Craige Blackmore: Well, good morning everyone. We're going to call the meeting to order. We have a quorum of committee members present. This is the Health Technology Clinical Committee meeting and it's an open meeting, so all are welcome. I'm Craige Blackmore. I'm the chair of the committee and, as I said, I will call the meeting to order. First item for business on the agenda will be an update on where we stand with the Health Technology Assessment Program. Any comments?

Josh Morse: Good morning. I'm Josh Morse. I'm the program director for the Health Technology Assessment Program. Thank you for being here today. Today's topic is intensity-modulated radiation therapy. I'm going to do just a brief program background for those who may not be familiar with our program.

The HTA program is located within the Health Care Authority, a state agency in Olympia. The program was created in 2006 through legislation. It directs us to use an evidence report and a clinical panel to make coverage decisions about whether agencies pay for certain medical procedures and tests. The decisions are based on the safety, efficacy, and cost effectiveness of the topics that are reviewed. Multiple agencies participate to identify topics and implement the policy decisions that come from this program, and they include the Health Care Authority, which includes Uniform Medical Plan and Medicaid, the Department of Labor and Industries, and the Department of Corrections. The agencies implement the determinations of this committee within their existing statutory framework.

So, the purpose of this program is to ensure that the medical treatments and devices, services paid for with state dollars are safe and proven to work. This program provides a resource for the state agencies that purchase health care. The program develops scientific evidence-based reports on medical devices, procedures, and tests, and we staff this clinical committee of practitioners from across the state to determine which devices, procedures, or tests are safe, efficacious, and cost effective.

Our objective is better health for Washington citizens, and this is a high-level overview of our process. So annually or semiannually, our director of the Health Care Authority selects topics for review. Once topics are selected, we contract with evidence vendors to produce our technology assessment reports. We bring them to this public meeting for a determination, and then the agencies move ahead with implementation.

The program's purpose is to pay for what works. The program is transparent. We publish all topics, criteria reports, and we have decisions and open meetings. It is based on the best available evidence. We contract again for a formal systematic report on the health technologies, and the decisions come from this independent committee.

The focus of the program is to determine if technologies are safe, effective, and cost effective. The decision basis for the committee: The committee is charged to give the greatest weight to the most valid and reliable evidence. Objective factors for evidence consideration include the nature and the source of the evidence, the empirical characteristics of the studies or trials that are available, and the consistency of the outcomes within comparable studies. Additional factors include the recentness of the evidence, the relevance, and the presence of bias.

This is a review, or a list, of the current topics that are selected for review by this program. Thus far this year, this committee has reviewed sleep apnea, bone morphogenic proteins, upper endoscopy for GERD and GI symptoms, and robotic-assisted surgery. Today's topic again is intensity-modulated radiation therapy. In November, the committee will be reviewing stereotactic radiosurgery and vitamin D screening and testing and moving into next spring, hyperbaric oxygen therapy and cervical level fusion, and you can see the other topics, which will be coming later in the year next year.

How to participate: The HTA program has a webpage. The address is shown there on the slides and is available. You can attend public meetings, as you may be today. All meeting information is posted on the web and e-mailed to those on our distribution list. You can sign up for our distribution list at the e-mail shown on this slide, which is SHTAP or State Health Technology Assessment Program @HCA.WA.GOV and request to be added to our list. You can comment on a variety of points through our topic review on proposed topics, on key questions, on draft reports, and on the draft findings and decisions that are published after this meeting.

You can present comments to the clinical committee at these meetings, and you can nominate health technologies. Anybody can nominate technologies for review by the State Health Technology Assessment Program. Thank you.

Craige Blackmore: So, the first item of business on the agenda is to look backward at our previous meeting, and there's two parts to that. First is to approve the minutes from the previous meeting and then the second component is a final review on the draft decisions and findings from the previous meeting. So, the minutes have been made publicly available. They've been distributed to the committee members. I would solicit either a motion to approve the May 18, 2012 meeting minutes or other comments from the committee.

Female: So moved.

Craige Blackmore: Do we have a second?

Male: Second.

Craige Blackmore: All right, all in favor of approving the minutes, please raise your hand. Any opposed? And abstentions? Okay. The second item from the previous meeting is to provide final approval for the decisions and findings. For those of you new to the process, in the course of the meeting, we go through the evidence and we come to a decision about coverage, noncoverage, or coverage under conditions and then following the meeting, the program staff draw that up into a formal document. That document is then again distributed and made publicly available for comment, and then is given formal approval… final approval or not, at a subsequent meeting. So, the two decisions we had at the previous meeting, the first is based on upper endoscopy for gastroesophageal reflux disease and GI symptoms, and the findings and decisions documented is in your packet, and I believe we did not receive additional public comments. Is that correct? No additional public comments. So, I will either accept a motion to approve the draft findings and decisions document for upper endoscopy or other discussion from the committee.

Male: Move to approve.

Male: Second.

Craige Blackmore: All right, all in favor of approval of the draft findings and decisions documents, please raise your hand. And any opposed? And any abstentions? Okay. One abstention. Same process for robot-assisted

surgery. Again, there was an opportunity for a public comment, but my understanding is we did not receive any further comments on the draft findings and decisions document, and therefore I will solicit a motion to approve from the committee or throw it open to further discussion, as indicated.

Male: Move to approve.

Craige Blackmore: Do we have a second?

Female: Second.

Craige Blackmore: All in favor of approval of the draft findings and decisions document on robot-assisted surgery, please raise your hands. And opposed? And abstention? Thank you. All right, that concludes the previous business and that moves us just a minute or two ahead of schedule onto the current topic, which is intensity-modulated radiation therapy.

We will now open the floor for public comments. We have sort of three categories of public comments. There are those of you who have notified us in advance that you wish to speak. We also have the opportunity, if you haven't notified us in advance and you wish to address the committee, we have a sign-out sheet out in the hall. Is that right? We have a sign-up sheet for people that are… so there is a sign-up sheet in the hall if anybody who's here wishes to speak and has not already let us know, and then finally towards the end of the comment period, we will go and see if there's anybody who has called into the meeting and wishes to speak. Right now, the phones are on mute, so we can't hear you, but we will check. We'll give you an opportunity towards the end of the public comment period. So, do you want to take over on the prearranged?

Josh Morse: Sure. So, we'll start with scheduled public comments and first is George Laramore.

Craige Blackmore: I'd just… before you start, I need you to say who you are, who you represent, if anybody, and also any conflicts of interest relevant to the topic.

George Laramore: Thank you. My name is George Laramore. I am chair of the Department of Radiation Oncology at the University of Washington. I have no conflicts of interest that would interact with this meeting at all. What I would like to do would be to make a few opening remarks on IMRT and then turn it over to a couple members of my faculty who will talk

specifically about IMRT for prostate cancer and for brain tumors. In its essence, IMRT is simply a method of delivering radiation therapy to tumors in a very conformal manner, nothing more than that. It allows the radiation oncologist to specify not only tumor doses but also limiting doses of radiation to normal structures. It is the only way one can achieve these optimal doses using conventional x-ray therapy with clinical linear accelerators that are in use today.

In evaluating whether IMRT would be of benefit to the patient, you need to consider the specific clinical situation and not necessarily focus on the types of tumors being treated, except to indications by Medicare for IMRT are couched in this language. There are four: Concave or convex tumors in close proximity to normal structures. That means something that's irregularly shaped and you have to irregularly shape your radiation field around it. Important dose-limiting structures that are so close to the target that IMRT is required for safety. Patient safety is paramount. Prior radiotherapy to adjacent structures, so you're worried about tolerance doses that are very critical, and finally, that IMRT will decrease the probability of toxicity by more than 15% compared to more conventional treatment methods, not couched in terms of whether you're treating lung cancer, brain tumors, prostate cancer, or whether there are indications within this subset of tumors. There are very strong indications that IMRT reduces side effects compared to 3D conformal treatments in many situations. This data was not noted in the report that you received, with this report focused on lack of level 1 clinical evidence. Neither the patient nor the physician wants to utilize an inferior dose distribution, which makes the lack of randomized trials looking at outcomes in the traditional sense of tumor control and survival understandable.

Finally, it's important to recognize that this discussion today is driven primarily by monetary considerations. IMRT has never been shown to be an inferior form of treatment. There is a cost differential to IMRT compared to conventional, the older methods of treatment because of the increased amount of work required by the medical physics team, the dosimetrist, and the radiation oncologist, as well as the increased capital investment because of the sophistication of the equipment required to deliver it. However, cost structure, alone, should not dedicate patient care. If there were no difference in cost between IMRT and the older forms of treatment, we would not be having this discussion today. I think it's important to recognize that underlying fact. With that, I would like to turn it over to my colleague, Dr. Russell.

Kenneth Russell: Is there a pointer or a device for controlling…? Thank you.

Hi, I'm Ken Russell. I am at the University of Washington, vice chair of the Department of Radiation Oncology and I have no conflicts. I would like to provide a 27-year perspective on what I've been doing, taking care of men with prostate cancer for the State of Washington.

I want to go back to some basic principles. I think our field is guilty of having a lot of nomenclature and a lot of technical jargon. IMRT is about shrink wrapping an organ and radiation very snuggly. I'm talking about prostate cancer today, but this applies to other body tumors, as well, and I'm going to use my pointer to work on the slides down here. The hallmark of IMRT, here is a cross-section of the prostate. Here are the radiation dose lines around it like a Topal map. Here is an individual's rectum that we're trying not to treat, and the hallmark of IMRT is this bend that avoids the rectum. You cannot do this with any other form of technology. The conformal technology of old had to bend the other direction. So, when we're treating prostate cancer, we're trying to do our best to cure the cancer and avoid things nearby, in this case this is the organ that's limiting and this is what IMRT lets us do.

When we treat men with advanced prostate cancer, here is another picture of a CT of an individual cross-sectionally. They're lying on the table here. The lymph glands of interest are in green. There's a little wiggle room around it in yellow, and these are the dose lines again. What we're trying to do is treat the lymph glands here and avoid the rectum here, and avoid the pelvis. There is no way to do this other than with IMRT. This is another view, a little more recognizable view of a person. Again, their head would be at the ceiling and their feet at the floor. We are trying to treat their prostate and their lymph glands, and you can see the donut hole here is what IMRT allows us to do is stay out of the middle.

I think there is a perception that if we don't use IMRT, we will use something called 3D conformal, and I want to clarify what we mean by that, 'cause that's another buzz word. If you don't use IMRT for the pelvis, there is no such thing as 3D conformal. This is what you're looking at. This is three views of a person's pelvis. These, again, are the dose lines like a Topal map. The highest dose is in the middle, less doses moving out, and it treats the entire contents of the pelvis, because there is no other way to do it.

Here's a direct comparison. So, when we're talking about men with advanced prostate cancer, on the left is IMRT. The high dose of radiation is in green. The lesser doses are outside, and we are able to put in this

boomerang shape with IMRT. If we are asked to go back to the old ways, which come before this, this is the way we will be treating these men.

Hopefully, we are not disconnecting me this soon. So, this is true for prostate cancer. I will say parenthetically this is true for anything else in the pelvis. My subject is prostate cancer, but this is true for gynecological cancer, certain GI cancers. The pelvic lymph glands are neutral when it comes to male versus female and to the type of tumor you are treating.

So, why IMRT in prostate cancer? We think it increases cures, it diminishes side effects. These side effects are significant, and these side effects have a significant impact on patient quality of life, even if they sometimes do not cost the healthcare system. I want to give you one specific example. This is one of my Boeing engineers. In terms of our nomenclature, he had grade 2 complications, and I will bring up grade 2, 'cause you'll see this rippling through my data a little bit later on here, which is considered mild, but here's his four-month log of his daily bowel movements. He has seven to ten bloody bowel movements a day as a consequence of his radiation. That's a grade 2 in my book. It's a grade 100 in his book. He keeps track of every bowel movement, whether or not he had blood on the tissue each day of the last four months. The medical cost to society and the cost to him is significant.

So, progress in prostate radiation over the last 20 years, the cliff notes version given our time constraints, higher doses are more effective. Higher doses have more side effects. Higher doses without more side effects is achievable only with IMRT, because we avoid these normal organs. We have better aiming. IGRT is another term we won't discuss today, and you guys are gonna discuss SPRT at your next meeting, so we won't go there.

A quick review, higher doses are better for randomized trials. The outcome is not survival. It's freedom from relapse by PSA criteria because the answers in prostate cancers take 15-20 years, and so if we try to make an advance in prostate cancer and ask for overall survival, there's gonna be one advance every 15 to 20 years. So, we use this as a surrogate, and it's a good surrogate.

Higher doses without IMRT give higher rectal complications on these dose-escalated randomized trials. The same grade 2 complication I talked to you about just now, when you go to higher radiation doses goes to 28% from 15%.

Technique matters. I'm going to quote a lot of data from Memorial Sloan Kettering, because they are the institution in this country that is most known for the largest number of patients treated prospectively with IMRT. Here are grade 2 complications based on dose. If you use a low dose of radiation with standard techniques, the complications are low. When the doses get higher with standard techniques, the complications get higher, and when you go to the highest dose of all but use the most modern IMRT techniques, you have the low complications associated with a much lower dose of the radiation.

Why do we worry about side effects in the short run? Because side effects in the short run lead to side effects in the long run. This is your risk of having a complication in the long run if you had one in the short run. If you had one at grade 2 in the short run, it translates into a higher risk in the long run. If you never had problems in the beginning, your risk of having complications in the long run is low. So, the take home message here is don't cause them in the first place. And better aiming, in addition to the IMRT, which is a sidebar to this discussion, is yet another step. If you'll aim even better, the risk of having problems here… these are people who remain well, and as time goes on, less well as the numbers drop. Those remain better off if they have better aiming with the newest technologies.

What I've said about intact prostate applies to the setting after prostatectomy, as well. It's the same equation. It's the same normal organs. It's the same issues at stake. So, there's better tolerance of IMRT than standard techniques when you treat men after prostatectomy who have recurred and have rising PSA indicating active disease.

Here is the incidents of grade 2 complications in men who have been treated with IMRT approaches down here versus the more standard approaches where the incidents of complications is higher.

So, just a couple of reflections. Prostate cancer patients live a long time. The difference in survival outcomes take a long time, and so I have to be very cautious interpreting results that say things look about the same at 5 years, at 7 years, or 10 years.

Late side effects accumulate. Again, it's best not to cause them in the first place. Evidence-based outcome research wants definitive randomized trial data. Some of these trials are just not doable. I've shown you some pictures. They're illustrative of the issues at stake. I have shown you some data on side effects for IMRT and prostate and given the documented differences between IMRT and non-IMRT in terms of side

effects given the advantages of high doses with lower side effects. If you had prostate cancer best treated with radiation, the crux is would you sign up for an IMRT versus non-IMRT randomized trial, and I think that underscores the difficulty in generating some of the data that everybody would like to see. Nobody, I think in this room having looked at these profiles and saying if they needed radiation, would sign up for the one that treats their whole pelvis. Thank you. I'd love to answer any questions, if that's appropriate. Otherwise, I'll move on.

Craige Blackmore: Who's next?

Kenneth Russell: With the permission of the chair, could I ask one question and one comment?

Craige Blackmore: You're welcome to, but I think you're out of time.

Kenneth Russell: The question I have is just in terms of the agenda for today. After all the public discussion is made, will there be value to having us remain, as will it be an open session for dialogue, or will it be a closed session and we should depart?

Craige Blackmore: This component we're in now is the public comment piece. Beyond that, there is no formal… basically, this is your opportunity for input. Occasionally, issues have come up and the committee has asked for further input. That doesn't generally happen.

Kenneth Russell: Okay.

Craige Blackmore: You're welcome to stay or go as you see fit.

Kenneth Russell: And my one comment with your indulgence is that I noticed in the formal report, there are areas that are going to be gray areas for IMRT, and I think all of us who are going to be taking care of patients with the gray areas would value having a structured methodology on how and when those cases come up that we have a structured way to present those cases for review and a workflow, a structured workflow, in these areas where we will have controversial patients that some would say maybe coverage, no coverage. We would value having some idea of how we will go forward to present those things in a way that would be standardized for all the kinds of cases that we might need to present in the areas where it is a gray zone. Thanks.

Craige Blackmore: Thank you.

Josh Morse: Our next presenter is Jason Rockhill. Dr. Rockhill, you have three minutes.

Jason Rockhill: All right. I'm Jason Rockhill. I'm a physician with the University of Washington Medical Center, and I will have a chance to meet with you guys next month, as well. I wanted to give a high level overview, maybe.

Craige Blackmore: Sorry, can you tell us if you have any conflicts of interest.

Jason Rockhill: Oh sorry, no conflicts.

Craige Blackmore: Thank you.

Jason Rockhill: The hallmarks of radiation therapy, very simplistically, are do not miss the tumor, spare critical tissue, and re-fractionate so that normal tissue that is in the treatment volume can repair itself and reduce the chance of long-term complications. However, many times, in order to achieve the best chance of tumor control, you are close to or exceeding the normal tissue tolerance. The longer we fractionate, the more likely there is to be less normal tissue damage and what we'd like to be able to do at some point is to deliver larger fractions, fewer doses that would require sparing normal tissue. The other cost component to radiation therapy is actually the number of treatments delivered, and if we can't have highly-conformal therapy, we are going to get around that normal tissue complication risk by delivering more fractions, which is ultimately going to potentially lead to increased costs, as well.

Very simple, the evolution of radiation therapy, we started with 2D conformal therapy. If you were treating this vertebral body, you treat a lot of bowel, and that's what makes a lot of us concerned by using high doses of radiation is that the normal tissue has to be able to repair. The middle slide there, there is 3D conformal and you can see you spare a lot of bowel. Ultimately, with IMRT, you can get even much more conformal and you can dose escalate, and one of the challenges of why IMRT has not been shown to be more effective is that we have to start with what is normal tissue tolerance at what is acceptable doses. We haven't really been able to dose escalate as much as we'd like. We know that the goal of evidence-based medicine is to use the best data, randomized control trials, and it works very well for drugs. You can give a dose. You can determine the maximum tolerable dose, and then you can do comparison studies. The challenge is, with radiation therapy is we're more like surgery, and it's been very hard to run randomized trials with surgical procedures, because our goals are very similar. We want to do the best job while minimizing the chance of complications. There is an operator-

dependency. So, in other words, your ability to design the radiation fields using either simpler or more complex technology varies on the individual that's practicing. We try to minimize that, but it's still a problem. Once again, we have to start with what is considered acceptable levels of normal tissue tolerances. We haven't been able to dose escalate with advanced technology. It's also expensive. It's not like a drug company or the companies that make these devices are going to pay for radiation therapy trials. They may pay for machines, but the actual cost of the physics and the support staff is not going to get covered. Once again, I mentioned this at the very beginning. Are we going to pay more in the long run because if we can't have highly-conformal therapy to spare normal tissue, we'll do more treatments? Clearly, there's going to be gray areas, and that's going to be challenge is to help guide people in terms of what is clearly an indication for IMRT and where is the gray area? Where is it personal or individual dependent? Lastly, not only am I a healthcare provider, but it's also my insurance. Thank you.

Craige Blackmore: Thank you.

Josh Morse: John Rieke.

John Rieke: My name's John Rieke, actually. You didn't do any worse than most people do with the pronunciation, and forgive my voice. I have a frog here today, but I'll try to keep clearing it. I am a radiation oncologist and practice in Tacoma, Washington. I am also the medical director for the oncology service line for Multicare Health System in the South Puget Sound region and I'm representing ASTRO today, the American Society of Radiation Oncology. I am on the regulatory committee for that organization. It's an organization supported entirely by dues and by the members. We appreciate the opportunity…

Craige Blackmore: So, sorry to interrupt. I have to know if you have any conflicts of interest.

