If you want to leave it the way it is or if you want to merge the reliability along with key question one.

Seth Schwartz: (inaudible)? I mean, I just want to say, so how are they going to do a literature search looking for reliability of (inaudible)?

Joann Elmore: Oh, there is a search term of inter-observer variability and intra-observer variability in midline.

Seth Schwartz: So, shouldn't that be (inaudible) as opposed to reliability?

Chris Standaert: Well, that is...

Joann Elmore: Well, that was my question... that is why I raised it to begin with because the word reliability may not have enough specificity.

Seth Schwartz: I mean, this is at the point here that we want the search for what we actually want to know.

Marie Brown: Yes.

Seth Schwartz: So, so then we have got to predetermine what we want to know.

Marie Brown: Yes.

Seth Schwartz: There you go.

Richard Phillips: I have another question here, and, and, it, for you people that see these people more often, but what about the issues of, of ruling out other things besides dementia? In other words, like, heavy metal poisoning for example, would you do studies on that, or would you do extracranial supravascular exams?

Joann Elmore: Well, they have already said here...

Seth Schwartz: Right.

Joann Elmore: ...under the key question that they have already undergone a comprehensive initial diagnostic workup and structural neuroimaging. So, they have already done it...

Richard Phillips: So, that...

Joann Elmore: ...and (inaudible).

Richard Phillips: ...that is what I am saying is that, that is assumed in these...

Joann Elmore: Yes.

Richard Phillips: ...patients...

Joann Elmore: That is assumed.

Richard Phillips: ...(inaudible). OK.

Joann Elmore: Right.

Craig Blackmore: Or already (inaudible).

Chris Standaert: Yeah. They have had an MRI to rule out, like, a tumor or NPH or whatever.

Joann Elmore: I am happy with the wording of...

Richard Phillips: I could see that.

Joann Elmore: ...one and two, as long as one is inter-observer...

Chris Standaert: (inaudible)

Joann Elmore: ...variable.

Chris Standaert: I think (inaudible).

Gary Franklin: I, I think the vender understands that.

Joann Elmore: OK.

Chris Standaert: I mean the (inaudible) should not be doing this stuff. We keep getting all these (inaudible) and specs and...

Joann Elmore: So, then move to number three.

Craig Blackmore: No, so, so, there is...

- Joann Elmore: Reliability.
- Craig Blackmore: ...there is a complicating factor and, and that is that there is no point in doing neuroimaging if you already know the clinical diagnosis. So, the only reason to do it is if you can predict what is going to happen in the future, right? So, if you can do clinical testing, you do not need to drop a grand on a scan. So, it is, it has got to be the accuracy, but it has got to be the ability to predict that before it is clinically apparent.
- Michael Souter: Predicted accuracy.
- Craig Blackmore: So, so it is not I did a bunch of people with advanced Alzheimer's, and I was able to predict what their clinical exam shows. It has to be, I did them some period of time before it was apparent.
- Seth Schwartz: If you want (inaudible) we can...
- Craig Blackmore: I do not care if you can predict somebody that I know has Alzheimer's.
- Seth Schwartz: But I want to know that there are, that there are characteristic things that they are going to see on this scan that correlates with, with a documented...
- Joann Elmore: I mean, I am hearing...
- Seth Schwartz: (inaudible)
- Joann Elmore: ...that you guys are interested in risk, its ability to risk predict, and that is not listed here in item three.
- Craig Blackmore: That, that...
- Joann Elmore: Clinical utility.
- Craig Blackmore: That is my point.
- Joann Elmore: So, in item three, I am hearing that we want to know how valid and accurate are they in risk prediction of subsequent...
- Craig Blackmore: Predicting...
- Joann Elmore: ...prediction of...
- Craig Blackmore: ...which individuals with mild cognitive impairment will progress to one of these categories, and I think, just because I do neuroimaging, not because I see patients clinically, but I think that is the relevant clinical question, right? That is what I see. We are doing this study because we have somebody with mild cognitive impairment, and we want to know what to do with them. We want to

predict the future. It is not, we are going to image somebody who has advanced Alzheimer disease to say yes, they have this advanced Alzheimer's.

Chris Standaert: But I guess the, so the issue is, the question says comparing the accuracy, diagnostic accuracy, to other things, so to genetic confirmation or to clinical diagnosis. So, if it turns out they are just as good a clinical diagnosis or no better, or less effective in clinical diagnosis, they probably should not even be done. People just do it because they can. If we can get, people like pictures. That is why they do it. They do not do it because it does anything. They do it because they like pictures so they, if the second question is important. So, if it is not as good as clinical exam, then, and it does not improve outcome in any way by getting imaging, there is no data that helps anything, then there is no point. You can make the...

Michael Souter: You, well, it is...

Chris Standaert: ...diagnosis elsewhere.

Michael Souter: ...yeah, it is pathology.

Chris Standaert: Which (inaudible) right.

Michael Souter: Yeah, and you are not going to go and take...

Chris Standaert: No.

Michael Souter: ...pathological...

Chris Standaert: Right.

Michael Souter: ...samples...

Chris Standaert: You do not get...

Michael Souter: ...from people.

Chris Standaert: ...any of that.

Michael Souter: So, again, this comes back to, you know, can you predict if somebody will get the disease, you know, so that there has to be this element of prediction.

Chris Standaert: There has, mm-hmm...

Michael Souter: Looking at an early study, a study of somebody, an imaging study in somebody in mild cognitive impairment who later turns out proven on biopsy to have...

Chris Standaert: Right.

- Michael Souter: ...the disease subsequently. That is what you are looking for.
- Chris Standaert: Right, well, and compare that to the ability of a clinical exam and...
- Kevin Walsh: Alone.
- Chris Standaert: ...cognitive tests to do the same thing. Yeah, because that is really what it is trying to supplant, essentially.
- Craig Blackmore: There, there is a second component, and that is the ability of the test to differentiate between the types of dementia, because that has prognostic and potentially therapeutic implications.
- Michael Souter: Mm-hmm.
- Joann Elmore: That is a good point.
- Craig Blackmore: Yeah. So, it is not just, I mean, accuracy we usually think about as a binary. It is either correct diagnosis or incorrect diagnosis, but what we are talking about here is putting into a correct one of four or five or x-number of...
- Chris Standaert: But can cognitive testing tell them apart.
- Craig Blackmore: ...so you would have to...
- Chris Standaert: That is what, that is what we are trying to figure out.
- Craig Blackmore: It is the same issue. Is it better than cognitive testing and at what point? Is it advanced disease or is it early disease?
- Marie Brown: That, that would be a question I think I would ask a neuropsychologist. I mean, they do all day testing. It is not just a clinical exam or a neuro exam. I mean it is...
- Craig Blackmore: And that is the comparator. The comparator is no psychiatric testing.
- Chris Standaert: Right.
- Craig Blackmore: I mean it is, it is, which is less expensive than (inaudible)...
- Michael Souter: But, but that is why, we, we actually do need to be careful because, I mean, there are some, you know, there are newer cognitive exams and there are neurocognitive exams. There is a (inaudible) that you can do and it takes you 15 minutes versus a battery of tests...
- Joann Elmore: Right.
- Michael Souter: ...that might take you four hours.

- Marie Brown: It takes eight hours actually and it has, having sent a number of patients and it is much more specific.
- Michael Souter: Well, yeah, but what I am saying is that there is a range there. I mean, there have been papers published on, you know, the (inaudible) and its utility in this scenario, which has said to take 15 minutes to do and people are actually using that to diagnose comm-, now you can argue about the accuracy of that, but that is why, I think, when we look at what, what, I mean, what we ask the evidence vendor, we need to be probably pretty specific and get expert input, you know, as to what constitutes the metric by which you actually make that, you know, you would standardly make the diagnosis at this point in time.
- Chris Standaert: Because also the clinical diagnosis does not mention neurocognitive testing as a separate entity. It just says clinical diagnosis, whereas neurocognitive testing is a discrete thing.
- Marie Brown: It is the gold standard in a lot of, other than pathology.
- Seth Schwartz: Yeah, the neuropsychiatric testing.
- Marie Brown: I mean, it is done by clinical psychologists with a specialist in neuro testing, I mean in...
- Chris Standaert: A neuropsychologist.
- Marie Brown: Yeah. Yeah.
- Craig Blackmore: So, I, I am told that we have Robin Hashimoto on the phone are you there, Robin? We are going to unmute you. So, she is our...
- Joann Elmore: And while we are unmuting her, I have a question for her about the genetic confirmation and accuracy and that some people can be at increased risk based upon a genetic marker. That does not mean that they are going to get it. So, I am not certain what we are looking for here to see if imaging (inaudible) genetic risk.
- Michael Souter: Isn't that the predictive (inaudible)?
- Marie Brown: Mm-hmm.
- Joann Elmore: It is a, it tests for a genetic marker and they are at increased risk, but that does not mean that they are going to get it. So, it is, it is (inaudible).
- Robin Hashimoto: So, can I, can I interrupt just a second. For inclusion, patients must be symptomatic. So, we would not be look, we would not be screening patients if they found any genetic markers. We would not be including those patients. So, they would have to have symptoms, meet the clinical criteria, and there are a

number of, of agreed upon clinical definitions of the various dementias, but one way to confirm that a patient with symptoms of Alzheimer's disease is a genetic marker of that, so. Does that make sense?