John Rieke: Forgive me. I should have said that. I have no conflict. We thank you for the opportunity for input and will not repeat our submitted written comments but stand by them. Your review is very comprehensive. I think our entire field will benefit from some of what you've accomplished here.

You will hear excellent technical summaries and have heard of one of the cancer patient's most important tools. Radiation is the drug, I'll recraft it in the term of a drug, that works, cures, palliates almost every cancer. It is limited only by toxicity. As pointed out in public comment, having this technology has been so important in some diseases that it is difficult to justify "non-IMRT." Data on usage that you have assembled is really

helpful. I was very appreciative for that part of the report. In it you'll see that the use in prostate cancer is high and head and neck cancer is high, and breast cancer is low, for example, and I think the important message to me, and I hope you, is that it demonstrates a form of main street outcome research. If IMRT was simply being done for the money, everything would be 100%, I assure you. The fact that it isn't demonstrates what main street has learned about this technology and the unanimity of opinion of the public commenter's that patients must have access is quite obvious.

I would ask one point about the assembly of data and that is, where is the Quantec data in your analysis? It's the definition of standard of care, in essence. Most of our planners use it, and I'd ask you to consider it. The dramatic increase in cost is all paid to the technical owner. The radiation oncologist in practice is paid no more. In fact, we're paid less per hour to do IMRT than 3D CRT, and I would ask you to just consider that in your cost analysis. We are not doing this for the money. Thank you.

Can I have 30 more seconds? Thank you. Lastly, this important technology and its improvements, such as VMAP, are available at virtually all of the Health Care Authority's insured's lives. Research with radiation therapy, federal and industry supported, always uses IMRT. ASTROS, Radiation Oncology Institute, the NCI, and the cooperative groups have refined, improved, and standardized IMRT nationally and it is the usual standard of care. So, please continue to support research and at a minimum, coverage with evidence determination at a minimum. Thank you from the society and myself. Thank you very much.

Josh Morse: Thank you. Our final presenter who is signed up is Joseph Hartman.

Joseph Hartman: Thank you, very much. My name is Joseph Hartman. I'm a practicing radiation oncologist. I represent my medical group, Radion Care Radiation Oncology, representing five physicians practicing in the south Puget Sound. We have three radiation treatment centers that we staff and on the… I am also speaking on behalf, without their formal permission, of the patients that I've been treating in the South Sound for over 20 years. I think many of the points that I would like to raise have already been brought to the attention of this committee by our speakers.

Craige Blackmore: Sorry to interrupt.

Joseph Hartman: I have no conflicts of interest.

Craige Blackmore: Thank you.

Joseph Hartman: Thank you. I'm not sure that in the 2-1/2 minutes that I have remaining I can elaborate in great detail on those, but what I think is clear is that although radiation oncologists and oncologists in general can argue and do argue about specific roles and situations in which IMRT can be utilized, what I think all of us can agree to is that the complication profile of radiation therapy is directly related to normal structures, the volume of the structures receiving high doses of radiation and as Dr. Russell alluded to, there is no other modality available that can limit the volume of structures adjacent to targeted areas for radiation therapy to a greater degree than IMRT. So, I support the use of this modality in areas where there have been adequate, in my opinion, clinical data that's accumulated to suggest lowering of toxicity and ability to increase dose levels that are delivered that does translate, in most tumor sites, into improved control of those malignancies.

I think there's one thing that all of us in this room have in common, and that is that someday we will all be patients. I would reinforce the argument that Dr. Russell made that if I'm sitting in front of one of my colleagues as a patient, I would hope that they would bring to bear the best technology available to improve my chances of recovering from this kind of an illness, which is devastating and life altering, in such a way that I can continue living my life in as best of a manner as possible with the fewest long-term complications. I will end my comments at this point, and I appreciate the panel hearing my opinions.

Josh Morse: Thank you, Dr. Hartman. So, we will check and see if anybody on the phone would like to make comments this morning. Is the phone muted?

Male: It's not muted.

Josh Morse: If there's anyone on the phone who would like to make a comment to the committee this morning, now is your opportunity. Thank you.

Craige Blackmore: So, we'll just check one more time. Is there anyone on the phone who wished to address the committee? This would be your opportunity. Okay. We'll close the public meeting... public comment period of the meeting and move on to agency utilization and outcomes.

Josh Morse: Slide's up.

Jeff Thompson: Thank you, Mr. Chairman. My name is Jeff Thompson. I'm the chief medical officer for the Health Care Authority. I represent Medicaid, the State Employee Benefit Program, and the Basic Health, and I'm here to

produce some utilization and recommendations from the agency medical directors. A couple of comments. I realize how uncomfortable it is to talk about costs, but I think if we sort of go back and look at CMS and their triple aim and ask how we can produce better care, better health, at reduced costs? If you look at the national quality strategy, it asks for how do we provide access to quality affordable healthcare. So, cost is in the national mindset. It is very difficult to talk about, and I know of no other program, state or federal in the United States, that does as good of a job as this program does in a public forum to discuss access, quality, and costs. So, as uncomfortable as we are about it, this is probably the best it's ever going to get where the public has an opportunity to comment, and experts have the opportunity to inform the state as to what is an appropriate evidence-based coverage decision. And so with that, I'll talk a little bit about what the agency is finding.

As in all new technology, it is always increasing with the opportunity to produce better health outcomes. Unfortunately, as we progress so quickly, sometimes we don't know if those outcomes are actually there. It is hopefully the promise of outcomes, but as we look at IMRT and many of these other new technologies, we find there are increases in the amounts of use in those treatments, both in prostate cancer going from 29 to 82%, but then spreading out into all cancers and a very similar analogy is the off-label use of medications, and our hope is that these technologies will actually produce better outcomes, but sometimes I think our opportunities are somewhat further ahead than our science is actually allowing us to do, and this is where the cost comes in. Right now, healthcare in this state is almost 30% of the entire budget. So, if we keep expanding that 30%, then education is no longer our priority, as dictated by the constitution in the State of Washington. So, we do have to talk about costs, unfortunately, and I know it makes everybody uncomfortable.

So, the question is, does IMRT actually improve outcomes? Does it actually reduce safety issues, and can we actually provide better care by enhancing the dose but in a smaller and smaller area, and what does the evidence say? Having looked over this on efficacy, cost and safety, it's a lot like PET scans where we have a new technology that's of phenomenal benefit in a small area but then has expanded to larger areas with a promise of improved outcomes, but the science is lacking. So, when the agency medical directors working with Mr. Morse look at all of these new technologies, we rank them on safety, efficacy, and costs, not necessarily on the evidence but just where it is in sort of our benefit decision making, and so our concern was is that now we have a new technology that may

be delivering higher radiation doses, so there is a safety cost that the agency medical directors need to look at for more due diligence.

There is the issue of efficacy. Where are we at this science, as we expand the use of these new technologies with the promise of better outcomes, but maybe the science maybe lacking, and so we have a medium concern on that. Then, when we look at costs, and that is what you pay us for as stewards of this program, the costs are escalating. So, we do need to look at value. We do need to look at access, quality, and costs.

So, a review of the agency's criteria and policies here. Again, they're a little bit all over the map, and I think it's just we're all struggling to find out, is there an answer out there? So, for Medicaid, we looked to CMS local coverage decisions and those are sort of mixed. We used Hayes, which is another technology, which gives B and C ratings and some D ratings for this technology, and then we look at NCCN, also the National Cancer Care Network and what are they saying about this, and it is all varied, and we use all these tools to actually make coverage decisions.

In the public employee benefits program, we're using the Regence Program, and for anal, prostate, and head and neck when medically necessary and then for other cancers where there is either radiation issues or need to protect structures. Labor and Industries also has some small costs and utilization, as it relates to firefighters and the Department of Corrections, again with NCCN.

As I've looked over this and looked over this, it is a struggle, and everybody is sort of interprets the science a little bit differently. If you even look at, in the technology, and you look at the Association for Radiology, even there it is a varied opinion, and so we're all again struggling. There are no National Coverage Decisions to guide us from CMS. There are three Local Coverage Decisions, as the locals. Region 10 is one of them, and again, it is similar to the commercial with prostate and breast but then other cancers are looking at prior radiation to reduce the dose or concentrate the dose or where there are other critical structures that are there.

So, in the safety where we had high concern, what are the potential harms? We looked at the appropriate duration and frequency. This is something, the frequency, which we didn't have, I think, and I would love to work with the University of Washington on this. A little bit of a side. When we start looking at cancer care in general, and we look at chemotherapies, we see wide variations in care. Even when we look at stage 1 breast cancer, huge variations in care, and we're working with the

University of Washington. So, we would like to work with you on this, because I think the frequency of use is varied, and I think that is related to some of the concerns here, because some people might want 30 and some people might want 50. So, that variation of care is also a driver of safety and costs.

We wanted to look at special populations and who needs to be having special considerations, and then looking at some cancers whether the issues around grades 1, 2, and 3 issues of outcomes like stomatitis in head and neck cancer or cosmesis in breast cancer were differential and something that we need to look at and those will be reflected in our recommendations.

On efficacy, again, I think our hope, our prayers to actually deliver better technology exceed our science, and so what is the evidence and the efficacy? This is where I think if we would look at how children are treated in the United States where everything's on protocol, but adults where nothing is on protocol unless you're in an institution. So this is… I think you said coverage with evidence design but what does that mean? Does that mean we're all agreeing to common protocols and we can then do registries and find out really whether this is in fact better is something that we need to talk about and then, again, special populations that we need to look at and then I'll cover a little bit of the costs, and I know how uncomfortable that is, but it is a high concern, as we have these new technologies come forward.

So, as some of the previous speakers talked about, it is about the planning where the costs are increased, and you can see in this head and neck cancer with billed charges that a large amount of the costs are built in on the front end, as the CTs are guiding where those nice pictures are and the greens and the reds are sort of defined in the IMRT planning and then delivery of 25 treatments. Just as a side, this was actually $10,000 in allowed charges, but there was $89,000 worth of billed charges, and so we are all trying to sort of wrestle with billed versus allowed charges. I have talked with some other insurance plans and maybe later on, as we get more experience with this, maybe we can look at bundling. Maybe we can look at doing something, because the actual complexity that we've designed here in the billing system is a bit mind-boggling, but bundling is not an option at this time.

When we look at the therapies across both the Medicaid and the PEB population, we see an actual increase in the number of clients that are being treated. These are adjusted for our increase in amounts of eligibilities, and we see that actually the average payment or treatment

costs may be dipping down a little bit, and this probably reflects, they started out in treatments and facilities, which have higher charges, and they are now moving into non-facility where the outpatient perspective payment systems actually have some control in the cost per treatment.

When we look at the differential between facility and professional services, and again, facility could be an outpatient hospital or it could be a freestanding service, you can see the difference here in what is happening with the PEB program, 23 versus 18,000. Medicaid, obviously, we never pay enough but 5 versus 9,000, and then when you bring the Medicare population in, that's where you get that expansive... Medicare pays at a higher rate than does the public employees or obviously Medicaid. Then, you can see the distribution around planning navigation and delivery of services.

Margaret did a very nice job of sort of articulating this across the different types of cancers, and obviously ENT and genitourinary are the highest. Genitourinary, at least for the PEB, probably results, although we didn't break it down with more prostate cancer utilization, and then broken down again by delivery, imaging, navigation, and planning. So, this is where we are with all the rest of the cancers, and it goes across the other portfolio.

In Medicaid, you see a similar type where it's genitourinary and head and neck, and again the PEB population and the Medicaid population are different. We have a large dual population that might be reflected in more head and neck cancers here and a younger female population than the PEB program, and that's why you're seeing some differential in sort of the size of these bar graphs.

So, to sum it up, the benefits, I'm again, like PET scan, I'm struck with the low levels of evidence, very small ends of studies, and if we were to get closer to randomized trials or case controlled trials, or cohort trials, we know that from our experience that the actual effect size gets lower and lower. Some of these effect sizes are very small in and of themselves, and they may even disappear if we had larger ends that were actually controlled. The historical trials in some of the studies that I read didn't account for chemotherapy or changes in practice patterns, especially when you're looking at maybe a decade ago of what those controls are and so that is, I think, a big deficit of the science here and a bias and then no controls. I don't think we're asking for randomized, double-blind, placebo-controlled, cross-over designs. I think what we're asking for is an appropriate amount of science that could be a controlled trial or something that would answer the things around safety. A randomized

trial will not answer the safety questions, but certainly when you look at the science here that grade 1, 2, and 3, the answer is not there, at least that I see in the science. Now, I don't use IMRT. I'm an internist and I'm now a bureaucrat, but as I look through the science, it doesn't comport with what I heard from public testimony, at least across all of the portfolio of cancers.

When I look at the risk, again, small ends, and I realize you want to do the best for your client, but how much of it is biased when you're bringing it forward versus good science to inform, and if we did a standardized decision aid and we actually told them what the science was versus our expert clinical opinion, would that differ? And again, how are we doing those comparisons? Do we actually... and all physicians have biased, bureaucrats have bias, and I think I do hear that you want to give the best informed consent, but are we giving it based on our opinion or the science, and I think that's something that I think this committee will do an excellent job in sort of sorting out. The controls for chemotherapies, they've obviously changed over the decades, and when you use those as comparisons, I think there are injections of bias there. Again, I think the randomized trials, again, I don't think it's about randomized trials but certainly cohort-designed trials are not sort of the standard of care in a lot of these things that we're looking at here.

So, in summary, we are concerned that there isn't an adequate amount of science to juxtapose these two therapies, which do have cost differentials. They are largely based on case series. Their controls are lacking. If you started parsing out these grade 1 through 3s, is there really good evidence that you're getting these huge benefits on safety? And the science just doesn't seem to be there on all cancers, and the cost analyses are mixed on this. In some, it's $1 million per quality adjusted life year, and on others they're using assumptions that don't comport with science. So, as always, our cost analysis, our quality adjusted life years per cost always are lacking.

So, our recommendations: I think for head and neck and prostate, because of the dosing that is needed for prostate and because of the structures that are in and around the head and neck, we want to cover those with IMRT, but for all other cancers, we want some evidence that IMRT is going to give us additional benefit with you need to reduce the radiation or concentrate the radiation. You need to try and save some of those vital structures or critical structures, and then we need to have a context about how you're going to use this within clinical trials. We always pay, when there's informed consent, with an IRB, but if you're experimenting without an IRB, is there informed consent? And I know

that sort of is fighting words, but I think we really have to be honest with ourselves. So, we want to cover these cancers, and we would love to work with the community, as you say, to standardize how we bring forward your clinical judgment that we need this and we have some of the people that actually do these prior authorizations. So, a promise that I'll give you is that we will look to try and see if we can't standardize how we do prior authorizations, and I'll work with Regence to do that. We're working right now with a number of people from the University of Washington and looking at some of the disease registries, the cancer registries, and we would like to work with you again. I think the issue that's not here is the variation in care. Every time I look at an issue that has never been looked at before, the variation of care is huge, and the quality issues are huge. So, again, we'll continue to look at that. Any questions?

Craige Blackmore: Questions from the committee?

Female: I have a comment and a question, Craige. The comment is in response to an earlier statement by someone when they said it's about cost, and as a committee member, I would say it's about care, and I'm very happy as a committee member evaluating any new medical technology, and we may find that there are new medical technologies that are less expensive. They need to be efficacious, they need to have a good safety profile, and we should have evidence. So, that's in response to the earlier comment about costs. Now I'll follow up that comment, though, with a general question about cost. It is so hard to get an overall sense of how much more expensive this technology is because there's multiple components to it, and there's multiple sites, but can you give me just a general sense? Are we talking a five-fold increase in cost? I just... some sort of bellwether to kind of help me understand.

Jeff Thompson: So, at least two- to five-fold.

Female: Two to five-fold?

Jeff Thompson: Yeah. It depends on the cancer. It depends on the number of treatments, and it depends on the payer, too. Thank you.

Craige Blackmore: Okay, we'll move on and hear from our vendor on the evidence report, but while you guys are setting up, I also want to take a moment, if I could, and introduce our clinical expert. The committee members are all selected for their experience in evidence-based medicine and with policy decisions we are not all experts in IMRT or some of the other technologies that are brought before the committee. Accordingly, we

always have a clinical expert who is present with us to help guide the committees in areas where we need a better understanding of the technical aspects and it's Dr. Foos?

Martin Fuss: Fuss.

Craige Blackmore: Fuss. Could you please just introduce yourself briefly and tell us your background?

Martin Fuss: My name is Martin Fuss. I am a radiation oncologist at the University of Oregon Health and Science University in Portland, Oregon and professor and vice chair of the department there. My background with the use of IMRT goes back to the year 2000, so very early on in the introduction of this technology, and I have the last 12 years obviously treated hundreds, if not thousands, of patients using this technology. So, I hope I can provide you some benefit perspective on why its costs are incrementally high over other types of radiation treatment, what is the resource utilization that justifies the increasing costs, and what is the perspective on the clinical use and [inaudible] clinical indications here.

Craige Blackmore: Thank you. Before I forget, do you have any conflicts of interest to share with us?

Martin Fuss: I do not have.

Craige Blackmore: Thank you. The way we structure this is we rely on the evidence vendor to give us a comprehensive and hopefully objective summary of the evidence, and we rely on the clinical expert to help us with the context and with a lot of the technical information that isn't the focus of the technology assessment. We don't have designated time on the agenda for you to speak, but questions will inevitably come up, and so we thank you for being here to help us.

Edgar Clark: Good morning. My name is Ed Clark. I'm a diagnostic radiologist, and I work at the Center for Evidence Based Policy at OHSU. I have prepared before this committee twice as a clinical expert, and I presented evidence from the Center for Evidence Based Policy on PET scanning in malignancy. Many people contributed to this report and although I'm the leadoff hitter, I have brought some of my teammates along to advance me if I get stranded on base here. So, today we're going to talk about intensity modulated radiation therapy and like the other speakers, I am going to refer to that as IMRT because it is a big mouthful.

This is the outline of our presentation, also the outline of the report, and I won't spend any time on this slide.

So, as background, half of cancer patients receive some form of radiation therapy, either alone or in combination with surgery or chemotherapy. The purpose of radiation therapy is to destroy or control sites of cancer without causing irreparable damage to normal adjacent tissues and to accomplish its goal, radiation therapy uses high energy waves to deliver energy to the tissues.

Radiation does cause damage to normal tissues, as well as cancer tissue. The potential harms of radiation therapy occur to tissues adjacent to the tumor and will vary by tumor type and location. The harms that I've listed in this slide are just examples of radiation side effects, and they do not represent either a complete listing or a list of the most common side effects.

This slide, which is small to project is a chart taken from the report. The intent here is, then on the following slide, is to place IMRT in the overall framework of radiation therapy... anyway, IMRT is in the longest tail in the center. It is one of the newer image-guided conformal methods, and it will be compared with 2D and 3D CRT, which is another form of externally administered radiation therapy.

Moving down one layer in the chart here, just make note that stereotactic radiation therapy is not the same as IMRT, although both can be performed together on the same patient, and stereotactic radiation therapy is the subject of an upcoming report and is not included in this report. And note also that IMRT, which is the left column, includes Tomotherapy and Arctherapy.

IMRT has FDA approval for sale, but this FDA approval does not require comparative studies on efficacy or safety, and the report that we provided provides a broader evidence analysis than required by FDA approval. IMRT has experienced wide clinical acceptance, and its use is growing in the United States. Dr. Thompson gave you these figures, as well, but for breast cancer the use of IMRT in cases requiring radiation therapy expanded from 1% in 2001 to 11% in 2005 and for prostate cancer from 29% in 2002 to 98% in 2008, and this is using SEER Medicare data.

IMRT is commonly used for brain, head and neck, breast, lung, and prostate cancer. To provide overall clinical perspective, we have listed the incidents figures for these cancers in the United States, and then the

third bullet point to provide some Washington-based perspective, we have listed the number of cases, this is not incidents, the number of cases for Washington PEB and Medicaid for the three years that were given to us and note that prostate and head and neck make up approximately 80% of all of the cases.

Modern external beam radiation treatment is conformal and conformal means that the radiation field is shaped or collimated to conform to the anatomy of the tumor. So, through pretreatment planning, the radiation beam is collimated or shaped, and the direction is chosen to give the best solution for radiation to the tumor and surrounding tissues that maximizes the dose to the tumor and minimizes the dose to the surrounding tissues. 2D and 3D CRT are conformal radiation therapy or conventional radiational therapy, are similar and the distinction is made on the basis of what diagnostic imaging modality is used to do the treatment planning. So, 2D CRT uses x-rays and 3D uses CT or MRI or some other 3D imaging modality.

IMRT does increase the conformality compared to CRT using hundreds of leaflets or collimators to shape the beam more complexly and also to vary the intensity of the beam. So, comparing CRT to IMRT, the IMRT beam is more irregular in shape, could be more narrowly collimated and also has varying intensity, as opposed to fixed intensity throughout the beam. In addition, there are an increased number of beam angles to deliver the radiation instead of two beam angles at right angles. In fact, for Tomotherapy, the radiation is administered in a 360-degree arc around the patient.

IMRT does require increased pretreatment planning and increased time during each treatment session, which does increase the cost of IMRT. This slide is taken from the report, and its purpose is to visually demonstrate that you do get increased conformality with IMRT. So, the top line representing CRT where the green organ at risk adjacent to the tumor is entirely included in the radiation field, and then with a more complex radiation field in the lower right hand column, we see that at least some of the organ at risk is excluded.

So, the PICO for our report, the population is adults and children with malignancies where treatment by radiation therapy is appropriate. The intervention is IMRT and the comparator is conventional external beam radiation, which we will, in the rest of the slides, I think refer to as EBRT or external beam radiation therapy. The outcomes that we looked at are patient outcome, survival rates, recurrence, metastases, quality of life

and harms, primarily radiation exposure and complications, cost and cost effectiveness.

We used the best evidence systematic review methodology. We looked for recent good quality systematic reviews or technology assessments and when we found those and there were only 16 systematic reviews for four of the cancers, we did a Medline search from the date of the systematic review search to the present. In the absence of any systematic review, we did a 10-year Medline search for individual articles.

Our inclusion criteria, we looked at clinical outcomes and we therefore excluded articles on dosage, dose ranging, and dosimetry unless they also included clinical outcomes, and I think the comment that why had we ignored a basis of data, and I think it was because it dealt with radiation contours.

So, there are four key questions. Key question 1 is outcomes. Key question 3 is subpopulations, and key question 4 is costs, and the literature for head and neck, breast, and prostate is much more rigorous, well not rigorous, but there is many more articles at least, and we included articles with at least 50 patients and studies that had a comparator. That is, that compared IMRT to EBRT. For the less common cancers, we included articles that had at least 20 patients, and we accepted both comparative and noncomparative studies.

For harms, for all cancers we included studies with at least 50 patients, and we looked at comparative and noncomparative studies. There were two exceptions to that. One is that for serious harms and for pediatric populations, we included studies with at least 20 patients. We quality assessed the systematic reviews, the guidelines, and the individual studies as good, fair, or poor. In addition, we used the grade system to rate the overall strength of evidence of the findings into high, moderate, low, or very low and strength of evidence here relates to the likelihood that further evidence would change the conclusions of the findings.

Four keys questions. They are all comparative. That is, please compare IMRT to EBRT for clinical effectiveness and efficacy, harms, including radiation side effects, and these are oftentimes referred to toxicities, subpopulations, costs, and cost effectiveness.

We obtained 2,100 citations of which 146 met the inclusion criteria, and these included 16 systematic reviews and 130 individual studies. An additional 12 citations were submitted during the public comment period and five of those met inclusion criteria and were incorporated into the

final report. The report was reviewed by two peer reviewers, one from OHSU and one from the University of Washington, and their comments were included in the final report.

An overall approach to how the rest of this presentation will go, we were going to present the findings for clinical outcomes and harms by cancer, 26 cancers in all that we found evidence for, and by strength of evidence. Key questions 3 and 4 subpopulations and costs we'll present in aggregate. Overall, there were no findings of high strength of evidence and only a few findings of moderate strength of evidence and if you want to follow along, the Appendix E in the major report called the summary of findings table summarizes the findings in a way that will match what we're talking about here.

Now, what are the weaknesses of the evidence? Dr. Thompson mentioned most of them. Most of the studies are case studies with either no comparators or historical comparators, especially in the prostate literature. There has been an increase in dose during this last 10 years, and we encountered studies that were comparing CRT at lower doses compared to EBRT at higher doses, or were studies that included patients at mixed radiation doses, and the results were pooled, and they made coming up with conclusions more difficult. Many of the studies that we looked at had different tumor stages at the initiation of treatment, which we thought was a compounding variable, and as Dr. Thompson mentioned, different chemotherapy regimens during the course of IMRT.

Now, this slide lists the abbreviations that we're using in this report and in the summary of findings table. On the right are the symbols that we use, and I want to spend just a minute talking about those. All of these arrows indicate comparison between IMRT and EBRT. An up arrow may mean that IMRT is better or worse than EBRT, depending on the finding that we are reporting on. The up and down facing arrows indicate conflicting reports where some of the evidence shows increase and some a decrease of IMRT compared to CRT, and finally the sideways facing arrows show no significant difference. Just one additional finding that I meant to mention is that for the up and down arrows, those indicate that the differences were statistically significant. So, in the absence of significant difference, then the sideways facing arrows are what we put in the table.

Craige Blackmore: Can I ask for clarity while you're on this slide?

Edgar Clark: Sure.

Craige Blackmore: Of the abbreviations, progression-free, disease-free, disease-specific, and biologically disease free.

Edgar Clark: Wow. We have basically taken these from the articles. So, this is the monitor that they were using. I think overall survival is pretty simple. Progression-free survival, disease-free survival, disease-specific survival are, I think, difficult to define generally, and they were defined in the article. Biologic disease-free survival is unique to the prostate cancer literature and what it means is that the PSA has not increased more than 2 mg/mL above the lowest post-treatment level. Does that help?

And we are going to present these... the results by cancer in the approximate order of the frequency of cases in Washington State, and these tables on the left will show the strength of evidence and on the right will show an individual finding. So, the first category is head and neck cancer. Key question #1, clinical effectiveness there is one moderate strength of evidence finding and that is that xerostomia or dry mouth-related quality of life is improved with IMRT. The other findings are low strength of evidence and those are other quality of life measures. There is no significant change, and there is no significant difference for overall survival, local control, progression free survival, or RFS. I can't remember.

Craige Blackmore: So, I'm going to…

Edgar Clark: Recurrence-free survival and disease-free survival.

Craige Blackmore: …I'm just going to be explicit here. When you say improved xerostomia-related quality of life, we're talking about decreased complications?

Edgar Clark: We're talking... no, this is actually an outcome measure, and this is people who have done quality of life surveys. So, we... it will show up as a harm on the next slide. I'll go…

Craige Blackmore: That's what I'm afraid of. So, I want to make sure. So, here we've got improved quality of life.

Edgar Clark: Improved quality of life by measuring by some quality of life measure.

Craige Blackmore: Xerostomia score, yeah.

Edgar Clark: Some questionnaire.

Chris Standaert: So, it's not the same as frequency as xerostomia?

Edgar Clark: That is correct. That's a... that will be reported as a harm. So, the outcomes measures are patient survival measures and quality of life. The distinction is [inaudible].

Craige Blackmore: I just want to be explicit.

Female: Exactly.

Craige Blackmore: This is better. This is an... this is a positive thing.

Edgar Clark: Yes.

Craige Blackmore: Because in the next slide, you're going to tell me that it's a negative thing.

Edgar Clark: It's going to be a lower incidents of xerostomia.

Craige Blackmore: Right.

Edgar Clark: So, this is clinical effectiveness, key question 1. Key question 2 is harms. Now, this is the flip slide of that. So, moderate evidence that xerostomia is lower in incidents with IMRT than EBRT, significantly lower, and when we previewed this with the medical directors, they asked if we could put some data in a few of these slides to give you an idea of what the actual range or level of... the order or degree of reduction. So, there were nine studies on xerostomia. In those studies, the incidents of xerostomia ranged from 7 to 80%, and the reduction in xerostomia with IMRT ranged from 43 to 62%, and that was statistically significant in nine… or eight of the nine studies. Very low strength of evidence for other harms or radiation side effects.

The prostate, clinical effectiveness, there is low strength of evidence for all of these findings. There is a decrease in local recurrence with IMRT and the measure for that was the need for additional treatment at three years and this is from SEER data and Medicare, 2.5 per 100 persons per year was the additional treatment required with IMRT and 3.1 per 100 for EBRT and that is statistically significant at less than 0.001. For biologic disease-free survival at 60 months, there is improved biological disease-free survival with IMRT. The rates are 74% for IMRT and 60% for EBRT. That is also significant at 0.001. Biologic disease-free survival at 30 months is not significantly changed and tumor control is not significantly changed, and the evidence about quality of life is conflicting. Now, for harms for prostate, there is moderate evidence that there is a decrease in

GI toxicity with IMRT. There's also low-level evidence for hip fractures with IMRT, for GU toxicity with IMRT, and no significant change for chronic GI toxicity or erectile dysfunction.

Moving on to lung cancer, the evidence is low or very low in strength and note here that for some of these very low there were no comparators, and in the absence of comparators, we are unable to make any kind of differential, or different, statements on differences. So, the evidence is that there is low-level evidence that for non-small-cell lung cancer there is an increase in survival with IMRT but no significant difference in local progression-free survival or metastases-free survival.

I won't just read out the very low evidence. For harms, there is low-level evidence that there is a decrease in pneumonitis with IMRT compared to EBRT, and then the remainder of the findings are very low level, and I should say that lung here includes mesothelioma, large cell and small cell lung cancer.

For breast cancer, key question number 1, clinical effectiveness, there is a moderate level of evidence that there is no difference in quality of life, low-level evidence that overall survival and disease specific survival have variable results, and they appear... there appears to be no difference in tumor recurrence of distant metastases with the use of IMRT.

For harms, there is a decrease in telangiectasia and moist desquamation with IMRT. Moderate strength of evidence as well that the other toxicities are not significantly changed.

The brain includes... I'm going to pause here. I excluded... I inadvertently omitted slides on female pelvis in your set. I will say that the female pelvis, which includes cervix, endometrium, and whole pelvic radiation there is one low-level finding and that is that there is increased overall survival for cervical cancer but no difference in local regional control, and for harms for cervical cancer, there is a low-level evidence that there is decreased late GI toxicity and no change in GU toxicity.

Okay, going on then to brain cancer. This includes glioma astrocytoma, meningioma, medulla blastoma, brain metastases, and pituitary adenoma, and you can see that the evidence here is all variable, both for clinical effectiveness and for harms.

Going onto the abdomen, the abdomen includes the esophagus, stomach, liver, pancreas, anus, and rectum, and I appreciate that the esophagus is not in the abdomen, but we put it in this category. Again,

the evidence is very low here for both clinical effectiveness and harms. Then, the kind of grab-bag at the end, thyroid cancer, sarcoma, skin cancer, and spinal metastases, again, evidence is very low in strength for both harms and outcomes.

So, moving onto key question number 3, subpopulations. We were unable to find any evidence on subpopulations for any cancer. For key questions number 4, cost and cost effectiveness, there is cost-only data for breast and head and neck and cost and cost effectiveness data for prostate cancer. The evidence is low in strength for all cost and cost effectiveness findings. So, there are two reports on cost for breast cancer. SEER medical database study showed a mean cost of $7,000 for EBRT and $15,000 for IMRT. A modeling analysis by Sue gave a range of direct costs of $6,000 to $11,000 for EBRT and $19,000 for IMRT.

For head and neck cancer, a single study from France showed direct costs for centers that had just begun performing IMRT of 14,000 euros and for centers that had experience with IMRT, a direct cost of 6,000 euros. For prostate cancer, there is a mistake on this slide. The Konski Study is from the United States and not from the United Kingdom, but Hummel wrote a technology assessment under the comparative effectiveness review from AHRQ. He identified two studies looking at cost and cost effectiveness, Konski and Pearson. They both calculated cost effectiveness, and they used different assumptions for survival and for the utility of toxicities and they came up with very different numbers for cost effectiveness. So, the costs for Konski are $21,000 for EBRT. He wrote two articles in 2005. The cost for IMRT is $33,000, and in a 2006 article $47,000, and incremental cost effectiveness of either $16,000 or $40,000 per QALY in those two articles. Pearson, on the other hand, calculated costs of $11,000 for EBRT and $42,000 for IMRT and gave a cost effective ratio of $700,000 per QALY, and I would like to expand upon those differences in the next slide.

So they both use 2005 dollars, they both used the [inaudible] articles that were referred to earlier to estimate the frequency of side effects. Konski considered low and intermediate risk prostate cancer while Pearson considered only low-risk prostate cancer, but the differences in… so the baseline data they used was pretty much the same, but the assumptions were different. So, Konski assumed a 14% difference in survival with IMRT better than EBRT, and he gave a large increase in utility to differences in GI and GU toxicity to IMRT. Pearson, on the other hand, assumed no differences in survival and only a minor increase in utility due to changes in rectal toxicity. One gives you an ICER of 16 or 40,000. The other gives you an ICER of 700,000, which is right. We quality reviewed both those studies and rated them as poor. Hummel and his technology

assessment, his conclusion was that the Konski assumptions did not agree with the existing evidence.

The MAUDE database is a voluntary database maintained by the FDA and two reports are present in there on severe adverse effects. One patient admitted to the ICU with severe skin reactions and one patient admitted to the hospital with hematochezia and anemia. The type of cancer being treated is not specified in the MAUDE database.

There are 17 guidelines identified, 15 from NCCN and 2 from Astro, and the two from Astro talked more generally about how IMRT should be performed and who should be performing it. They don't deal with patient-specific guidelines. The NCCN do. All the guidelines were rated as poor in quality, and for the NCCN guidelines, this poor rating came about almost exclusively because we were unable to determine if they had done a systematic literature review, and we had several communications with them by phone and by e-mail and wound up still being uncertain about the rigor of their literature search. There are 11 appropriateness criteria from the American College of Radiology. As you know, those are not true guidelines but they do relate to various aspects of care, and the recommendations are varied by malignancy, and this table is also in the report and it has 3 columns. The left hand column is those cancers for which IMRT is usually not appropriate or recommended. The center is those for which IMRT may be appropriate. And the right is the… those for which IMRT is usually recommended or appropriate, and you will notice if you look at that chart that there are some cancers that appear in more than one column including cervix, which appears in all three columns, and the differences here are clinical stage and clinical presentation.

Coverage policies, Dr. Thompson reviewed these. There are no national Medicare coverage decisions. There are three local coverage decisions that affect Washington. The bottom one is probably more helpful. It indicates that IMRT is standard treatment for brain, head and neck, prostate, and selective cases of thoracic and abdominal malignancies, selective breast cancers, pelvic and retroperitoneal tumors.

AETNA requires that critical structures be located near tumors that cannot be adequately protected with EBRT. Group Health covers IMRT for head and neck, and prostate cancers. Regence covers IMRT for anal and head and neck cancer, and for prostate cancer after surgery, and breast, lung, and other abdominal and pelvic tumors that may be covered if critical structures were in the field... in the radiation field that is.

So, overall summary, key question 1 there is only moderate strength of... the only moderate strength of evidence findings are for quality of life and those are that for head and neck, there is an increase in xerostomia related quality of life with IMRT. For breast, there is no significant difference in quality of life. There are no findings on other patient outcomes of any type for any survival, recurrence, disease-free recurrence. There are no findings of moderate strength for any cancer.

For key question 2, the moderate strength of evidence findings are decrease in telangiectasia and moist desquamation for breast cancer without significant difference for other toxicities. For head and neck cancer, there is decrease in grade 2 or greater xerostomia, and for prostate there is a decrease in cases of acute GI toxicity with IMRT.

There is no evidence of subpopulations on costs for breast, head and neck and prostate by IMRT costs more than EBRT in the range of cost effectiveness was $16,000 per QALY to $706,000 per QALY.

Guidelines: IMRT is said to be usually appropriate for breast, prostate, head and neck, cervical, and nonsmall cell lung cancer, but it may be appropriate for the others that are listed there.

The limitations of the evidence: There are a limited number of systematic reviews, only for head and neck, prostate, breast, and glioblastoma. Many of the studies lack a comparator or have only a historical comparator, and many of the studies did not adjust for the compounding variables that we have mentioned, including radiation, postradiation treatment plan and the presence of various forms of chemotherapy, patient age, tumor stage, and difference in the standard repair over time, and the baseline literature is primarily a series with small sample sizes. Thank you.

Craige Blackmore: Thank you. At this point, I'd like to ask if there are committee member questions specifically about the evidence report and then we will see if we can get those questions answered, and then we will take a break. Then, we'll come back and go into a more general discussion among the committee, but at this point, are there any specific questions about what we just heard from the evidence report?

Male: Can you remind me, again, why the evidence for female GU cancers was left out of the…?

Edgar Clark: Sorry. When we went through…

Craige Blackmore: It was an error? It was a mistake?

Edgar Clark: It was an inadvertent omission. We totally reorganized this talk after we presented it to the medical directors, and in the course of doing that, I just did not get the female pelvis slides in this set.

Craige Blackmore: So, you do have the summary data on the female pelvis in Appendix E, which is in your notebooks. I don't have the exact page in front of me, but page 10. Thank you. So, the information is there, we just did not have a slide on it.

Edgar Clark: When I was rehearsing this a few days ago, I said, hmm, there's no pelvis data. That's when I found it.

Male: So, I'm... the reason I'm bringing this up is if you look at the incidence data, it's fairly significant. So, I'm... I'm proposing that we at least cover it as a topic even though it was left out of the presentation.

Craige Blackmore: We should definitely cover it as a topic. It was left out of the presentation, but it is clearly included in the evidence review. It's included in the material that we're provided with, and I think it's included here. We just lacked a slide. So, I'm comfortable that we have that information. We can refer to the tables when we get to that point in the discussion.

Carson Odegard: I just have one small correction here, Dr. Clark, on GI toxicities for prostate cancer. You have an increase in the appendix, an increase of GI toxicities as opposed to decrease. So, it's just a small correction.

Craige Blackmore: So, where are you?

Carson Odegard: I'm under key question 2, under prostate cancer. Moderate evidence.

Craige Blackmore: Do you have a slide number?

Carson Odegard: It doesn't have page numbers on here.

Craige Blackmore: Oh, in the tables?

Carson Odegard: This is in the appendix, right.

Craige Blackmore: So, you're saying there should…

Carson Odegard: It should be decreased GI toxicity.

Craige Blackmore: …there's an error in the tables?

Carson Odegard: Right.

Craige Blackmore: Can we get confirmation?

Edgar Clark: In the table, it says decreased GI toxicity.

Carson Odegard: It should... well, it says increased GI toxicities in the…

Edgar Clark: Okay, that was a... that was an error that we picked up, and I thought we had sent a correction on that, but you're correct. It should be decreased.