Joann Elmore: So, we are going to get a functional MRI and see if it is associated with a certain genetic marker. How does that help us?

Michael Souter: Well, certain genetic markers in a symptomatic patient. It is elevating the bar.

Joann Elmore: They could have a genetic marker, be symptomatic, but you do not know until they die how to classify them.

Chris Standaert: That is the problem.

Joann Elmore: So, let's make certain you work on key question three, then, because we want to get at the utility of all this and make certain that we do it appropriately.

Chris Standaert: So, is the intent just the imaging or is the intent to get at the best way to diagnose different forms of dementia?

Joann Elmore: That is key question three, and we should be real helpful in guiding that one. I am hearing from you guys risk prediction so that if they have sort of a mild cognitive impairment and people want to start getting these fancy tests, does it help you with prognostics.

Craig Blackmore: I mean, I think it is captured here. The first one is, how often...

Joann Elmore: (inaudible) diagnostic classification.

Craig Blackmore: ...what is that? I mean...

Joann Elmore: ...impact on diagnostic classification.

Craig Blackmore: Post-test probability of disease, right?

Joann Elmore: Yeah, and risk prediction.

Craig Blackmore: Risk prediction, yeah.

Joann Elmore: Like, by diagnostic classification if you mean sort of are they at high risk versus low risk for a future disease.

Michael Souter: Your risk prediction is going to be contingent upon your diagnosis.

Craig Blackmore: Diagnostic certainty. I believe they have Lewy Body dementia, and then I have a test and now I think it is Alzheimer's.

Chris Standaert: Right. That...

- Craig Blackmore: It, it is diagnostic certainty.
- Chris Standaert: Yeah.
- Craig Blackmore: Or, in this case they are saying defining it as the amount of time the most likely diagnosis on the clinician's mind changed and also define it as a level of diagnostic certainty and whether it changed. I do not know that there is going to be a literature on this, and it is hard to equate that with, you know, clinical outcomes.
- Marie Brown: And so, are we looking at whether or not we are really going to pay for this next level of diagnostic testing. Is that what the real bottom line is?
- Joann Elmore: What is the, we should ask what extra benefit do you get from doing this test.
- Craig Blackmore: Incremental benefit.
- Seth Schwartz: Right, yeah.
- Joann Elmore: Like, what, what benefit does this give above and beyond everything else that is existing?
- Craig Blackmore: So, how often do we get a better, a better diagnose, a more certain diagnosis, a more correct diagnosis?
- Joann Elmore: And is that helpful to have that more correct diagnosis.
- Chris Standaert: Does it equate to better outcome or (inaudible)?
- Joann Elmore: And right now, we are not asking that question, is it helpful to have a more accurate diagnosis. So, we should just (inaudible) our advisor.
- Michael Souter: Well, well then, yeah, we need to know from the clinical advisor, is there a time window of therapeutic intervention, you know, and, you know, what the size of that window is.
- Marie Brown: And our clinical expert is on the phone right now?
- Craig Blackmore: No, she is with, she is with the, she is our evidence vendor.
- Marie Brown: Oh, evidence...
- Craig Blackmore: She is with...
- Michelle Simon: Can we get the clinical expert involved in key question formation?
- Craig Blackmore: They are involved. They are just not with us today, right?