Carson Odegard: Okay.

Craige Blackmore: And I'm sorry, Carson. You were under prostate?

Carson Odegard: Prostate.

Edgar Clark: Page 17 of the appendix.

Craige Blackmore: Right, okay. Yep.

Edgar Clark: In the middle?

Craige Blackmore: This should be a decrease in GI toxicity.

Carson Odegard: Under moderate.

Edgar Clark: Decrease.

Craige Blackmore: Thank you.

Marie Brown: I have a question about the practical differences between moderate level of evidence, low, and very low. While certainly there were some differences… there were some less than ideal research designs in some of the studies, and that would make it low or very low. Could you talk a little bit about the differences? How you defined, exactly, low and very low?

Edgar Clark: I'm going to ask for… the one that lists them all? Well, I have to say that this work required five or six people working full time, and I did not do all of the assessments... the quality assessments. We actually quality... we

had two people quality review every article. Then, I'm not sure that I could speak very high, but the differences... I'll let Heidi Krist who headed the team up talk.

Heidi Krist: So, this is based off of the grade terminology that they use. As you can see, all the definitions are there. I think there's two things that are important. Can you hear me okay? There's two things in this that are important to take into consideration, which is the estimative effect and then how much confidence we have in that estimative effect. So, that's what you'll mainly see between the differences of these different ratings, and so your particular question was between low and very low, is that…

Marie Brown: And moderate and low.

Heidi Krist: Okay. So, if you look at the definitions, like on moderate, for example, further research may change the estimative effect and will likely have an important impact on our confidence in that estimate. When you get into low and to contrast you see further research is likely to change the estimate and very likely to have an important impact on our confidence. So, how much can we trust these effects and how much was it due to chance if further research was to come out? Is that going to change our confidence in these estimates, basically, is what this is saying. So, when you get into low and very low, as you can see, your confidence in these effects is declining. When you get into very low, we really don't know. This is what the study is saying, but with further research that could definitely change. So, we really don't know if further research comes out, what that may say.

Marie Brown: And I think it's important for me, when I remember that it's really about lack of evidence rather than something about quality.

Heidi Krist: Well, quality does go into this.

Marie Brown: Right.

Heidi Krist: Yes, definitely. I mean, we definitely take into consideration the quality of the studies. As you see up above on that first bullet, you know we are assessing the individual quality of all of these studies with good, fair, and poor, and that definitely goes into account in the grade methodology, because you're also looking at the consistency of the evidence. We've pointed out where there is inconsistencies in the evidence, so that's also something that's really important, the effect sizes, how large of an effect size is there. Those all go into play in how much confidence you have in those estimates of effect.

Michelle Simon: Just to follow up on that, I have a question about some terminology that's used in the report. At the bottom, at the very bottom of page 61 when you're discussing the pancreas, it says subsequently by published studies it says a fair quality cost effectiveness study and goes on to describe Murphy 2012 and then in the summary, overall summary of that section, it says one poor quality cost effectiveness modeling study. So, fair quality, poor quality, what are those? Are those equivalent?

Edgar Clark: No.

Michelle Simon: Okay.

Edgar Clark: That's a report written by a lot of people. That's an inconsistency.

Michelle Simon: So, can we assume it is indeed a poor quality cost effectiveness study on the pancreas at the top of page 62?

Edgar Clark: Fair.

Michelle Simon: Okay.

Female: Fair quality?

Edgar Clark: Fair quality.

Michelle Simon: And remind me again what the difference between fair and poor is, then? Is it this?

Craige Blackmore: Fair and poor.

Michelle Simon: Okay, because I see high, moderate, and low. I don't see poor, fair.

Edgar Clark: Well, the…

Michelle Simon: But the systematic review…

Edgar Clark: …the individual studies, top [inaudible]… the individual studies are rated good, fair, or poor.

Michelle Simon: Okay.

Edgar Clark: And the overall strength of evidence takes into account the consistency and the quality of the available studies.

Michelle Simon: So, the summary, in this case, is incorrect. It's actually fair?

Edgar Clark: That's correct. We should have you as a proofreader.

Michelle Simon: Okay.

Heidi Krist: Do you want me to… I can comment on what that means. Like on the economic evaluations, for example, a good quality economic evaluation has a low potential for bias from conflicts of interest and funding sources. Typically, the modeling of the studies that have gone into it are a good quality. When you get into more fair quality, they have incomplete information about methods to estimate the effectiveness and the cost of the intervention. The analyses may not consider one or more important variables, and the choice and values of those variables are not completely justified. When you begin to pour, there's just really clearly lots of flaws, and you just cannot trust what they did, as far as what studies went into that modeling or if any went into the modeling, itself.

Chris Standaert: I have a somewhat related terminology question when they're ready.

Edgar Clark: Let me just say that the definitions of good, fair, and poor are all included in the report. Pages 53 and 54.

Chris Standaert: One more terminology question. You guys have a number of things that you say very low estimative of effect, and then you say there's no comparator. I mean, we're comparing two different things. So, if there's no comparator, that means there's no information, not a very low estimate. That means there's…

Edgar Clark: Very low strength of evidence.

Chris Standaert: But there's no evidence, not very low... there's nothing. It says no comparator, so it's just giving me a list of sort of side effects of one treatment without having any idea what happens when the other treatment is nothing. That's not any evidence, right?

Edgar Clark: That is correct, but, we have been asked to include evidence of side effects even if there are no comparators, so that's why those were included. You will recall when I said that when we looked at harms, key question 2, we looked at studies that were both comparator and non-comparator studies for harms, and we did that also for outcomes for the less common cancers. This was in an effort to try to ferret out.

Chris Standaert: Right. I'm just point out we just don't know, but he's giving us one side.

Edgar Clark: That's correct.

Heidi Krist: So, just to add to that, so if we don't identify any evidence on a particular intervention or cancer, we'll just say blatantly there is no evidence out there. And to your point, what we do is we will assign a very low overall strength of evidence to say, as you have said, we don't have a comparator. We really don't know…

Chris Standaert: We don't know.

Heidi Krist: …anything about this. So, that's where that very low comes in is we really don't know. There's no comparator, so we don't know how much better it really is compared to…

Chris Standaert: Okay. I had a question on the Hummel, these issues of cost effectiveness. So, the numbers are wildly different, obviously, and the Konski study says a 14% difference in survival for IMRT versus EBRT. Where did that come from? You have another study saying that's not valid, but did he just pull that out of the air? Did they just pull this out of the air, or where did that number come from? Is there a basis for having that number that... that's a big number, and that dramatically shifts the economics here. It seems odd they would just make that up.

Carson Odegard: As a followup to that question, you also mentioned that one of the studies looked only at low-risk prostate in patients and the other looked at low and moderate-risk prostate patients, and I wasn't sure what that meant, both in terms of the indications for IMRT and the likelihood of having harms and dosing and that sort of that thing, and I didn't know if there was any data in the efficacy data looking at prostate cancer that was stratified based on risk of the cancer or stages or anything like that?

Edgar Clark: I think this might be a question that our clinical expert could help with, in terms of risk of high risk, low risk, prostate cancer, and stage…

Martin Fuss: It's obviously low risk, moderate risk, high risk taking into how it relates to the ultimate prognosis of the patient. After that… that go into that is the pathologic grading, Gleason score in this particular case, plus PSA values. So, the estimate in outcome in classic white patients by their disease stage here into likely outcomes. Low-risk disease obviously having a favorable outcome in the first place. Here, the survival benefit of one modality over the other may be difficult to prove and may require long followup times and that's one of the traps that we are falling into

with prostate cancer. So here, we have to rely on surrogate, one surrogate being a PSA, or the freedom from biological… the biological recurrence-free survival, meaning a lack of an increase in the PSA value over time. So, this is one of the predominantly reported outcome measures in prostate cancer and secondary in point to potential better tolerance of one treatment over the other in terms of reducing GU and GI toxicity, both acute and chronic.

Carson Odegard: And based on the risk of the cancer, would that affect the dosing recommendation for IMRT for those cases?

Martin Fuss: At this point in time, we don't necessarily stratify radiation dose by low, intermediate, or high risk. We do, however, approach those treatments differently in the sense of either delivering radiation therapy alone or in combination with, for example, on one occurrence.

Marie Brown: And does that include the aggressiveness of the cancer cell type?

Martin Fuss: Well, that's inherent to long, intermediate, and high risk, and, in fact, we are not necessarily treating the same volume. If you have a low-risk cancer, which is confined to the prostate gland only, has a relatively low PSA, has a relatively low pathologic grading. In this particular case, only the prostate gland is being treated, because there's a low probability that this tumor has moved on to regional lymph nodes. However, if you look at the high risk side of the spectrum, so now we have a tumor that has likely a high PSA, it is a more extensive stage of disease, the tumor may no longer be confined to the prostate gland exclusively but has a higher risk of lymph node involvement. Here, we are treating the prostate gland, seminal vesicles, and lymph node chains if we treat them with radiation. So, the whole treatment concept changes. Not all of this volume can receive the same radiation dose, because if they are looking into the mid 70 grades of a radiation dose to the prostate gland. You cannot deliver that high of a radiation dose to the lymph node chain or into the proximity to structures that risk, bowel and bladder being those two structures that are a particular risk.

So, at the same time, if you have the assumption of having microscopic disease out in the lymph nodes, they may not need a mid 70 grade radiation. So, that's how we have to look at it.

Carson Odegard: So, just in terms of understanding these cost effectiveness studies, is it reasonable to assume that they were looking exclusively at low-risk patients, then those patients would have had radiation exclusively directed at prostate but not had regional lymph nodes treated, so the

side effect profile might have been lower than for the studies that included moderate risk patients where the radiation fields might have been larger, and the risk of toxicities might have been higher. Is that a reasonable assumption?

Martin Fuss: I can't… I think it's a reasonable assumption to assume that we are looking at a favorable risk prostate confined to the prostate where the prostate is the target of the intervention.

Edgar Clark: Your question about survival... I have the article here in front of me, and I can't quite come up with how they calculated the improvement in survival, but the utilities were obtained from 17 patients with intermediate risk prostate cancer undergoing IMRT without hormone therapy or randomized in-house phase 3 clinical trial.

Chris Standaert: That's a very small number.

Edgar Clark: 17.

Chris Standaert: Yes.

Edgar Clark: One-Seven.

Chris Standaert: Yes.

David McCulloch: I just have a quick question about, and this may be something that comes up in talking to our clinical expert, but on the basis of the evidence review, is there any information at all on the costs acquired in dealing with the complications of any therapies?

Edgar Clark: The cost data that we gave you… the cost data is direct costs of the treatment. The cost effectiveness data for prostate would include the costs in the modeling, includes the cost of taking care of the side effects.

Marie Brown: The current side effects, not long term? Like, not the next set of side effects if the bowel were over-radiated?

Edgar Clark: Well, without going into the articles in great detail, it depends on the way the model is set up and I can't tell you that the…

Marie Brown: Is the assumption correct that if there are more at the time side effects, then there will be more long-term side effects and that will cost, and those costs are another set of costs that will likely need to be considered, if you looked at this in the bigger picture?

Martin Fuss: Well, yes.

Marie Brown: Yes.

Martin Fuss: Acute side effects do predict for chronic side effects. Chronic side effects do come with cost, cost in terms of quality of life and cost to the health system.

Marie Brown: Right, but they're not in this particular consideration, but they would be if we took a broader perspective? If we looked at life case over time?

Craige Blackmore: So, I guess one, if I might, rephrase what you're asking. Maybe this is what you meant, I don't know, but it's what I'm interested in. Do the cost effectiveness analyses, what is the time horizon on those?

Edgar Clark: Yes, I'm trying…

Marie Brown: Yes, that's what I was asking.

Edgar Clark: I'm trying to... okay... the time horizon... this is from the Hummel technology assessment. The time horizon is 15 years for Konski and lifetime for Pearson.

Craige Blackmore: I think it's a little after 10:00, so why don't…

Chris Standaert: Could I ask one more question?

Craige Blackmore: Yes, sure.

Chris Standaert: I had one more question, just on sort of a level of evidence and study. Sometimes, when we aggregate these things, we sort of lose the detail we would like, and I heard what the speaker said earlier, and maybe I don't know enough about the evolution of how this particular technology came into the marketplace, but it seems like it would have been a natural thing to perform an RCT on when it first came out. You had a distinctly different method of doing something with distinctively different costs and planning with a theory that it does certain things, and you had an existing technology, and you do mention there are several RCTs in here. I was curious about the design of them and the quality of them and did they really just do this sort of apples and oranges? We did one technique, then we did the other technique, and is there... do people actually do this? Is that what they did?

Edgar Clark: My team here has the list of every article that we looked at. So, there were two RCTs for breast and one for head and neck, and I'm… to be honest with you, I don't remember the details of those. We have them all here.

Craige Blackmore: So, we're going to take a break in a minute, and if I could, if you… during that break, maybe you guys could have an opportunity to drill down a little and try to figure that out. Joann, you want to ask a question before we…?

Joann Elmore: You want it before or after? I'm flexible.

Craige Blackmore: You're anxious, let's…

Joann Elmore: I'm not anxious. I am... well, okay, I will ask my question, then. I want to thank our evidence vendors for dealing with the challenging topic on so many anatomic sites. It was challenging for us to review, and I feel for the radiation oncologists because now that this has gotten into clinical practice, they have a hard time studying it, and I have a question for our evidence vendors about the potential for bias in reporting of the harms by both patients and providers in these studies, and I will preface this question by saying the biological plausibility of a reduction in harm, it kind of makes sense, and secondly I need to be honest that I am often quite harsh and critical of primary evidence, as I'm reviewing it, but it seems that we only have a handful of RCTs. These are case series and cohorts. Patients are not randomized. They are not blinded, and in many of these case series, they are often seeking the providers that have this new technology. They may be reading on the internet that it's better. They may be told in their informed consent process that this is better. And so, can our evidence vendors please share with us their thoughts on the potential for biased in reporting of harms?

Edgar Clark: I think you've stated it very well. I think there's a huge potential for bias in selection, in publication, and in, as you say, it's not blinded. I mean, one of the things that struck me when I first undertook this project, and I'm not a radiation therapist, so this is not something that I came with a lot of preknowledge about, is that if my doctor said I had to have radiation therapy, and if it costs twice as much, I'd pay twice as much. I mean, it just seems obvious. So, I suspect that the possibility of an individual patient reporting side effects, they might report very differently. So, I think there's a very large bias, or potential for bias.

Male: And just one added question. Just to try to clarify the definitions. I know we talked about this before, but the definitions of survival. When you

went through the articles, I know they gave their own definition of disease-free versus progression-free survival, but across the board, is there a possibility that they're saying some of the same things?

Edgar Clark: Sure.

Male: And that it's just the nomenclature that they're using?

Edgar Clark: Yes, I think so. I mean, I think you're looking at measures of local control. That is, has the tumor come back or has it... is there a recurrence? Did it ever go away? Are there local metastases? Then you have… that is the patient died but he didn't die of the cancer. That would be a disease-specific survival. For many patients, they have advanced other illnesses. So, there are a lot of different definitions that probably, if you were to spend another 100 hours you could cram them down into smaller categories, but we basically tried to reuse the terms that they used to the extent that... to aggregate when we could but basically use the terms that they gave.

Male: Thank you.

Martin Fuss: Could I make one comment here?

Craige Blackmore: Sure.

Martin Fuss: Looking at... we like to look at such outcome measures, overall survival, local control rates or the lack of local control and then systemic failure rate. But they failed to capture relevant outcome metrics that relate to quality of life. If you look at rectal cancer, for example, the overall outcomes here, in terms of survival, may not change with one of way of delivering radiation versus another, but the local recurrence rate of the tumor may change significantly, and we have this situation in this particular type of disease, and it is highly relevant because in local recurrence of rectal cancer invades the sacrum and causes intractable pain, for which no therapeutic measure exists. The patient is highly dependent on pain medication. So here, the metric that fails in terms of survival yet provides significant outcome benefits to a patient, and that's often very difficult to summarize in a table. That's why one metric shows the benefit, the significance of that benefit to the life span of the patient. It may be dramatic, and I just want to highlight that, because we talk about the focal treatment where the potential of [inaudible] often resides, it is in the improvement in local control in the first place, as we do not increase the overall radiation dose, which is a focused radiation dose better and stay away from other tissue, avoid complications, and

improve local control and while that not always resolves in the ultimate outcome benefit in terms of prolonging survival, it may yield quite dramatic benefits to the patient, and that's a lot softer.

Carson Odegard: To turn that same question back to our evidence vendors, I don't know that we saw that there was a significant difference in regional disease control. Do we see that in any of these tumors in the data?

Edgar Clark: There was no moderate strength of evidence of any form of local or general survival improvement for any of the cancers that we…

Carson Odegard: Not survival?

Marie Brown: Recurrence.

Carson Odegard: Disease-free recurrence?

Edgar Clark: The only outcome measures for which we found a moderate strength of evidence were quality of life.

Craige Blackmore: Okay.

Edgar Clark: Local control, whatever measure.

Craige Blackmore: So, we're going to take a break. That's not to say I want to cut off the conversation and the questions. We can resume, but we'll take 10 minutes and come back here at 25 after 10:00.

I'm going to have the committee members resume their seats, please. If I could have the committee members take their seats. We'll call the meeting back to order. Well, we have a quorum, so I'm going to call the meeting back to order. I know there's a couple committee members who are still trickling back in. So, this portion now is the committee's time to deliberate among itself. We also still have, of course, all of our people here to help us provide... answer additional questions, as they come up, but at this point, it's our charge to start to look at the evidence and start to work our way towards a decision to cover without limits, to not cover IMRT, or to cover under some conditions, which we would then define, and what I would like to do at this point is just get some perspectives from among the committee members where they think we are and what questions we still need to drill down on a little further. I don't mean everybody has to give me an opinion, and this isn't binding, but this is just sort of a summary of where we are at this point. Is there anybody who

would like to take a stab at getting us started? We're not all too busy eating, right? Okay.

Joann Elmore: Well, with prostate cancer, it seems that this approach is the standard of care and is used in, what did they say, 98% of the patients, and I think that's... if I looked at areas where there's… the data is stronger, relatively, I would say that's the one area that I would feel comfortable moving forward with supporting. Now, there's lots of other things, but that's one thing.

Craige Blackmore: So, prostate cancer, so I guess I mean the report is structured around different organ systems and we don't have to approach things from different organ systems. It seems to make some sense, and what I'm hearing from you, I think, is that we should not consider this as a global issue but to try to look at it through the different body parts, if you will, separately. Is that... does that resonate?

Joann Elmore: Well, that's the evidence. I mean, the evidence is also different in those body parts that I think it's really about the strength of the evidence, not as much the body part, but they seem to be highly related.

Craige Blackmore: Okay. Can I get some views from some of the other committee members on sort of where we are as a starting point. Seth is raring to go.

Seth Schwartz: I think it's pretty clear that there's no high level evidence in terms of efficacy or decrease in harms for any of the different body sights. I think we did see some marginal, moderate level of evidence of at least of decreased harms in terms of head and neck and prostate. I think... and then there's just a real dearth of data on most of the other body areas, which is difficult. I think one of the things that was brought up by Dr. Laramore was about the concept of this being a tool and really the interesting issue is the... what structures are around the area of interest, and that's I think hard for us, as a committee, to differentiate based on data. So, for instance, you know, breast cancer in particular may not be, whether it's the skin that may not be a big issue, but if it's deep and it's right next to the heart, that might be a different issue. Now, clinically, I don't know if that's just a... that's not a clinically meaningful example, but just, I think that's the issue that is hard to… I think hard to [inaudible] out when we're talking about making recommendations for some of these other areas that have lesser levels of evidence.