- Josh Morse: We can ask Robin. Robin, have you consulted any experts on this?
- Craig Blackmore: Yes, we have been working with Lisa Fulbert. She is at OSFU. I can, I can hear you guys. You are kind of going in and out, but if there are specific questions you would like me to ask of her to inform the key questions, I can certainly do so. Please just pass them on to me.
- Chris Standaert: Well, specifically it would be considering neuropsychiatric testing as a diagnostic approach, formal neuropsychiatric testing.
- Robin Hashimoto: I am sorry. Was that, is that a question for me?
- Chris Standaert: Yes. You asked for questions, yeah.
- Joann Elmore: In other words, do you want clarity in key question number...
- Chris Standaert: It is number two...
- Joann Elmore: ...two about accuracy.
- Chris Standaert: ...not just clinical but, but in what a doctor might do in an office versus a neuropsychology evaluation, which is a formal eight-hour...
- Robin Hashimoto: Right.
- Chris Standaert: ...all day deal.
- Robin Hashimoto: Right. I think, it is my understanding that there are accepted criteria or guidelines for diagnosis, and they are different for the different dementias. So, that is typically what the physician will use, but yes. Patients usually undergo an initial workup. They undergo blood work. They go, undergo a lot of questioning from both them and from somebody who can, you know, vouch for the history of the changes, and so I think there can be a lot of different tests that are performed and, and it is a whole bunch of different things that go into a clinical diagnosis and then structural imaging is also something that would be performed as part of that initial diagnosis. So, really, what it comes down to is that there are, there are, from my understanding, just a small percentage of patients, after all of this is done, in whom the diagnosis is not clear, and those are the patients that are going to be referred for functional neuroimaging.
- Michael Souter: So, so one of the points that we were asking about earlier one was, you know, we can see there should be relative consistency in how we do a patient history and how we do a neurologic exam, consistency...
- Robin Hashimoto: Mm-hmm.
- Michael Souter: ...in how we get structural neuroimaging and consistency...

- Robin Hashimoto: Right.
- Michael Souter: ...with blood work. The element of variability...
- Robin Hashimoto: Right.
- Michael Souter: ...that we wanted to confine was about the cognitive testing to make sure that there was some element of standardization in the cognitive...
- Robin Hashimoto: OK.
- Michael Souter: ...testing that is entertained.
- Robin Hashimoto: OK.
- Marie Brown: And so, our patient, our target population, is really people who have not been diagnosed with, or do not have a clear diagnosis having had all these other tests, which is a little different than where we were thinking of the bigger population of people with dementia. This is really people who, who have not been diagnosed given everything else that has happened.
- Michael Souter: Right.
- Marie Brown: I mean, they have been appropriate, accurately, or...
- Carson Odegard: Or there is a question on...
- Marie Brown: ...there is a question. They have a, yeah.
- Chris Standaert: The question we are going to get at the end is, should all these fancy imaging tests be paid for? That is what we are going to have to say. When/if do you pay for SPECT, MRI, PET in the diagnosis of a patient with dementia: That is going to be our question at the end. So, we need to understand what data there may be that tells us how helpful that is in any way in terms of making a diagnosis or managing these patients. That is the only way we are going to decide whether they are worthwhile or not. So, the, as little (inaudible) whole algorithm for how people decide, well then you say, well then they may go get these tests in uncertain circumstances. I suspect that is not the case. That is, in effect, the problem is that people want to do them much more often.
- Richard Phillips: Yeah.
- Chris Standaert: And so...
- Joann Elmore: Right.

- Chris Standaert: ...the issue then is deciding compared to these other tests, compared to neuropsychological testing, compared to a history, compared to a standard MRI, where, is there evidence that these improve outcomes or value in some way for the patient that they would be worthwhile covering?
- Joann Elmore: Is it compared to or is it in addition to?
- Chris Standaert: See, I do not think it would be in addition to.
- Joann Elmore: In addition to, because right now...
- Chris Standaert: Right.
- Robin Hashimoto: It would be in addition to.
- Joann Elmore: ...he, I am hearing from everyone that the most important question is, is functional neuroimaging helpful to patients and caregivers.
- Chris Standaert: Yeah.
- Joann Elmore: Is it helpful at all?
- Chris Standaert: Right.
- Joann Elmore: Whereas right now, key question three has to do with it compared to other diagnostic tools, and the stem of all of these key questions assumes that they have already had comprehensive...
- Richard Phillips: Yeah.
- Joann Elmore: ...initial workup, structural neurological...
- Chris Standaert: And see, that is...
- Joann Elmore: ...they are assuming they have already had everything.
- Chris Standaert: ...that is where I get confused. I mean, if they have already had...
- Joann Elmore: I think that key question three is basically, does it help the patient or the caregiver at all?
- Chris Standaert: Because that...
- Joann Elmore: Does it provide any...
- Chris Standaert: Right.
- Joann Elmore: ...net benefit above and beyond what is already being done.

- Chris Standaert: I mean, I was thinking these would be, do you get neuropsychological testing or do you get a PET?
- Richard Phillips: Yeah.
- Chris Standaert: So, if that is your question, it would be useful to know which one you should get and which one makes a better, gives you a better answer for your patient. If that is not the question and they are all going to get neuropsychological testing anyway, then it is an added, what is the added benefit of doing this? Question three, as it is phrased now, sounds like it is a first where you are trying to decide should you do all this clinical stuff, get (inaudible), get functional testing, or if you just do the PET and find out what they have. Does that make sense?
- Michael Souter: Well, well if there is, sorry.
- Michelle Simon: Does it make any difference in disease in the timing of the test, as well, like some tests are important to do earlier in the progression, or is this later?
- Michael Souter: Yeah, that is, that is the question, the clinical window of opportunity, yeah. How much time? At the risk of being repetitive, I think that, you know, the, that we, the issue of what type of cognitive testing you are doing is, is an important one, you know, because based on, you know, going, adding up all the exam, the cognitive testing you have got there, it is just that a quick 15-minute exam may not be useful in comparison to something you have taken all day to do.
- Kevin Walsh: But really, in the real world, most patients who get this diagnosis do not get the eight-hour neurocognitive testing done.
- Michael Souter: Yeah. That is...
- Kevin Walsh: They get the...
- Michael Souter: ...that is one of the...
- Kevin Walsh: ...15-minute...
- Michael Souter: ...reasons people developed the (inaudible).
- Kevin Walsh: ...they get the 15-minute exam, and these studies, if we, if there are any, are going to be looking at the eight-hour test. So, I am just...
- Michael Souter: So, there is some...
- Kevin Walsh: ...at this point, I am just saying, I, I really am, am doubtful that we get, there is going to be much clinically-useful information here.
- Michael Souter: There are some studies on the, on the shorter data.
-

- Craig Blackmore: So, I think, also Robin, when you are looking at the, the accuracy of all this, it is important to know the time course and sort of the spectrum of disease.
- Robin Hashimoto: Mm-hmm.
- Craig Blackmore: That we are not interested in the accuracy of FMRI, for example, in patients with such advanced dementia that it is clear clinically what they have. We are interested in the accuracy of that test and the clinically important window, which would be at the time when the other tests are ambiguous, the clinical exam, etc.
- Robin Hashimoto: Mm-hmm.
- Craig Blackmore; And, and obviously things are much more accurate if you look at people with extreme disease than if you look at people with the earlier form of the disease. That that is the clinically relevant window.
- Joann Elmore: That is part of...
- Robin Hashimoto: Right.
- Joann Elmore: ...key question two and key question five. Key question five is subpopulation. So, not just younger age but the window of opportunity within the spectrum of their own disease.
- Craig Blackmore: Mild disease versus end stage.
- Joann Elmore: Mm-hmm.
- Michael Souter: Yeah, no, I think Chris's point is a good one. I mean, so question six is, is saying compared with other diagnostic tools. This is really, you know, what does it add?
- Joann Elmore: Yeah, it is not compared to. It just...
- Michael Souter: Yeah, that...
- Joann Elmore: ...does...
- Michael Souter: ...is what I am saying.
- Joann Elmore: ...does not help at all.
- Michael Souter: What does it add?
- Richard Phillips: In addition to.

Joann Elmore: In addition to standard of care or?

Marie Brown: Well, I suspect because of the type of diagnostic tool it is, it will be used more commonly than neuropsychiatric testing, because you could, this is a, this is much, it is probably quicker and easier to get.

Michael Souter: Un, unless we say...

Kevin Walsh: It will be...

Michael Souter: ...differently.

Kevin Walsh: ...become more, it will become more available, because there are not many people doing neurocognitive testing around.

Chris Standaert: Not a lot people do an FMRI either, I do not think.

Kevin Walsh: Oh, if we approve it there will be.

Joann Elmore: What did you guys decide on key question three? Please tell me. We basically want to know, does it help at all? Are you rewording key question three?

Michael Souter: I think three is OK.

Craig Blackmore: No, I think we are, I guess we might add maybe in addition to clinical outcomes care, caregiver outcomes if those are ever discussed.

Michael Souter: Something about caregiver stress and burden there.

Craig Blackmore: Yeah. Is it on there? Oh, it is there. So, yeah, it is there. OK, well, let's move on.

Josh Morse: So, for clarity, and maybe Robin got this, but did we eliminate key question one?

Group: No.

Josh Morse: No, OK. Thank you.

Craig Blackmore: Is, Robin are you on osteoporosis, as well?