Craige Blackmore: I think we've seen in some of the other policy decisions that the decision has been general in the sense of saying if there's a critical structure that

would be in the field, as an indication to sort of avoid micromanaging each of those individual decisions. Kevin, do you want to…?

Kevin Walsh: Well, I guess the next question I would ask in regards to what you just said was, so we'd leave the definition of critical up to who?

Chris Standaert: It's all relative. This is a tricky one, because this is the horse... the cart came before the horse here. This is now standard of care for some procedures, which becomes difficult then to sort of talk about changing. We don't... we have the… history is full of great theories that have flatten when faced with human reality, you know? And is this one of them? I don't know, but it's well penetrated and used, and in a lot of unanimity amongst the coverage policies in terms of avoiding critical structures and errors of prior radiation, and there's a logical rational for that but not a lot of data behind it, which is somewhat frustrating. We have some data on specific cancers with less local side effects, which would seem to sort of support the theory, but we don't have any great, sort of long-term outcome data on anything, which is frustrating. So, it's how do we wrap our heads around all of that? I'd still like to know more about the RCTs that are there, just so I can get some sense of what... how people tried to tackle this problem and the realities of what they did.

Edgar Clark: We have three RCTs on breast cancer and one on head and neck. I'm going to use the Haze, I guess they call it the report. Directories. Let's just summarize them. So, for breast cancer, there are three RCTs. One is from the Royal Marsden Hospital in London. The 306-women divided into 150 and 156 patients, randomized. They were early breast cancer, and they were trying to... respectively trying to compare for adverse late effects of whole breast radiation. The inclusion criteria, if you want to get this detailed or not?

Group: Yes.

Edgar Clark: Okay. Inclusion criteria were early breast cancer, T1-3A, no 0-1, no metastasis. Microscopic incision of the tumor, [inaudible] confirmation of invasive cancer, higher than average risk of radiation induced normal tissue changes by virtue of breast size and normal breast shape. Radiation therapy prescribed to the whole breast under the care of Royal Marsden Hospital. Previous malignancy was an exclusion criterion.

Let's see, they have 90% had tamoxifen and 50% had chemotherapy. They were not blinded. There were no measures of toxicity or complications; 21% were non-evaluable because they did not have

followup photographs. They were judged among clinical photographs, and they didn't evaluate survival and treatment failures. That's one.

Kevin Walsh: So, what was the outcome?

Edgar Clark: Oh! You want to know the outcome?

Chris Standaert: Those would have seemed to have been pertinent, yeah.

Edgar Clark: Typically, more patients treated with standard radiation exhibited changes in breast appearance than those undergoing IMRT. Those had better breast appearance.

Michelle Simon: In the non-blinded with 21% without the outcome [inaudible].

Edgar Clark: Right.

Michelle Simon: Okay.

Edgar Clark: There's another one from Toronto, a multicenter study from Canada, 358 women enrolled, 331 were eligible, 170 versus 160. The purpose was a phase 3 double-blinded RCT comparing the effect of IMRT to standard radiation for acute skin reaction, pain, and quality of life. Conclusions, IMRT is associated with significant lower rates of acute skin reaction, moist desquamation, and standard radiation therapy. Limited duration of followup, clinical outcomes such as survival and treatment failures were not evaluated. Do you want me to go to the exclusion criteria there?

Chris Standaert: No, we got that one.

Edgar Clark: We got the feeling of it?

Chris Standaert: Yeah.

Edgar Clark: Okay, but two reports of the same group from Cambridge Hospital in the United Kingdom, 815 women randomized to IMRT or control, 411 and 400 patients, early invasive cancer. Comparing late toxicity and the results suggest that IMRT and standard radiation do not differ in breast shrinkage, acute toxicity of grades more than two, rates of individual toxicities. However, IMRT is associated with a lower risk of telangiectasia.

Then, we have one study on head and neck cancer. Let's see here. This is squamous cell cancer of the oropharynx, larynx, or hypopharynx. Sixty patients allocated, 28 to CRT and 32 to IMRT, analyzed on an intention to treat basis. The proportion of patients with grade 2 or worse salivary gland toxicity was significantly lesser in the IMRT arm than in the comparison. Late xerostomia and subcutaneous fibrosis were also significantly lesser with IMRT, and this is from India.

Chris Standaert: So, all of those look like complications and none of them actually looked at the effectiveness of the treatment?

Edgar Clark: Yes. I wouldn't say that.

Chris Standaert: That's astounding.

Edgar Clark: I mean, in general, of the articles that we looked at, three-quarters…

Martin Fuss: Can I comment on that?

Chris Standaert: Yeah, yeah.

Martin Fuss: I don't know. If you want to ask me to shut up? I mean.

Chris Standaert: No, it's just I'm curious.

Martin Fuss: So, you have to see those [inaudible] you're right? Looking at those studies of toxicities, yeah? Let's look at the breast trials first. Why do we look at that? Predominantly in females with large breasts, radiation therapy can cause quite significant acute side effects, reddening of the skin, most desquamation, pain intolerance, and now it affects the [inaudible] later in life, shrinkage of the breast or the outcome, the cosmetic outcome of the treatment can be quite problematic for large-breasted women. So, the recent theory is that using conventional treatment techniques, a significant amount of radiation dose ends up right under the skin medial and axillary. So, those are the two areas where the skin breaks up. Really, IMRT here is not used to better treat the tumor. It is, in fact, to more homogeneously distribute its radiation dose throughout the breast to avoid radiation hotspots under the skin and into soft tissues medially and axillary. So, the design here cannot be better tumor control, because you're treating the same volume to the same dose. You just do it more homogeneously to avoid the side effects that we frequently observe.

So, here, the only endpoint outcomes in terms of survival or local tumor control can only have been the secondary endpoint in that study, because it was not designed to really improve those outcome measures in those randomized trials. So, the primary endpoint improved normal tissue toxicity and thus quality of life, what's definitely made in those studies. The same for the head and neck population.

Again, the same tumor volume was created to the same radiation dose. So, we are not expecting to better the outcome in terms of local tumor control or survival in those patients, but conventionally treated, the vast majority of patients develop xerostomia, dry mouth syndrome to the degree that patients walk around with a bottle of water all the time. They literally do not produce saliva often at all anymore. So, sparing out the parotid gland and allowing that gland to function after the comprehensive treatment course in patients who may have an extended life span is a significant quality of life improvement. And again, the trial is not designed for better local control and survival but purely designed to reduce the very common toxicity and at that time [inaudible] was reached. The challenge here is none of those randomized trials has or had a design to improve survival as an outcome measure.

Chris Standaert: Yeah, no. That's my… my sentiment wasn't meant to minimize the importance of the complications, but the question of efficacy. Is it equivalent…

Martin Fuss: Is it well…

Chris Standaert: …is it equivalent, better, or is it equivalent, better or worse? But that's…

Martin Fuss: It's equivalent, but it's not better.

Chris Standaert: But the studies weren't even designed to show equivalency of the study, of the treatment is my... so we have this question of is the…

Martin Fuss: Well, the secondary... the secondary endpoint of those trials… the data have to be in there. The local control rates were no different between the two [inaudible].

Michelle Simon: They didn't record their data.

Martin Fuss: The head and neck trial did not record on the local…

Chris Standaert: I don't think so.

Edgar Clark: I would say that the vast bulk of the literature describes side effects.

Chris Standaert: Right.

Martin Fuss: But this is outcomes.

Chris Standaert: That's clearly where our data is.

Edgar Clark: So it's…

Marie Brown: That's outcomes, reduced toxicities and outcomes.

Chris Standaert: Oh, it is yeah, and it's an important outcome, so I'm not…

Marie Brown: Yeah.

Chris Standaert: It's just that the effectiveness of the primary treatment is what I'm curious about. The efficacy there.

Martin Fuss: So, if you have the outcomes… the survival outcomes reported here. Three-year [inaudible] and my estimates with local regional control and overall survival when non-statistically significant at a level of 0.45 and 0.81 for previous CRT and IMRT arms respectively. So, there's an equivalence in clinical efficacy with respect to tumor control.

Craige Blackmore: So, I think from the standpoint of organization, we have to decide what we mean by effectiveness, safety, and cost and I'm going to just put out there as an idea, and you can give me feedback, I would suggest when we talk about effectiveness we talk about whether the tumor comes back and the patient dies, and when we talk about safety we talk about the toxicities. That's not necessarily the way everybody thinks about it, but just in terms of simplifying our task, then we can divide those two out, as I think we're sort of prone to do here. So, it just allows us to make conclusions about effectiveness and conclusions about safety that wouldn't necessarily be the same based on the evidence that we've heard. Does that sort of resonate with everybody?

Joann Elmore: I understand that, and it makes sense on one level. The worry I have is that if we put reduced toxicity in the safety category, and we tend to give more weight to the efficacy… if something may be not proven to be effective but it's safe, that may have a different kind of weight in our minds than if something is effective in reducing toxicity, as part of the effectiveness.

Craige Blackmore: Yeah, I mean I guess I would say if we believe it reduces toxicities, then we would say it's more safe than the other, but I mean, again, I'm just making a suggestion.

Joann Elmore: Okay. I understand that then, okay.

Chris Standaert: I think we saw the same dilemma in our slides. You pointed out early on that data is presented twice.

Craige Blackmore: Right.

Chris Standaert: So you have complications presented, as it is a health-related quality of life outcome measure and complications reported as a side effect, which is a safety issue. So, the same issue is presented both in the context of an outcome measure, which would be effectiveness and in complications, which is... so it's, again, we got the data the same way with that same dilemma in it.

Craige Blackmore: And I... I think, and again this is just one person speaking, it's not necessarily what everybody believes, but I think, as I look through this data, we're gonna find there's not much that really tells us about effectiveness in terms of tumor control. So, we then can, you know, I think it's hard to conclude... for me, it's hard to conclude that it's more effective or less effective. I think I would either say it was equal or unproven. That's sort of where I am, and again, this is just working through it. It's not binding, but then I think that would allow us to kind of focus the bulk of our conversation around what we're calling safety, meaning are there fewer side effects, really, fewer toxicities. So that…

Marie Brown: I would go with that, yes.

Craige Blackmore: Carson?

Carson Odegard: I have a question for Dr. Fuss. One of the doctors mentioned that it's hard to design these studies, or it's hard to have effectiveness studies done because of dose escalation, that you can't escalate dose because of the levitation of the surrounding tissues sparing the normal tissues. So, can you just elaborate on that? I mean, how do you know what the normal tissue dose limitations are for toxicity?

Martin Fuss: So, we actually have a pretty good empiric understanding of normal tissue dosed tolerances. Over the years the number of highly voted publications have been... found their way into literature ranging from surveys where radiation oncologists were essentially queried and asked,

so what do you think is a safe dose to give, let's say, to a spinal cord? What volume of a kidney can be exposed to radiation without losing the relevant clinical function of this organ system, and more recently, I think John pointed out that we have a body of data that we call Quantec. It's a very good document indicating what radiation dose can be safely delivered to what percentage of each structure. Let's say the liver. The liver will fail if the entire organ receives more than 30 Gy of radiation.

Carson Odegard: Okay. That's exactly what I was asking.

Martin Fuss: And, at the same time, you can quantify those as the likelihood of having a complication then with the likelihood of higher than 5% over the next five years or the likelihood of higher than 50% over the next five years. Obviously, as a field we are not terribly tolerant of 5% spinal cord injuries. That would mean that 1 out of 20 patients would lose their ability to walk, [inaudible] bladder and bowel, as a consequence of radiation therapy. So, this is a side effect where we want to be on the much less than 1% side. Same for blindness of the optic nerve and chiasm. So, for some organ systems, we do not have perfect data, because we don't push the envelope, because the complication result would be so dramatic.

On the other hand, based on those escalation trials, I think we have a very good idea of bladder toxicity, what percentage of a bladder can be exposed to what radiation dose before we run into chronic GU complications? The same for the rectum. We have very good data for the kidneys. We have good data for, or increasingly better data for the lung. What likelihood of the complication comes along with those treatments? So, I think in developing our clinical treatment plan, which is a document that every radiation oncologist has to render for each patient, because we have to define I want to treat this patient at a certain dose level over so and so many fractions, and I want to use IMRT, and then there has to be a justification. Why do I use IMRT? Not just because I have a machine. Yeah, that's not good enough. We justify that we use IMRT because the target volume stands in close proximity to the spinal cord. The necessary radiation dose for the tumor may be 60 Gy to spinal cord tolerance, safe tolerance, may be less than 50 Gy. So, obviously now I think I do have a significant dose differential, and I have a challenge of treating that—treating all of my tumor while protecting all of my normal structure. I think that justifies IMRT, and so there is very good data that we typically quote in our clinical treatment plans.

Now, how can you stipulate that in your requirements is very difficulty; but there is good guidance data as to when do we expect clinically-relevant toxicities?

Carson Odegard: Well, that's great. Thank you. That's very helpful.

Seth Schwartz: I have a separate question for our clinical expert, and one of the comments that was made in looking at these articles is that a lot of them use historical controls, and there was a comment that it wasn't really looked at very well in terms of what adjuvant treatments people might have had, whether there had been changes in chemotherapy or other things that people might have gotten along with the radiation, and I know that we are covering a lot of different organ systems and probably a lot of different treatment regimens, but I'm curious just in general. So, say pull out a couple, prostate and head and neck, can you comment at all on whether there have been concurrent changes in the chemotherapy or other adjunctive treatments that may affect side effects?

Martin Fuss: Those are maybe not the optimal tool, but if we look at the whole set of GI tumors for example, patients do live longer. We make cancer a chronic disease. We are increasing the success in getting there, having patients live with the diagnosis of cancer, because we do now have... and that's the challenge with [inaudible] controls. Those are likely patients treated in their 80s or 90s where we may not have had a second and third line chemotherapy regimen plus targeted agents available, that each of them have a window of efficacy that may range from a month to years. So, if someone goes into a second line therapy at the time of failure, has local control or disease control for over six to nine months until that drug fails in its effectiveness and we switch him over to a targeted agent, and the second targeted agent or a third targeted agent, and each and every time, hopefully, we get to a certain window with the drug [inaudible]. So, we push the survival time. So, yes, there is a significant bias with time more recently with treated patient populations even if they have a shorter fall off and we have longer survival, and it may not be the right [inaudible]. It may just be that the sequence of all therapeutic modalities available to us.

Edgar Clark: Could I comment on this? Our original draft, Dr. Kim reviewed as a peer reviewer, and we had excluded all articles that included chemotherapy along with radiation, because we felt it was a compounder that we couldn't separate out, and it was at his suggestion. So, in the last two or three weeks before it was published, we went back and included all of the chemotherapy studies, as well, for all of the tumors.

Craige Blackmore: I'm just going to take this opportunity to point out to the committee that you now have a new Appendix E at each of your places dated September 6th, because there were some typos in the Appendix E that was distributed initially dated August 17th. So, remove the August 17th and use the September 6th if you want a reference.

Any other questions or comments? So, let's focus on toxicities, which we are covering under the umbrella of safety. I would like to continue this sort of committee members starting us off and getting us grounded, and I would like to hear people's thoughts on where the evidence takes them in terms of effective IMRT on toxicities. Can I get a volunteer? Kevin?

Kevin Walsh: Conceptually, it seems to make more sense to me to go by body part and discuss this than in general.

Craige Blackmore: Okay.

Kevin Walsh: Because, it seems like there's a few where there is…

Joanne Elmore: I would just pick two. Start with prostate then do head and neck, then do the others.

Craige Blackmore: So, get us started on prostate and/or head and neck? What does the evidence speak to you?

Kevin Walsh: I thought that in head and neck that the incidents of xerostomia seemed to be significantly decreased with IMRT compared to external.

Joann Elmore: Significantly decreased, right?

Craige Blackmore: Quality of life increased. Incidents of complication decreased. It was presented both ways in the table. Any other thoughts on that? Is that a place we're comfortable with?

Group: Mm-hm.

Craige Blackmore: How about prostate? What do we think of the evidence on prostate and toxicities?

Richard Phillips: Well, the only moderate evidence was the decrease in gastrointestinal toxicities, but low evidence of GU toxicity and hip fracture. Erectile dysfunction, there was no significant difference. The problem with the evidence is that there's very few moderate categories here on harms and so that's what the evidence suggests for prostate.

Craige Blackmore: Any other comments on prostate? How about breast?

Kevin Walsh: Can we go back to prostate for one second. The only other thing that we've gone about this efficacy question, and there actually is a little bit of data on efficacy, improvement in efficacy for prostate cancer. It's low-quality data, but when you look at that study looking at the 60-month biologically... who knows what to make out of that, and I guess particularly with all the controversy about PSA, I don't know what to make out of that, but there is some data there. I don't know what it means, but there's something there.

Craige Blackmore: Okay. Does anybody want to comment on breast?

Chris Standaert: We have the same issue. We have moderate evidence that sort of less skin and local effects from IMRT that do make a difference for the subjects receiving it.

Michelle Simon: There's also one study that shows equivalent quality of life, moderate strength of evidence on that study, too.

Craige Blackmore: So, maybe a little conflicting evidence?

Michelle Simon: Exactly.

Kevin Walsh: Well, and that big randomized trial with 800 patients in it, didn't that show there was no difference?

Joann Elmore: Telangiectasia only. It didn't state how many other many, many outcomes were potentially studied.

Craige Blackmore: So, I've got decreased moist desquamation and decreased grade 1 to 3 telangiectasia. No change in acute grade 2 or greater toxicities. No change in grade 3 or 4 skin, and then another study with no change in quality of life. I think those are the breast... no, there's one more. No, that's it. So, are there any of the other areas that had data that was worth discussing?

Kevin Walsh: On the safety side, I guess.

Seth Schwartz: Can I ask a question for our clinical expert on brain? I'm struggling with brain, in particular, because in most of the other areas we're talking about avoidance of critical structures, but brain inherently seems like a critical structure. So, I'm... we only have very low quality of evidence,

which I assume means that there were basically no controls in these studies. Do we have any controlled studies at all looking at any of the brain cancer types?

Chris Standaert: If I can remember back to the stabilization data, there were no cases of brain being treated with this particular mode of radiation therapy. Like there was zero if I recall for Washington State data. They didn't have any, so I assume this is not the preferred modality for brain. That's one of the other things we're talking about.

Martin Fuss: That is actually a surprising data point to me that you have a [inaudible] in the brain, because brain is the treatment site commonly treated by IMRT and assuming that this was Medicare?

Edgar Clark: Medicaid and the state employees.

Martin Fuss: It's actually surprising that the number for IMRT….

Craige Blackmore: Margaret, do you want to…?

Margaret Dennis: Head, neck, and brain data was added again [inaudible].

Craige Blackmore: Okay. So, brain was included on the head and neck?

Chris Standaert: Didn't you have a column that said brain? I thought I saw a brain that had nothing above it. That sounds all wrong, but.

Carson Odegard: They have brain.

Joann Elmore: That explains why head and neck was so expensive.

Seth Schwartz: Some people would describe surgeons that way.

Chris Standaert: There was brain, wasn't there a category of brain in one of those bars?

Craige Blackmore: Okay, so we'll just take that brain was included in the head and neck, which is why no cases appeared in our data.

Martin Fuss: Then my comment to brain may be that it may help your decision making, brain metastases are often not nice [inaudible] lesions. That's one shape of a typical tumor. A primary tumor by far most of the time has an extremely complex shape with concavities and convexities, which is difficult to follow, more extensive, and then it is also the proximity to structures at risk, the eyes, the optic nerves, the chiasm, the pituitary,

and the pituitary stalk and/or brain stem. So it often can be a challenge by many structures at risk when treating predominantly primary brain tumors and pituitary adenomas. Brain metastases, more often than not, are not as challenging.

Seth Schwartz: Which makes it interesting that if it is… it makes sense that it's as anatomically complicated and risky as that, but yet, there's no evidence that there's a difference.

Chris Standaert: Just going back to the data for a second. So on slide 8 of the evidence review has a brain of 0, so that is using slide 8. The brain number of IMRT cases for Washington 7, Medicaid 0. So, is there a difference in sort of how the… like were you assuming that brain was not in head and neck and so you assumed that and said 0? Is that what happened? Or did you have data saying that there were none?

Edgar Clark: I just took that from the report.

Chris Standaert: So, just sort of like how it was omitted in your… and clumped in your report, you pulled it out? Okay, I got it. That's where, okay.

Craige Blackmore: So, I think… I mean if I could try to summarize where we are in a sort of a global sense, the concept behind IMRT is that it allows a more focused dose of the radiation to the tumor with less dose for the adjacent structures and that's sort of logical, and it makes sense that you wouldn't want to radiate structures that you didn't need to radiate, because that would have toxicities. Then, we're stuck with the problem that we don't really have any data to show that A, using the IMRT is as effective in controlling the tumor as the sort of standard, but, at the same time, there's no reason to believe it would be any different, because the dose is still being administered. We have, again, sort of the theory, one of the foundational theories, I believe, of radiation oncology that if you don't radiate normal tissue, that's good, but yet our data on how that effects the patient is pretty limited, and it's limited to a couple different body areas and other areas where we really don't know much of anything.

So, I think it, in my mind, it kind of gets down to making a judgment as to do I believe this theory and do I accept not radiating normal tissue, as a surrogate for patient outcome, and I think, to my mind, I am sure that it is a good surrogate for patient outcome up to a point, but probably not indefinitely. Probably, when you get into small changes and probably in some dose ranges, there's not going to be a difference in outcome with the sorts of choices that we're observing. Are we at that point, I have no idea, and the challenge to me is making the judgment to support or not

support what we believe is a higher radiation dose to an area that doesn't need it at a higher cost. I know I didn't put that elegantly, but that's sort of me trying to summarize where I think the challenge is in this.

David McCulloch: Can I make a comment, Craige? Let me make a kind of philosophical comment, and then it'll get down to why... what's guiding my thinking. Again, despite the accent, I've actually been in this country for 28 years. I'm an American citizen and a professor at the University of Washington, but still when you look at the differences in the way, I mean, these things are wrestling with costs, never ending rising costs, if you look at what's going on in the USA versus most of the rest of the world, we just do more of everything. We have more CT scanners per capita than any other country. So, we do more CT scans. We do so many more CT scans, but we are undoubtedly generating tens of thousands of unnecessary cancers in the population over time.

We have more PET scanners than anywhere else, so we do more PET scans. We've got more interventional cardiology centers, so we could stent into people who would do better off not having stents in them. We now have more robotic surgeon machines, so we're just going to use them, and the argument that keeps getting made by the impassioned people who love these cool new tools is, you know, the arguments made well, we've already got the overhead of the buildings and the machines and the staff to use it, so we might just well use them. So, the biggest driver of cost is scope creep. So, if you get some marginally believable evidence that in a couple of specific cases you can get as good life and death outcomes, fewer side effects, we're told we shouldn't be swayed by the fact that it's actually massively more expensive for tiny incremental costs. And if we just leave it, then those practitioners can then just dabble at looking at it and, well let's try it for this, let's try it for that. In no time at all, you find that we're just doing it everywhere. That, you know, I would argue that cancer outcomes in this country are marginally better than anywhere else in the world if at all for massively increased costs, and all those incremental yet another hundred thousand dollar drug that if you give it for fifth-line treatment might improve disease-free survival by a highly-statistically significant 17 days, but overall survival is unchanged. I mean, that's what… we're getting into this kind of almost... I don't know where it's going to end, and I feel as if with that kind of framework, I would like, you know, I'm feeling we should be voting for very limited and specific criteria and as Jeff Thompson was arguing, we should demand that these are only used in protocol-driven agreed upon by the community so that we limit this kind of allowed variation in practice that people can just decide, well, I've got the tool and I don't have any prostate cancer patients to treat this week,

might as well bring in a couple of people with fill-in-the-blank and we'll try it.

So, I'm, I mean, I'm thinking, which is really bringing this back to conversation that you've been guiding, Craige, is that I do think we should... I'm leaning towards covering for a couple of very specific conditions and not for others until there is some discipline in the wider healthcare community to actually agree to protocols that will actually look at meaningful outcomes over time. I'm done. I'll get back off my soap box.

Craige Blackmore: Any other comments? Mike?

Michael Souter: As the other Scot... ex-Scot become a naturalized American Citizen on the committee, again, not quite as long here as David, I share a lot of his observations and thoughts on this. I am a little bit more sanguine about perhaps the need for some data. I think that it's... we're all here because we believe in the concept of evidence-based medicine. I think we've demonstrated that. We do have to be careful, ourselves, that we don't fall into some of the intellectual pitfalls that accompany that. You know, the whole parachute paradox is something that's held up time and time again to kind of warn us against the strictures of falling in too blindly. So, I think, I agree overall with what you're saying. I think that there are distinct pathologies here that we can identify that where clearly the principle of confining a radiation dose and reducing collateral damage to biologically sensitive and physiologically sensitive is perhaps a better term structures nearby is an important one, and I think it's difficult to ignore that and say that there's no evidence to support it. That we probably shouldn't cover. We can't do that. I think that, to me, makes no logical sense.

The concept of okay, it's here let's use it, I agree is something that needs to be curtailed. The question is how do we curtail it? Do we curtail it from the point of view of just saying, okay. Unless it's specifically laid out, we're not going to cover it? Then that, to me, again, I get concerned about diminishing innovation, because we both come from a country, and I emerged there a little bit more recently than you where the ability to push the envelope in terms of making progress is severely curtailed by the lack of innovation and the overly tight strictures being placed on that. So, I do think about that, again, as well.

So, I think that we've… when we think about trying to curtail the 'what ifs' and the 'oh it's here, let's use it' categories, we should be, maybe again going along with what the agency director proposal was of having

distinct, and I know we've talked about this before here, with varying degrees of success but having a registry or seeing anything that gets done outside of some very anatomically identifiable pathologies would need to be covered in a structure or registry.

Chris Standaert: This is all difficult. I mean, I agree with much of what you just said. I think the... we have a fundamental dilemma sometimes, again, in that we... the data here is lacking, as it almost always is when we talk about these things, or we wouldn't be talking about them. When you take subjects like this and you parse it out into 25 different distinct clinical entities, we assume they're all different, and maybe they are all different, but some get very uncommon, and some will just, realistically, you'll never get data for. If somebody's going to do a large RCT, it's probably going to be on prostate or something that's relatively common that's utilized a lot, and that's what you get data for, and then you're left with the idea of do you extrapolate that out and follow the theory if one or two studies prove that… or seem to imply that the theory of more focal radiation to the tumor with less spread to things you don't want to irradiate is better, do you extrapolate to everything else? So, when you start drawing lines, do you say well nobody studied glioblastoma very well, and nobody studied X, Y and Z so we're not going to cover them, or do you assume they're like other things? And it gets very hard. You really can box things in too far, I think. It's also dawned on me, I appreciate what Kevin said, he used words like critical. I'm a language guy, I like language, and vague words are very frustrating when you put them in, because people don't know what to make of them and whose judgment is that to decide? And what do you do if more data comes, or how do you play with vague words? I mean, we're in a vague situation, so, that's some of what I struggle with, how to balance all those.

Craige Blackmore: You know, I'm not sure it's that vague, to be honest, and I'm going to ask Dr. Fuss, but I mean, it seems to me that critical structure terminology that's in some of these other decisions is quantifiable in the sense that you can calculate the dose that will be administered to the adjacent structures, and you know what their dose tolerance is. I mean, how objective is the criteria about... is there critical structure in the field? I mean, critical... is that a vague term, or can we operationalize this?

Martin Fuss: No. I don't think it's a vague term. I think we have a very well-founded understanding of what... how much radiation dose is tolerated by what organ system, and I think there's a really straightforward limitation, because that's what we assess, as a radiation oncologists, once the radiation plan is generated. We, just to give you a little bit of an insight into the process, we often start out with a 3D conformal plan, because

it's probably faster to deliver, it's less resource intense, it is cheaper to the health system, and then we look at the result of that plan and see if the kidney and spinal cord and obviously the liver and let's say the optic system receives an excess radiation dose that does not render delivery of that plan safe. At that point in time, we go back to the drawing board and say let's develop an IMRT plan, which now harnesses the power of the computer to spare that particular structure and obviously now, if everything works as it should, you get a plan that achieves that particular goal of still exposing all of the tumor to radiation dose and sparing a particular organ system. This can be numerically quantified, and it's a typical process that happens in our world all the time. We don't always run the 3D plan first and then IMRT plan second, because with time, we learn, we know what the expected result with a 3D plan would look like. The four-field box on the prostate is a four-field box on a prostate, and I know the direction will be included in its entirety into that radiation field, and I know that I won't be able to deliver 78 Gy or 80 Gy with a good tolerance. I know that I'm risking 20-25% complications that will stick with my patient with a high likelihood over the remainder of his life, but yes, we do have good data behind it.

David McCulloch: Just one quick question. I don't want to distract from the train of thought right now, but the thought just struck me. How often do you actually have to engage in re-mapping, and is there a difference between the 3D technique and the IMRT technique? If you're losing volume of tumor, is there any difference, or do both therapies require re-mapping?

Martin Fuss: Yeah, we call it adaptive re-planning in our field, but remapping is actually a good term for it. So, that means the tumor shrinks, the relationship between tumor and normal structures change, as normal structures fall into a radiation field, for example, because the tumor shrinks away, and at that point in time, we have to replan and that is the situation that we may encounter with both 3D and IMRT.

Seth Schwartz: There was a slide earlier, and I'm sorry I can't recall which slide it was, but it was showing actually decreased costs in delivering IMRT over time, so it showed that early delivery was like $12,000 and then up to 2005 and then it had gone down to $6,000. Does someone know which slide I'm talking about?

Marie Brown: It was expense, I mean expertise. Wasn't it the difference between people who were new at doing the procedure?

Seth Schwartz: That was my understanding.

Edgar Clark: The study you're referring to is a study from France that looked at evaluation of IMRT with and without experience in the centers.

Seth Schwartz: And the cost went down by half. Was that what we said?

Edgar Clark: Yes, approximately.

Martin Fuss: Again, there's probably a bias with technology development in there, as well, but effectively if you establish an IMRT program specifically related to physics costs and your dosimetry costs. The dosimetrist is the one planning the plan, the medical physicist is our safety net. Yet they do the quality assurance on the machine. They QA each and every plan so they measure it out and initially you would measure it out using different devices, compare those devices, compare the outcomes, and it's just time. With time, you become... the process is streamlined, obviously, protocols emerge, and thus your resource utilization goes down. What stays the same is the requirement on your technology and the usage of your technology. I mean IMRT is much more taxing on your linear accelerator than 3D conformal radiation therapy, and in such that technical component will always stay higher with IMRT than with 3D conformal radiation therapy, and so the professional resource usage will always stay high as well.

Chris Standaert: Cost is so hard to figure out on our data. It is, you know, and you look at the data and is it the people are billing less, is it people just decide to reimburse less? And you can get more efficient, but in our system, the initial values under Medicare are assigned based on initial surveys of time, so as people are getting more efficient they get paid the same amount whether they're efficient or not. So, it's hard to extrapolate these costs, because people aren't paid by the hour to do it, necessarily, I don't think. The data is so fuzzy. It's clearly a lot more expensive, but I don't know how to look at subtle drops over time from what I saw, because I don't know what the cause of them is.

Seth Schwartz: No, I agree with you. I mean, I think everyone's raised some really great points here, and I think I'm struggling with the same things that everyone is, which is that conceptually this makes sense. Empirically, it makes sense, and I'm sure that there's... they probably have reams of data about how they've got better about delivering 3D external beam radiation and the toxicities went down. So, I think that conceptually we don't disagree that delivering less radiation to structures that don't need it is a bad idea. I don't think that's up for debate. There's clearly the question of does IMRT actually achieve? And we're not seeing great data on that, but there's certainly suggestion of that in the better studied

areas. So where we have higher volumes of patients in prostate and head and neck, we are seeing that affect with IMRT.

So, I guess where I'm thinking is it probably does what they think it does, and I agree with Chris's comments that we're certainly just not going to get data about a lot of these areas, because there aren't going to be enough patients, and clearly the medical community is convinced that it works for reasons that seem obvious. So, those studies, likely, are not going to get done, and yet, I completely agree with what David said about the fact that we don't want this, I mean, we've already seen a huge escalation in costs for this without clear benefit in some areas. So, probably what that has somewhat to do with is the definition of critical structures, while it's well-defined, is vague. So, we've heard, obviously the optic chiasm is important, and your spinal column is important, because you don't want to be paralyzed and incontinent and blind, but whether you have a little bit more red skin, how significant is that? I think those are... those are the areas that I think are hard to quantify, and that's when I think the cost effectiveness data becomes important, because we can't necessarily define quality of life, but quality of life data becomes very important here, and I think that we're not seeing really conclusive evidence that the quality of life is better, but certainly a suggestion that it may be in some areas, but if we can look at the incremental cost effectiveness, the quality of life improvement of not being paralyzed is probably huge. The quality of life improvement of having less telangiectasias on your left breast is probably not as huge, and we may be seeing incremental cost effectiveness ratios of $700,000 per QALY for breast and $15,000 for head and neck cancer where you can't swallow.

So, that's the kind of data I think we really want to see to be able to sort of parse this out a little bit. So, that's kind of what I'm struggling with here.

Kevin Walsh: I don't feel a struggle at all here. I feel like I'm involved right now in trying to get a series of 12 community health centers accredited for patient-centered medical home, and the amount of evaluation of care that we have to do in order to meet the accreditation requirements is astounding, and we're such a small fish that most of you wouldn't even notice us in the ocean, but yet we're required to do that. The fact that these kinds of technologies are allowed to just kind of go for it and see what the market will bear is almost impossible for me to tolerate.

I have no question that there's benefit to some of these technologies, and I support the notion of finding out, and that's why I think that the

only way to move forward with these situations where we don't have evidence is to decide if we're going to stand on the fence of saying we will let this go forward with the condition that data is collected and data is evaluated so that decisions can be made over time about whether there's effectiveness or not. Or, we say cut it off because there's not evidence, and I'm wholeheartedly on the side of saying let the stuff go forward with some real definitions about what's required. There have to be, and that's why I think that Jeff did a nice job of kind of laying it out. He set some conditions that will allow people, over time, to collect that kind of information so that we can all make decisions about with the limited amount of money, let's better define what works so we know what to pay for and what not pay for.

Craige Blackmore: So, yeah, Richard?

Richard Phillips: One of the things I struggled with, as I went through this, is I thought the questions that were asked were not really focused on the clinical issues that come about, in particular, I'll take one example. In prostate where there seems to be some advantage to using this technology, and yet, there's no comparison made to brachytherapy, which seems to me to be, or should be in the discussion. I don't, obviously we have our... our discussion is set by the questions. I'm not asking to go after that. But, it's a distractor for me, because I'm... in a sense I'm making... I'm going to be forced to make a decision without really looking at the scope, and so I've asked our consultant about the issue of brachytherapy without getting into too much detail about it, but are we really seeing the full picture here to be making the decision? Should we be doing that? Does that make sense where I'm coming from? In other words, I'm trying to figure out, is that really... are we really... do we really want to compare against external beam radiation, or should we not be looking at a broader scope, if we're going to be making the decision on this? Is that a fair clinical question?

Martin Fuss: That is probably a fair question, but it's very difficult to give you a good answer on. Obviously, there are different treatment options for prostate cancer, and they range from surgical treatment options over... they range from surveillance. Let's start at that point, which is the lowest cost treatment option. Or there's surgical treatment to internal radiation and external radiation in different ways, shapes, and forms, both internal and external we can deliver in different ways and it's a... essentially, we have established that surgical procedures, brachytherapy and forms of external beam radiation therapy, provide the same outcome in terms of biochemical control, which we extend to provide us comparable

outcomes in terms of survival outcome-proven data on sufficiently mature levels. We do have some data [inaudible].

But I think the problem here is we can't propose to pay... it's also an expertise question. I'm an external beam radiation specialist. I'm not a brachytherapy specialist. So, do you now stipulate that patients undergo brachytherapy? Not every patient is not a brachytherapy candidate, so what do you do? Where do you cut the line there? I just think it's extremely difficult. Why does a patient decide to be surveyed versus the next one who decides for surgery and the third one for one form of radiation therapy? Our health system allows for all of those options.

Craige Blackmore: I... go ahead Carson.

Carson Odegard: Yeah, I have just a question on costs, and I don't have the table in front of me, but it was an agency table on comparing PEB versus Medicaid delivery versus planning costs, and I was just wondering, because on PEB expenditures, delivery and planning costs are about the same. It's like... I don't have the table, but it was like 45% delivery, 35% planning, but in the Medicaid population it's 45% delivery and 25% planning, and I'm just wondering how that happens for IMRT? Where is the difference in planning? Why would planning be half of the delivery costs?

Chris Standaert: Slide 11? Is that what you're looking at?

Carson Odegard: Yeah. I'll have to go…

Seth Schwartz: You're right. That's really high.

Carson Odegard: It was real high, and I just wondered what... why the delivery cost would go up in Medicaid and planning costs would go down.

Craige Blackmore: Have you found the slide in question?

Chris Standaert: Slide 11 is the one I see, but that doesn't say totally…

Edgar Clark: That was in Jeff's material.

Carson Odegard: It wasn't in Jeff's... yeah, it was in Jeff's material.

Chris Standaert: It says planning charges under PEB were $11,000, delivery of 27. Under Medicaid $3,200 versus $11,000. So, a different ratio to a degree. I mean, the costs are totally different, because that's what they allow. How they determined what they allow, I don't know.

Craige Blackmore: So, I mean, I guess we're confronted with…

Carson Odegard: It may not be important to this discussion, but I just... I just wanted to bring it up to…

Craige Blackmore: Yeah, I mean, we're confronted with the costs of the bizarre nature of the US reimbursement system, which is arbitrary and capricious, but it's what we're stuck with, so I don't pretend that's an answer to your concern, but it's the reality.

So, I don't sense that we're at a consensus, and I'm not sure we ever will be, but I think we should start to move through the decision instrument and see if we can make a decision. So, I'm going to ask the committee members to turn to that document, which I think is in the very back. Yeah, it's in the very back. So, this is our HTCC Coverage and Reimbursement Determination Analytic Tool, and the committee members are all intimately familiar with this document. Basically, it lays out the principles upon which we will make a decision, and that is based on the evidence, assigning the greatest weight to the evidence which we feel is most valid, and we are charged with looking at the effectiveness, safety, and the cost or cost effectiveness of the technology under evaluation. So, we have a table on page 6 of the instrument, which really defines the outcomes that the committee has used in its decision making. Staff has prepopulated that document with the outcomes that are relevant. So, the first thing we need to do is see what they have prepopulated here corresponds with our perceptions of what the appropriate outcomes are. So, there is a whole list of safety outcomes, and they are the toxicities that we've talked about and then the efficacy and effectiveness outcomes is where we get into the effect on the tumor and recurrence, disease-free survival, and all the various metrics. Does anybody have anything that isn't on this list that they're considering in their decision making that we need to add? I'm not seeing blindness here, which would be one of the toxicities we've talked about.