Josh Morse: No, she is not.

Craig Blackmore: She is not, OK.

Robin Hashimoto: No, I am not.

Craig Blackmore: Thank you.

Josh Morse: Thanks, Robin.

Robin Hashimoto: Thank you.

Craig Blackmore: Alright, let's read.

Kevin Walsh: These questions look good.

Craig Blackmore: They want us to take on the USDA.

Kevin Walsh: Both of these studies have huge financial implications, huge.

Joann Elmore: Both of what studies?

Kevin Walsh: I mean both of these modalities.

Joann Elmore: OK, OK.

Kevin Walsh: Both of these...

Joann Elmore: Key question, I mean, topics?

Kevin Walsh: Yeah.

Chris Standaert: Yeah. They are going to get more and more.

Craig Blackmore: So we are, we are asked, we are basically... the idea here is that we are going to either enforce the preventive services taskforce recommendations or amend them. We are going to look at the data and those recommendations.

Kevin Walsh: But the recommendations do not have coverage implications.

Craig Blackmore: So, we are going to...

Kevin Walsh: Our decision will have coverage implications.

Craig Blackmore: ...frame it, yeah.

Joann Elmore: This is really for osteoporosis and not osteopenia, correct?

Kevin Walsh: Yeah. Well, that is where...

Joann Elmore: (inaudible)

Kevin Walsh: ...no.

Joann Elmore: So, we are not (inaudible)?

Kevin Walsh: No. Osteopenia is kind of a re...

Joann Elmore: Yeah, I know.

Kevin Walsh: Oh.

Craig Blackmore: Osteopenia is not enough calcium in your bone, and osteoporosis is a specific diagnosis.

Joann Elmore: Right, it is, disease progression.

Marie Brown: Yes, right.

Kevin Walsh: Can be.

Craig Blackmore: Well, osteopenia can be caused by other things other than osteoporosis.

Kevin Walsh: Right, but you can see osteopenia early in the progression to osteoporosis.

Chris Standaert: So, I guess what, what, so what I would want to know also is, when do you screen? So, the preventive taskforce says 65. I have seen things down as low as 40 in other places, but so when do you screen? What age, what is an appropriate age, at which to, because we are going to get that question.

Kevin Walsh: Well, that is a good... that is a good question.

Chris Standaert: And the frequency. They have a question about the minimum effect of the transition from low to normal, normal to low BMD or such treatment effect, but I would be curious on a routine basis. So, on a routine healthy individual or patients, like, what that certain risk factor is. When do you screen and what is the frequency of screening?

Kevin Walsh: It is our evidence.

Joann Elmore: Rescreen.

Kevin Walsh: It is...

Chris Standaert: Rescreen, yeah.

Joann Elmore: Data on rescreening.

Chris Standaert: Yeah, so...

Joann Elmore: In different populations.

Chris Standaert: ...what is the data on initial screening in different populations and what is the data on...

Joann Elmore: That should be, like, a key question itself, perhaps.

Chris Standaert: ...yeah.

Craig Blackmore: Can we just phrase it as what, what age, what is the optimum age for initial screening based on the evidence and...

Kevin Walsh: Well, you are going to come up with NNT...

Chris Standaert: And it is effected by...

Kevin Walsh: ...basically.

Chris Standaert: ...by a...

Craig Blackmore: I mean, at the end, we want a...

Kevin Walsh: ...number needed to diagnose.

Craig Blackmore: Yeah.

Kevin Walsh: Like, how many screening, how many screening tests do you need to do to find a positive.

Craig Blackmore: The expected output from us is going to be screening recommendation.

Chris Standaert: Yeah.

Craig Blackmore: Screen at age 65 in women.

Kevin Walsh: Right, that is why we want to know...

Chris Standaert: And re (inaudible).

Craig Blackmore: Does the key question reflect that?

Joann Elmore: It should.

Chris Standaert: Yeah.

Joann Elmore: It should be what is the starting age, if there should be...

Chris Standaert: And how often...

Joann Elmore: ...and, there...

Chris Standaert: ...should you do it.