Chris Standaert: Any sort of neurologic impairment? Blindness, spinal cord paralysis and all that stuff.

Craige Blackmore: Yeah, so we, you mean we have a general category of neurologic.

Seth Schwartz: And then under costs, I think we've talked a little bit about long-term costs of managing complications.

Craige Blackmore: Yeah.

David McCulloch: Are you wanting to go through all of these singly?

Craige Blackmore: I want to make sure that we capture the outcomes that we're including in our decision making and not discuss them in detail but make sure that the factors that the committee is weighing are noted, but I don't want to go through each of these in detail.

So, next up in the process is to well, just in terms of framework, I think there's two ways we can approach this. We can look at the question from a general perspective of IMRT or we can individually look at each of the body parts or organs. My suggestion is that we look at the general question and if we felt one organ was more appropriate than another or one type of cancer we could include that as a condition of coverage rather than having separate discussions on each of the many areas in question. I'm seeing nods. Okay.

So, I'd like then to move towards the first voting question. So, this question would be nonbinding and looking at whether we felt there was sufficient evidence under some or all situations that the technology, IMRT, is effective, safe, and cost effective when compared to 2D or 3D external beam, and your choices are unproven, equivalent, less, and more, and to be clear this is under some or all situations. So, if you felt that there was one situation where it was more, you should so indicate say for more effective. You would only use equivalent if you felt it was equivalent under all circumstances. Does that make sense? Okay.

So, these are the tan cards. So, this is everything. So, if I felt that IMRT was more safe under one circumstance but the same in all the others, I would vote more, and I don't know what I would do if I thought it was more in some and less in others. I guess in that situation I would vote more. Okay, so the first question is effectiveness. IMRT compared to external beam standard 2D, 3D, is it unproven, equivalent, less, or more effective?

Josh Morse: I see 11 unproven.

Craige Blackmore: All right. The next question is, is IMRT safer or unproven, equivalent, less safe, or more safe under some or all situations?

Josh Morse: 11 more.

Joann Elmore: With the caveat that this could be just one disease. Many others are still unproven.

Craige Blackmore: In some or all. And then, finally cost effective.

Josh Morse: 7 unproven, 4 less.

Craige Blackmore: Okay. Does anybody want to comment at this point? Okay. So, we have three choices. We have cover unconditionally, cover with conditions, and don't cover at all. The cover with conditions, of course, we stipulate the conditions. I'm assuming if we go there that that's going to be in part based around which organ we're looking at. At this point, I would like to try to narrow us down, because it helps us structure and get to the final decision, and that's to kind of get a gestalt of are we leaning towards a decision of unconditional versus conditions? Are we leaning towards a decision of no cover versus conditions? Or are we all over the board? I'd like a sort of unofficial straw poll, get a sense for where we are so I can lead us in the rest of the discussion. Let me ask some opinions. Are we headed towards a no coverage decision?

Group: Mm. No.

Craige Blackmore: So, we're headed towards either a cover decision or a cover with conditions decision, and that allows us to think about what those conditions might look like, and at this point, we usually ask that the projector be turned on, and we start to get some text on the board so that we are all on the same page and understand what we're talking about, and then I will ask members of the committee to suggest some proposed conditions, and there might be one set or there might be multiple sets for us to consider and we use that as a point of discussion. So, does somebody want to take a first stab at what the conditions might look like?

David McCulloch: Well, I would say, Craige, the straw... a good place to start might be a slight [inaudible] of Jeff Thompson's presentation, which looked pretty reasonable to me, but…

Craige Blackmore: I'm going to have to find that.

Marie Brown: Page 8 of the handouts under Jeff's presentation.

Craige Blackmore: So, I don't know, Margaret or Christine, whoever's in charge of the projector over there, did you catch what we got? We're going to use, as a starting point, what Jeff had on slide 16. I have to find it. There it is.

Chris Standaert: So, if I read that right, then anything other than head, neck, and prostate would have to be in a clinical trial. That's what that says?

Craige Blackmore: No.

Chris Standaert: Am I reading…?

Craige Blackmore: No. That's not what it says.

Chris Standaert: Oh, I thought these were all the same conditions.

Joann Elmore: No.

Chris Standaert: They're different conditions.

Craige Blackmore: 16.

Chris Standaert: So, history of previous radiation, spare adjacent structures or clinical trial.

Craige Blackmore: These are ors.

Chris Standaert: They're ors, not ands. I thought they were ands, not ors.

Craige Blackmore: No, they're ors. So…

Chris Standaert: So, you could…

Craige Blackmore: So, the last one, the clinical trial is a given basically regardless of what we decide. Even if we decide no cover, if they're in a clinical trial, the agency still has the ability to pay for that. So, that's kind of a given. We don't have to worry about that too much. I'm not saying we shouldn't leave it up there, but just... so go ahead.

Chris Standaert: Just as a, you know, the rationale for prostate and head and neck are that there are critical structures nearby? That's why you do it that way? It's not something... that's why you're doing it. So, I mean, Aetna actually just says for approval of IMRT, Aetna requires critical structures located close to the tumor, cannot be adequately protected using conventional EBRT, which covers everything up there. It covers head, I mean, that's why you're doing head and neck and prostate. It's just much cleaner language, and it says specifically you sort of... the idea that you're trying to protect the critical structures by avoiding EBRT is sort of what they're after, which I think is sort of the point. So, I actually kind of like that

language myself, and I think it covers everything up there. It's no less restrictive than what Dr. Thompson put up.

Kevin Walsh: It doesn't cover the last line.

Chris Standaert: The clinical trial.

Kevin Walsh: Yes.

Chris Standaert: I have no problem adding that. Certainly, if people want, yeah.

Marie Brown: So, remove the history of and just keep up spare adjacent critical structures and undergoing clinical trial.

Chris Standaert: Yeah. Critical structures located close to tumors cannot be adequately protected using conventional EBRT.

Seth Schwartz: Well, I think that makes sense. But is the previous radiation separate as shown, because it may not be as critical structures, but it may be, if you're worried about dose.

Chris Standaert: You know, that's a question for the expert, but I assume that as you're calculating the dose the structures nearby can take and you calculate in the exposure they've already had over the course of a lifetime, and then you sort of say that we can't radiate this piece of skin anymore, so we have to sort of collimate it down somehow so we can avoid that skin, that's how you would do it, I would think.

Martin Fuss: That's pretty much accurate. You factor in the prior radiation exposure.

Chris Standaert: Yeah, it's all in the same thing.

Martin Fuss: And the exhaustion of a certain [inaudible] is left.

Chris Standaert: Right.

Richard Clark: I asked Dr. Fuss if he could think of any generalized conditions, and I think he had a very interesting suggestion.

Martin Fuss: Well, in general, we... I would say 95+% of IMRT treatments are used for curative intent treatments in patients who have a life expectancy of 12 months or longer, because if you think of sparing normal tissues as one of the key arguments for using IMRT, then time for toxicities to manifest is relevant. However, in select palliative indications, it may come down to

patients who have had radiation in the past. You do have to factor in that the tissue could sustain injury earlier than 12 months after treatment. So, I mean, this can't be a… but I mean, this is a general consideration. I don't know if this is something that you want to verbalize like that, but it is implied if you think… it obviously applies to head and neck [inaudible]. It applies to the patients that we treat [inaudible].

Craige Blackmore: Other comments or other suggestions? One suggestion is to use this based on some of the other policy decisions and recommendations. Are there... Joann?

Kevin Walsh: I would propose getting rid of the head and neck and prostate lines assuming that the statement spare adjacent critical structures captures those, as well as other critical structures. I would get rid of the 12-month survival, because, as you described there is some application in palliation, in palliative situations. So, I wouldn't hold it to just curative and leave the other three.

David McCulloch: But, I think you need to be careful about, I think the time interval is a good question. We don't want to have this being done by somebody who has the legitimacy of the position of saying well, yes, we are doing something palliative. The differences they expected to make is one of, you know, a week. We want to guard against that, again, as well.

Kevin Walsh: Your point is better than mine. I agree with that.

Craige Blackmore: So…

Chris Standaert: But would that be…

Craige Blackmore: I struggle with 12-month as arbitrary.

Chris Standaert: I mean we saw no data on a number anywhere. I appreciate what you're saying, and it probably may well be true, but that was not part of our data set, at all. So, that's... we don't have any data to 12, 10, 14, 24, 6. I got no idea, and…

David McCulloch: But knowing how much money we've spent on people in their days and weeks of life.

Chris Standaert: But that whole question is the whole radiation... that goes through the whole field. I assume not just this particular thing. That goes for every aspect of radiation and oncology.

Craige Blackmore: Is there a way to phrase spare adjacent critical structures to prevent toxicities within the expected life expectancy or some... I mean, I'm just thinking out loud. Because what you're trying to... that's what you're trying to do, right? You're trying to prevent toxicities that will arrive within... arise within their expected lifetime, but I don't know how to put that into words, but is that what we're trying to say? Joann can do it. We have Joann.

Joann Elmore: Well, I'm going to have us back up though first, because if it's my understanding of the direction you're taking, you're recommending coverage with condition with the condition being those that are stated there, and I disagree with that for the following reason. I'm disappointed at my profession that we now have a standard of care of IMRT that there's inadequate data on efficacy and low-quality data that it improves toxicity. With that said, I think all of these, if it is covered, data needs to be collected.

Chris Standaert: I don't think... I mean, these things actually would be well served by a registry. You're assuming relative similar clinical effectiveness, but you're really after sort of complications and costs, which you can get through a registry very easily, but registers are not easy, and I don't think we have the authority to mandate our registry. I would like to.

Joann Elmore: Well, I'm worried about the efficacy issue.

Chris Standaert: But I don't think we have the authority for that.

Joann Elmore: Because it was low-quality data, and I would ask in the future that they give us data on statistical power with these low-quality studies. How do we know that there isn't harm? You know, I doubt there is, but how do we know that there is not harm with these new technologies?

Chris Standaert: Right. We don't know it doesn't... we don't know that it does not work as well. We don't know. It may well not work as well, and we don't know that.

Joann Elmore: Right.

Chris Standaert: We're just assuming.

Joann Elmore: So, how can we approve covering something if we don't know if it works, as well, with important outcomes of, you know, cancer recurrence and life. It worries me a little.

Craige Blackmore: A lot of decision making worries me, but we still have to make a decision.

Martin Fuss: Can I interject something here?

Craige Blackmore: Sure.

Martin Fuss: Then you would have to step back and apply the same to 3D and 2D radiation therapy techniques, but that has never been formally tested.

Craige Blackmore: Maybe we should.

Joann Elmore: That's a good point.

Martin Fuss: [inaudible] that we have. This is not historically how we have these… bring radiation therapy…

Craige Blackmore: I don't know, I mean, if we stipulate a registry, we're requiring the agency medical directors to institute a program that has a registry in it, and I don't know if that's what's in our realm. It would be nice to encourage that, but I don't know that we have the ability to require it, and actually, I don't think I would favor requiring it, because that introduces its own set of access issues that…

Joann Elmore: Almost 100% of people are getting IMRT with prostate, so they're already having access.

Marie Brown: And we have to think about the cost of medical director review, also.

Seth Schwartz: Do you think it's as much as one of these rounds of…?

Joann Elmore: I don't think so.

Craige Blackmore: This gives the medical directors a lot of leeway, and I mean we should solicit their input next, but I think if they… within... the way this is worded, if they wanted to preapprove prostate, they could. They could say, well the prostate is next to the rectum. That's good. That's all you need. And then for something else, they might have a different process, but I mean... what do you? I don't know whose best to answer the question, but in terms of operationalizing, you hear where we're trying to go. Are the sorts of conditions that we're laying out that are based, in part, on what Jeff Thompson suggested. Is this something that could be put into effect?

Female: It would be much easier to operationalize if the specific diagnoses are included in the conditions. So, if head and neck cancer and prostate cancer were left in.

Craige Blackmore: Why is that?

Female: Because there's a specific ICD-9, which we can enter into our system in order to control whether or not certain treatments are paid.

Chris Standaert: But then you still have the issue of spare adjacent critical structures, which is everything else.

Female: Right, and those cases could be placed on PA. So, in terms of operationalizing a decision, if specific diagnoses are included in the language of the decision, it is much easier to operationalize.

Chris Standaert: But we can only include a couple of… okay.

Female: My other comment is that there's been no discussion about the pediatric population. I mean it was included in the PICO. So, I don't know if the committee has any other thoughts.

Edgar Clark: There were, I think, only two cancers that had any pediatric patients. One was medulloblastoma, which is primarily pediatric patients and the evidence there is quite weak, and I think that there were a few head and neck cancers. There were a few pediatric patients in some of the head and neck cancers.

Craige Blackmore: So, what I'm hearing is that on the operational side it might be better to keep in the yellow highlighted head and neck cancers and prostate cancer. So, I guess I would ask the committee if the intent of our thinking was to include those, and if we only took them out because we thought it would make things easier, in which case we could put them back in, since we're told that would make things easier.

Chris Standaert: I would like them out, because the language is inelegant, but if that's more effective for them, it means the same thing, as far as I can tell.

David McCulloch: Could you repeat she said? I'm sorry, I didn't hear it.

Craige Blackmore: What she said?

David McCulloch: Yes.

Craige Blackmore: She said it's easier to operationalize if it says head and neck cancer and prostate cancer if we wanted the coverage to include those, because then they can screen those out of their... what they would otherwise use, which would probably be a preauthorization process.

David McCulloch: Because every time we're saying it's an adjacent critical structure, somebody actually has to look at that and exercise a decision, a subjective decision on whether this is critical or not.

Craige Blackmore: So, they're gonna have to do pre-auth on all the use of this technology unless we specify exceptions that they can track.

Chris Standaert: Are we including brain and head and neck, or are we not including brain?

Craige Blackmore: We haven't discussed that.

David McCulloch: It's in your head.

Chris Standaert: I understand. It depends on the day, apparently, but yeah.

Seth Schwartz: I also just want to get back to that point.

Edgar Clark: Our report distinguishes between, I mean, head and neck is oropharynx, nasopharynx, hypopharynx, and larynx, and oral cavity.

Craige Blackmore: Head and neck does not usually include brain.

Edgar Clark: Yes.

Craige Blackmore: Or spine for that matter.

Edgar Clark: So, head and neck, in our report, refers to those group of tumors that the ear, nose, and throat surgeons would not normally be involved with.

Michelle Simon: I'm not in favor of adding brain, because the research really wasn't strong on brain. We looked at the head and neck cancers.

Seth Schwartz: Yes, I would agree with that. I don't think brain needs to be pulled out separately. I think the only things we saw data on that was arguably of moderate quality were head, neck, and prostate. I think to pull out any other individual diagnosis without data doesn't make a lot of sense.

Craige Blackmore: The only reason to do that, and I'm not saying we should, would be to conclude that the brain is a critical structure.

Chris Standaert: Ahead of time. We would be calling it out as a critical structure.

Craige Blackmore: And again, we don't have to, I mean, I'm not…

Michelle Simon: It would be included, though.

Edgar Clark: Your next meeting will talk about SRT. You're going to get a whole day's full of brain there.

Kevin Walsh: I would like to propose one more change. I'm going to propose that all of these be required to be in the context of a clinical trial.

Chris Standaert: So, not treat at all, except in a clinical trial?

Marie Brown: Even head and neck and prostate? Okay.

Craige Blackmore: So, I'm seeing at least a couple nods.

Kevin Walsh: It's because we're not trying to prove, I mean, we're not... there's no data here that says it's more effective. The data says that there's a change... that there's a difference in quality of life.

Seth Schwartz: That's not entirely true. We didn't talk a lot about it, because of the data. I don't think there's any data that showed it wasn't as effective. I think that there was some equivalency. There was low quality data that was of equivalence and there was some low quality evidence of improvement.

Kevin Walsh: I'm sorry. I misspoke. It's no more effective…

Seth Schwartz: Correct.

Seth Schwartz: Well, you can make that argument, but I think, you know, so that's what I'm saying.

Kevin Walsh: So, I think it is worth requiring the additional work of a clinical trial.

Joann Elmore: That disadvantages rural people.

Craige Blackmore: I'm willing to accept... I think it's probably equivalent, and I think, and if I say it is equivalent, I'm willing to accept coverage on the basis of safety. So, the only way I would need the trial is if I wasn't sure it was as effective as traditional external beam and while I'm questioning whether

it's any more effective, I think it's probably at least as effective just based on the fact that you're still radiating the tissue.

Joann Elmore: In the same amount. Didn't they say that?

Kevin Walsh: So, your supposition is that here's the technology that's somewhere between 10 and 70 times more expensive than another and because we can prove it's just as effective, that's a reason to pay for it?

Craige Blackmore: No, I would only pay for it if I thought it was safer, if it was saving significant toxicities.

Kevin Walsh: Which is exactly why I think the information needs to be... there needs to be more information and it needs to be more rigorous with study.

David McCulloch: But that wouldn't get captured within the confines of a trial. A trial misses out safety data. Trials miss out safety data all the time. If you want a trial in terms of your rather real-world safety data and effectiveness, then you've got to look for a registry. I'd favor a registry before I would a trial.

Craige Blackmore: Were you saying trial in the general sense meaning investigation or were you saying a randomized clinical trial?

Kevin Walsh: No. I don't mean randomized clinical trial. I mean collect some kind of ability to look at the effectiveness and the side effects of what people are doing to get a bigger end…

David McCulloch: Then we're talking about a registry.

Kevin Walsh: …than 10 and 17 to make these decisions on.

Chris Standaert: I mean, you know, if you looked at it from a big picture perspective, a registry would give you great data, I would think, if you could do it, and from the cost of all this stuff, it probably would turn out to be very cost effective to do, but they are very hard to operationalize, and I, although I would love to say you have to do this, boy, I don't know that we have the authority, because that means creating an enormous infrastructure to run our registry, which we can't... I don't think we can mandate at all, and that's my problem. I would love to see it, and I'm sort of, once again, disappointed in sort of our standpoint, disappointed in the state of our knowledge and the belief systems of our…

Kevin Walsh: Chris, we have to develop a registry for diabetes. We have to develop a registry for asthma care. Do those…

Chris Standaert: [inaudible].

Kevin Walsh: Did those cost as much to implement, to deliver, as these? No.

Chris Standaert: No, I agree with you. It would be a cost-saving thing.

Kevin Walsh: It's not too much to ask.

Chris Standaert: Right, but there's specific federal legislation that mandates who can do that.

Kevin Walsh: I'm trying to level the playing field here.

Chris Standaert: Right. But we can't... I just... somebody can correct me. I don't know if that's within our legislative prevue to mandate a registry.

Male: I think you'd be creating the circumstances coverage would be covered. It wouldn't be mandating the Health Care Authority to create a registry, but it's a situation in which the Authority would pay for. If the registry existed, the patient's on the registry, and the insurance would pay for it.

Kevin Walsh: Yeah, I agree. I don't think the state has to own the registry, but I can guarantee you that not for profit institution is going to develop one.

David McCulloch: Unless they have to.

Male: Craige?

Craige Blackmore: Yeah.

Male: You have made decisions in the past that specified that it would be covered... coverage with evidence developed, and it wouldn't be the responsibility of the agencies to pay for or establish those studies, but somebody could do that if they really thought it was important, and then if some... if that happened, if there was a prospective observational study with appropriate collection of data, and it was for breast cancer, and if somebody participated in that, then we could cover it. So, you could do it like that. Conditions on the first two, and some of the others only if there's appropriate observational studies going on.