- Joann Elmore: ...should be another key question that reflects once you have done it, what are, are there any indications or repeat (inaudible).
- Michael Souter: So, tracking, yeah.
- Chris Standaert: Right.
- Michael Souter: I was going to come onto that. There is a difference between screening to make the diagnosis and then tracking to establish therapeutic response.
- Chris Standaert: But then, yeah, so it, well it is both. There is the rescreening. So, you may screen somebody at 60 who is healthy, who is fine, so when do you do it again?
- Michael Souter: Right.
- Chris Standaert: And then there are patients who are 60 that are not healthy. They are osteopenic or osteoporotic. You treat them and then you want to know when do you do it now.
- Richard Phillips: Yeah.
- Chris Standaert: So, you do it in a year, do you do two, do you do five? You know, so that is, that is what we are going to get, these questions about...
- Craig Blackmore: So, what did the evidence...
- Marie Brown: Well, in primary...
- Chris Standaert: Yeah.
- Marie Brown: ...care, we often start screening right after menopause for a baseline. I mean, I do not know if that evidence based.
- Craig Blackmore: Right.
- Chris Standaert: Is that?
- Marie Brown: And that after people have completed a year of menopause then you get a baseline and then look how that changes over a certain period of time, but the question is whether that is evidence based.
- Chris Standaert: Right, exactly.
- Craig Blackmore: So, it would be helpful to have explicitly stated in here what is the evidence supporting specific age thresholds for initial screening and specific intervals for repeat screening and what is the evidence supporting specific age, or specific yearly intervals for follow-up, so.

Chris Standaert: Yeah, rescreening in a healthy population and monitoring in...

Craig Blackmore: Monitoring.

Chris Standaert: ...a population under treatment for...

Joann Elmore: Just surveillance.

Chris Standaert: ...bone, low bone density, yeah.

Craig Blackmore: And that is probably not going to be randomized.

Marie Brown: Well, and what...

Chris Standaert: I do not...

Marie Brown: ...are the factors that contribute to that, you know? A mother with osteoporosis has a...

Chris Standaert: ...and, and (inaudible) patient characteristics...

Marie Brown: Right.

Chris Standaert: ...that affect these numbers.

Marie Brown: Right.

Chris Standaert: Right. So, is there a certain population you should be screening at 50 and a population...

Marie Brown: Right.

Chris Standaert: ...where they should not be screening because it does not help until they are...

Marie Brown: Right.

Chris Standaert: ...65 or 70.

Michelle Simon: (inaudible) 30s.

Chris Standaert: Right.

Michelle Simon: (inaudible)

Chris Standaert: Yeah.

- Joann Elmore: Now that you guys have hopefully figured out the surveillance question of repeat screening and follow-up, can I ask two other questions? On key question one, it talks about is there evidence that it improves patient choices? What is meant by that? Does it improve patient choice that you do the test, they find out, oops, you know, maybe they should be doing more weight bearing exercise and drinking their milk? I mean, what is meant by that?
- Michael Souter: Maybe it just refers to hormone therapy, and people may, that may be an element of choice that takes you another direction, going with hormone therapy.
- Joann Elmore: But that is clinical management decisions, isn't it?
- Chris Standaert: I would think so.
- Michael Souter: I do not know about patient choice.
- Joann Elmore: Yeah, patient choice.
- Michael Souter: Yeah? If you put it under a bracket (inaudible) well, you know?
- Joann Elmore: Mm-hmm.
- Michael Souter: Should you be (inaudible)?
- Marie Brown: Interesting choices I have seen patients make depending on what the results of their DEXA scan were and what they decided they better start doing. So, once there is sometimes a documented risk, patients change behavior in a way I could not get them...
- Joann Elmore: (inaudible) by benefit.
- Marie Brown: ...to change before.
- Joann Elmore: And sometimes, sometimes that is a really good benefit. They start exercising.
- Marie Brown: Right.
- Joann Elmore: Even though the test was not indicated. OK. So, you guys have clarified what is meant by patient choices. You guys seem satisfied with that. Then, on key question three, assuming that all individuals found to have osteoporosis receive treatment, is that really what we want to assume, or do we want to ask them, first of all, of people that are found to have osteoporosis, how many people in the real world actually complete treatment? Because of, if it is a low percentage, then why should we assume in coming up with a number needed to test, because that, if in the real world you test a bunch of people and only 60% of them will actually undergo treatment, then you come up with this model and answer key question three and assume 100% undergo the treatment. That is

false data for us. So, shouldn't we ask them to give us some descriptive data on what percentage?

Michael Souter: Isn't that just normalizing this, I mean, because...

Chris Standaert: Yeah.

Michael Souter: ...we are removing a variable.

Joann Elmore: But I would like to find out, and I am sure there is data on what percentage of women that have been tested that have osteoporosis actually undergo and complete the treatment. I would just like to know that information's background.

Craig Blackmore: So, you would, you would make the argument that we might it is not cost effective to screen because we would tell a woman we are not screening you because many other women would not undergo treatment, even though...

Joann Elmore: It has been done for the last ten years and only 42% of people will undergo the treatment.

Craig Blackmore: So, you do not get it because we do not think all the other women would get the treatment even though you might tell me you would.

Joann Elmore: I would like to...

Craig Blackmore: I am just, you know.

Joann Elmore: ...know that information.

Craig Blackmore: I am posing the question.

Joann Elmore: I want to, I want to know the information.

Chris Standaert: Yeah, I mean, they try.

Craig Blackmore: They may not know the answer to that.

Joann Elmore: (inaudible) the background.

Michael Souter: Intellectual curiosity is not necessarily the same thing as ethics, so.

Chris Standaert: I think so. I think they are trying to get at, so if you, assuming you do it and, you know, how many of these do you have to do to prevent a fracture, assuming you are actually going to treat everybody who should be treated, and so, in that way.

Michael Souter: Assuming.

Chris Standaert: Because we are moving the, it is removing the variable you are talking about.

Joann Elmore: Yeah, OK. I will look it up on my own then, the percentages of. Because I know patients do not like some of the treatments.

Craig Blackmore: Well, I am sure. I do think...

Joann Elmore: (inaudible) one treatment (inaudible) too.

Michael Souter: I do think, just in terms of actually, you know, advising the vendor that, you know, Michelle's point about, you know, key question two for, you know, the people who are at early risk from surgery, say for example, you know, should be reflected in that group, as well. Yeah, (inaudible).

Marie Brown: And early medical ones, too, and...

Michael Souter: Yeah.

Marie Brown: ...just not surgical. We have 42-year-olds that stop menstruating.

Michael Souter: And we have got...

Marie Brown: Lose their estrogen...

Michael Souter: ...(inaudible)...

Marie Brown: ...in their early 40s, right?

Michael Souter: ...is the same as the 65-year-old.

Josh Morse: I got part of it. So, is the assuming all individuals receive treatment or should we just leave it open or?

Chris Standaert: No.

Josh Morse: No.

Chris Standaert: That removes the component. The screening question. They are important.

Josh Morse: OK.

Craig Blackmore: OK, other thoughts, or? OK. Thank you, we are adjourned.

Joann Elmore: And we need to thank you...

Craig Blackmore: Well, actually...

Joann Elmore: ...for such a great meeting.

Craig Blackmore: ...before we, before we adjourn.

Joann Elmore: You do a great job. Thank you.

Craig Blackmore: Thank you, before we adjourn, we do have a phone meeting to make sure everybody is there July 11th, and that is for purposes of finalizing some of this decision-making so that it can be in the next benefit year plan thing.

Michael Souter: Do we have time for that meeting?

Josh Morse: Yeah, that meeting is scheduled for 8:00 a.m., I believe. I can confirm that right now.

Craig Blackmore: So, this one, this is an add-on. It was not on our schedule until recently.

Josh Morse: It should be on your calendars now. I believe Christine has sent the invites within the past couple of weeks.

Joann Elmore: 8:00 a.m.

Josh Morse: Friday, July 11th, 8:00. We have scheduled it for up to 90 minutes. It could be substantially shorter than 90 minutes.

Richard Phillips: Now, we, we need to be at a computer when we do it, right?

Josh Morse: You need to at least be at a phone. We will, we are optimistic it will actually be a webinar, which would include a computer.

Richard Phillips: That is what I mean.

Craig Blackmore: And the materials will be sent out in advance. The agenda will be to approve the decision that we just made and the minutes from this meeting. That will be the business that must be tended to. That could take 90 minutes, but it is also possible that it will take substantially less than that.

Marie Brown: So, 8:00 to 9:30 basically is the meeting schedule.

Josh Morse: But we need a quorum to get through that, right?

Craig Blackmore: We need to have a quorum.

Chris Standaert: Yeah, a quorum.

Craig Blackmore: But it might not be a very long meeting.

Richard Phillips: Well, if we do not have a webinar, I think it is important you send out the documents the day before, at least, so we can read it, read what...

Josh Morse: The materials will be provided two weeks in advance, as we typically do for a meeting. This will be the same as usual meetings.

Richard Phillips: Gotcha, gotcha.

Craig Blackmore: It will be basically the first half hour of what we did today. Thank you, we are adjourned.