Joann Elmore: So, I'll make a proposal then?

Craige Blackmore: Please, go ahead.

Joann Elmore: I propose that if it's one of the three main ones, brain, head and neck, or prostate cancer, and... not brain? Okay. So, if prostate or head and neck and the underlying treatment is in the context of a clinical trial registry or submission of data is presented to the state on outcomes, and we say just cancer outcomes or toxicity. That would be the first part. The second one would be any of these sort of spare adjacent critical structures and data are submitted.

Craige Blackmore: So, I missed that. You're saying?

Joann Elmore: If head and neck or prostate, and they're submitting data, I would feel comfortable covering. The second is if it's in one of these spare adjacent areas where you're worried about toxicity, and they're submitting data.

Chris Standaert: You're adding the same clause to both.

Joann Elmore: I know.

David McCulloch: So, make that…

Joann Elmore: So make it... okay, so make it the three things then. So the… get rid of brain on the top and you have head and neck cancers, prostate cancer, and then move that spare adjacent critical structures to the third. So, if one of those three, and then… and then and then here's where we can wordsmith. They're undergoing treatment in the context of... undergoing treatment in the context of an evidence collection. That might be better, because I was going to say a clinical trial, registry, or… and I was thinking of adding in just basically have them have to submit data to the state on outcomes, and then you can put in parentheses, e.g. cancer recurrence, mortality, toxicity, closed parentheses. It's vague, it leaves it up to the individual practitioners and groups, as to what they submit, but at least it means you're going to hopefully get something out of it.

David McCulloch: Why do you need to submit data to the state? Why not just have a registry as long as you can [inaudible] to the state that you've got a registry.

Joann Elmore: Because I don't know whose going to run the registry and…

David McCulloch: Yeah, but that means that somebody in the state has to be in a position to receive it, audit it, check it.

Joann Elmore: How did we word it earlier when we did this?

Chris Standaert: Well, we didn't do it this way. I mean this, I, you know, as a fundamental issue I don't disagree with the idea at all. From a practical standpoint, I mean, trying to develop an initiative registry is a massive undertaking, and it's very difficult to do, and it's very difficult to do with complex data. So, somebody really has to put a lot of brain power and time and money into it. It would be a good thing to do. I totally agree. You flip the delivery system on its head a bit doing this, and I understand what you're saying, Kevin, but the things you have came from federal legislation saying just this. They made the legislation from patients under [inaudible] was designed to do just that, and if you look at sort of all the different levels of federal legislation and reporting and PQRS and all this sort of stuff, it's very unclear what the effect of all that is. So, and it's a huge sort of cost in there. I'm just a little worried in terms of how this would actually be operationalized, and I have no idea, and I'm a little worried what happens to access. Do you create different levels of care for different people and different populations and different things, because you're spending it?

Kevin Walsh: We already have created that. That exists today. That's our healthcare system today.

Chris Standaert: I understand that, but I... the operational effect of doing this is very unpredictable. There's a lost of cost and structure to it. There's no precedence for it, and there's no means of knowing who the hell is going to do it, and that's the problem. And that's not us. We're not the... that isn't…

David McCulloch: What... what's the goal here. I thought that we were agreed that we would cover the... everyone seemed reasonably persuaded that it was logic for head and neck and prostate cancers. Everything else that we want to address is kind of like stop there, the what-ifs and maybes, and that's where I think the value of a registry comes to the fore of that if you can persuade people that... now, I think it would be nice to see it extended to head and neck and prostate, you know, as well just to benefit, but I don't really see the same need to exert the inhibitory effect of there, as much as I do in the kind of what-ifs and maybes category.

Joann Elmore: I think it's…

David McCulloch: Which is all other cancers.

Chris Standaert: You're also... this is one piece of a big field of radiation oncology, and you know, again, you're... the effect in the world of doing this, I don't know, and it's almost like there should be, when we start talking... we're talking about one little piece of radiation oncology as a subset, as a little thing, which is sort odd, because I don't know why. It would be nicer to talk about our other topics all at the same time so you put them in perspective, but I... personally, I'm perfectly comfortable with what Jeff Thompson had put up the first time, and I agree with the idea of all this. I just very much worry about the operational effect of it and how this is going to run and where money monitoring decisions, where all that's going to come from. There's no champion to do it at the moment, and I'm not sure the state's going to do that.

Kevin Walsh: And if we don't, we're basically putting no controls on its use.

Craige Blackmore: I think we would be putting no controls on its use in prostate and head and neck, but we would... there would be a preauthorization process whereby somebody would have to show a justification for the use of this technology in terms of not causing x-number of Gy to Y organ where there is, I believe, longitudinal data showing that the probability of adverse effects goes up. I mean, I think I'm willing to accept that even though we don't have as much as we want to, because we never do, but I'm willing to accept that if you use this, you're going to cause less rectal and GI complications than prostate cancer. So, I don't want to put a barrier in that circumstance. I'm willing to accept that xerostomia is decreased in head and neck and that is an important quality of life. I think there are probably other circumstances like that, that it's near the spine or some of the other conditions we've talked about. I think... I don't have the ability to micromanage those. Leaving it up to the preauthorization process is far from perfect, but it seems to be the best that anybody's been able to come up. Then, I think beyond that, meaning the rest of radiation therapy, I haven't seen any reason to use it. So, in that context, there should be research or it shouldn't be used. That's where I am. It's a little different from where you guys are, but that's why there's 11 of us. Richard?

Richard Phillips: Yeah, you recall that when we... one of the first two ones we did I think was in low back pain, and we... some of us argued at that time for a registry because there was a 10-fold variation in the utilization across the state, and at that time, I mean a very reminiscent... this discussion's very reminiscent of it, because at that time, basically, we shot it down by the medical director who said we can't afford it. In COPE, for example, we spent about a quarter of a million dollars a year just to do the cardiac stuff. I'm sure this would cost a half million dollars and in order to make

these kinds of decisions, it might be more than that, I'm just guessing, but the point is we get into policy decisions and I don't think we can do that. I think we sort of have to come to some compromise. I really agree with what you're saying, what both Joann and Kevin are saying. I think we ought to have some way to get the data, but we also have to be... have our heads above water on this whole thing and come to something that makes sense. I think we're going to have to compromise on this and maybe we have to accept some things we don't want to accept, but I don't think we have the money. I don't think we can make policy.

Michelle Simon: I don't think we need to say who has to come up with the money for the registry or put it on the state necessarily, but the reason we're in this position is the FDA did not require trials of efficacy of this tool before it was widely disseminated, and I really think the paradigm should be that there are trials before you bring out a new, expensive technology and show that it's effective. Show that it's safe. Show that it has some cost effectiveness or do something behind it. The cart behind the horse... or horse behind the cart situation here. So, I feel that the evidence on prostate cancer and head and neck cancers are persuasive enough that we can approve those, but I feel very strongly that we should not provide approval to other cancers without the caveat that there is some evidence collection taking place, and we don't have to get into the policy of how that happens, but we should have that as our recommendation.

Richard Phillips: I think you're saying exactly what I would say, too. I don't think we can specify, and I'm not sure that... it may be an empty statement. But it's not when we leave it to them to make a decision, but what else can we do?

Seth Schwartz: Well, I think the challenge is you're talking about developing infrastructure that doesn't currently exist. Now, that might happen in a week, it might happen in a year, it might take 10 years to do, and so in the meantime, what you're saying is that patient who has a tumor right next to their optic chiasm or right against their spine is going to be paralyzed and is going to be blind, because you're denying coverage to them period, across the board, if you don't leave in this critical structure statement, and that's what I struggle with, and I don't think clinically I feel at all comfortable taking that out. I mean, I think there's a lot of smart people who have been thinking about this. Clearly, there's cost concerns here, and I wish we could address it and tackle it more conclusively, and if we could... and if we knew that we could set up a registry tomorrow, I would completely agree with you, but I just think in practice that's going to hurt a lot of patients, and I'm not comfortable with that at all.

Chris Standaert: I agree. I mean I've watched a number of registries try to go up and boy, it is really hard to do, and if you look around the world at successful registries, they're really uncommon and they tend to be very dichotomous sorts of things. Yes, no. Recurrent hip fracture, no recurrent hip fracture. Infection, no infection. That's what they tend to be, and even those are really hard to do, and you're trying to do… suggest a mandate this be done, and it's very hard operationally, and I completely get it. I completely agree with the whole FDA thing. It drives me crazy, but then we run into the issue of what other folks have said, that you... if you have a tumor in your optic chiasm, you have a tumor in your spine, do you spare the spinal cord? Somebody whose had prior radiation to their chest for something else who now has a focal lesion somewhere you want to get at, but you've already exceeded their sort of lifetime tolerance of their cord. What do you do? And you're drastically changing what is a standard of care for those patients at the moment. And I understand there's a big [inaudible] of data, but I have the same concerns.

Seth Schwartz: I would just remind you that these are the recommendations that Jeff put down, that he said the agencies could live with. I am hard pressed to think that they are going to cut off therapy for all these cases until they build a registry. I don't think that's realistic.

Michael Souter: Can I propose that we go back to head and neck. We cover head and neck. We cover prostate. We cover spare adjacent critical structures to expect toxicities within the expected lifespan, and then anything else has to be in the context of a registry, which will encourage those people who want to experiment and develop and look at what happens if we irradiate muscle tumors, for example, to develop a registry in that kind of context. It will now be up to them.

Chris Standaert: That's essentially what Jeff said the first time. The only line you're taking out is…

Michael Souter: The only thing we're taking is... well, we're taking clinical trials, as Craige said, would get covered anyway.

Chris Standaert: Right, and you…

Michael Souter: What we're really talking about is something that…

Chris Standaert: Some other evidence.

Michael Souter: …is more embracing.

Chris Standaert: And you're taking out the sentence on prior radiation, but that's almost still covered in the spare adjacent critical structures, because that's a calculation of lifetime total dose.

Craige Blackmore: So, we basically have two proposals. We have the proposal that Jeff gave us at the start, except we seem less happy with the prior radiation therapy. So, that's proposal number one. Proposal number two is that basically we add 'must be in the context of some sort of investigation' to head and neck and prostate and previous radiation, etc. So, I haven't stated this well, but proposal one is basically Jeff's slide minus radiation therapy and proposal two is those conditions and you have to be in some sort of investigation. Is that a fair summary? So, I mean, I think we have coalesced around those two issues, or those two choices?

Kevin Walsh: No, I don't think you... I don't think you expressed Michael's proposition accurately.

Craige Blackmore: Did I not express?

Joann Elmore: His is the third.

Craige Blackmore: Okay, then let's try again.

Michael Souter: Okay, so, essentially what I'm saying is cover with conditions head and neck cancers, prostate cancer, sparing adjacent critical structures, which can include history of previous radiation therapy, because that becomes a critical structure because of the threat to its liability. And then anything else has to be done in the context of ongoing data collection in a registry, which I think is superior to a clinical trial.

Craige Blackmore: That's exactly what Jeff gave us in slide 16.

Michael Souter: Well, no, not quite.

Craige Blackmore: Okay.

Joann Elmore: He has just moved the spare adjacent structures up to the same level as the other ones.

Michael Souter: Yes.

Craige Blackmore: Okay. So…

Michael Souter: I'm injecting registry, as opposed to clinical trial.

Richard Phillips: If something is not covered in a registry, then it wouldn't be covered at all. That's what you're saying.

Michael Souter: Right.

Richard Phillips: So, you're insisting on a registry.

Craige Blackmore: No, no, no, no.

Chris Standaert: He said or. He didn't say and covered in a registry. He said or. So, for things that aren't discrete lesions where you have to protect something else for whatever reason, you have to have them in some sort of study, not just a clinical trial, but any other sort of study. So, you're actually expanding coverage a bit and trying to encourage people to do something else short of a clinical study to track what they're doing is what you're doing.

Michael Souter: Right.

Chris Standaert: Versus this alternative, which is sort of that none of this happens unless you're studying it is what you guys are saying.

Michelle Simon: That's not what I'm saying.

Chris Standaert: That's not what I'm saying. Isn't that what you're saying?

Kevin Walsh: Mm-hm.

Chris Standaert: You have none of this happening unless you're studying it.

Richard Phillips: Right.

Craige Blackmore: And what's Michelle's... what's your?

Michelle Simon: I was saying thumbs up to head and neck cancer and prostate cancer. I think the evidence is strong enough with that, but I would say for other things, I would prefer that there was a registry to develop evidence on the others that we have no evidence for.

Craige Blackmore: Okay, so we're doing good. So, we have head and neck. We have prostate. We have spare adjacent structures, and then the next line should say everything else, go with me, not and/or, say everything else.

Richard Phillips: Everything else. All other types of cancers.

Joann Elmore: That's the same thing as or.

Chris Standaert: Same thing as or.

Craige Blackmore: It's all good... no, just... and then get rid of everything else below it. Erase everything else.

Joann Elmore: Oh, you mean [inaudible].

Craige Blackmore: Get rid of all that. I'm getting you somewhere. Don't worry, Joann. It's going to be okay.

Chris Standaert: All other circumstances, or? Is that what you mean by everything?

Craige Blackmore: Yeah, yeah. We're... we'll wordsmith in a second, but just get rid of that. So, the places where we disagree is where we have the line for investigation, right? Whether we call it a registry or whatever. Some people think it should be everything else and below. Some people think it should be spare adjacent critical structures and below, and some people think it should be everything. Is that fair? Is that a fair summary of where we are?

David McCulloch: I think you've captured it accurately.

Craige Blackmore: Okay. So, now all we need to do then is come to a consensus on where we put that line, where we put that threshold. So, it would be nice if there were two choices, because it makes it easier to vote, but there are 11 of us, and we need to vote or we can discuss further. I think…

Joann Elmore: I think we can vote.

David McCulloch: Do you mind if I make one more comment?

Craige Blackmore: Go ahead.

David McCulloch: The spare adjacent critical structures is the underlying theme of [inaudible] and it implies specifically to head and neck and prostate but it applies to many individual situations, and even in the registry, patients

are… you can tell if they are broke into too small a population of individual indications, locations, reasons why you're using them to generate a meaningful amount of data, because it's not one other organ. If you cut like that this is breast. The breast topic is a different topic. I just want to say that, because what I would stipulate is that a good clinical reason for necessity is given and that has to be specific.

Craige Blackmore: Okay.

Martin Fuss: That needs to be said.

Chris Standaert: I think I'd like to ask one question of the expert in terms of the line we took out on prior radiation. We're reading that as not any significant change to what you actually might do because sparing adjacent critical structures is a lifetime calculation. Do we lose or gain anything by taking out the line on... how does that change the game if you take out the line of prior radiation? Are you making a narrower pool, or is it really not... doesn't make a difference? If you leave it…

Martin Fuss: It depends on your approval process. If you have prior radiation at the same area immediately adjacent, the assumption will be that there's some exhaustion of tolerance.

Chris Standaert: Right. Then it's automatic approval.

Craige Blackmore: Okay. So, Marg…

Chris Standaert: Or you could make that argument under this case. One would be an automatically approved and one would be argued.

Craige Blackmore: Margaret's going to move the lines for us, or Christine, or somebody. So, A goes to the top, B goes where A is, and C goes where B is. And you turn yourself around. So, are we all board on with this schema here, with what we're trying to decide?

Group: Right.

Craige Blackmore: So, I need a vote on As, Bs, and Cs, and I'm going to wait for her to get it up there so we're all on the same page.

Chris Standaert: I'm going to go back to that radiation thing one more time.

Craige Blackmore: Okay.

Chris Standaert: So, the operational effect is that… and cleaner is better for me. I like it better cleaner. The operational affect of that means that if we put in prior radiation that would automatically be approved like head, neck, or prostate. If we don't put it in, then people have to make their case for it; and the state specifically asked us to put in head and neck and things that would be approved automatically anyway. Is it helpful to them, and they asked for the [inaudible], is it helpful to them to have the line about previous radiation, or are they okay with it not being there? Is that easier or worse to implement for them? Because you asked that we…

Heidi Krist: It's fine not being there.

Chris Standaert: It's fine not, okay. Then I'm good.

Craige Blackmore: Okay. So, I need... so what we're voting on is what we think the conditions might look like should we elect to cover with conditions, and this is not your binding vote. You'll have an opportunity again to vote, either cover, not cover, or cover with conditions, but this will be the set of conditions that we use for the cover with conditions choice. So, I would like a show of hands for option A.

Michelle Simon: So, that's all A?

Craige Blackmore: That means everything gets investigation. You have to have investigation under any of these indications. Okay? B means head and neck is clear, prostate is clear, and anything else needs investigation, and how many votes do I have for that? That was Michelle's, okay? And then line C means... line C is not in the right place. Line C should be above the everything else, but line C means head and neck is okay. Prostate is okay. If you can spare adjacent... if you're going in to spare adjacent critical structures to prevent toxicities within the expected life span, that's okay, but everything else requires some form of investigation. So, votes for that one. What is that? 8? Okay. Okay, so this seems to be the set of... yes.

Joann Elmore: I just want to add one point of clarification about the evidence that I just had verified. When thinking about the effectiveness, in other words effectiveness of cancer recurrence and death, these are low-quality studies, but more than that, when they give the little arrow going this way, meaning no significant difference, they didn't point out the fact that most of these studies are underpowered and they are not adequately able to tell whether it's worse. That's why I wanted to get more data.

Craige Blackmore: Yeah, I... thank you. Is that... does anybody want to revote, or are we... that doesn't?

Michelle Simon: No.

Craige Blackmore: Okay. Any other points? Okay. So, let's go back to the sheet. So, I think we're ready to move to the binding coverage decision vote. Does anybody have anything that they want to bring up before we get to that point?

Joann Elmore: Can we get wording for this? Can we make sure I got it right?

Craige Blackmore: So, or we should talk about the wording or the…

Joann Elmore: It's what you deleted.

Craige Blackmore: Data is being collected for an investigation.

Joann Elmore: Evidence is being collected. It's what you deleted. That's why I told you to save the bottom one. Oh, look at her go. She's gonna go find it. Oh, I could have just told you. Evidence is being collected.

Craige Blackmore: No, the undergoing treatment part.

Joann Elmore: Evidence and treatment.

Margaret: So I put a [inaudible] there?

Joann Elmore: Mm-hm.

Craige Blackmore: Yeah, you don't need everything else. Just or is fine.

Richard Phillips: That's basically what Jeff had, only you have an or in there.

Craige Blackmore: Yeah, I mean it's…

Richard Phillips: Yeah. It's... it's…

Craige Blackmore: An adaption.

Richard Phillips: The or is the difference.

Craige Blackmore: We made it. Okay. Is the wording... are we happy with the wording?

Male: I would put registry [inaudible] study [inaudible].

Craige Blackmore: Etc.?

Male: I wouldn't keep… etc. or e.g. so you don't specify those are the only choices. Not ET. Phone home.

Seth Schwartz: The only comment I would say is that I think the wording to prevent toxicities within the expected life span is a little bit vague about what that means. I mean, I think we kinda know what that means, but…

Chris Standaert: We're trying to cover a lot of ground, but…

Seth Schwartz: Yeah.

Chris Standaert: I mean that seems like the idea.

Craige Blackmore: Do we want just spare adjacent critical structures, or do we want the to prevent toxicities within expected?

David McCulloch: I like the prevent toxicities.

Chris Standaert: I like those there. That makes it... it specifies the intent... the intent to keep adjacent tissues over the course of the lifetime.

Craige Blackmore: And these guys will operationalize it with... okay. Okay, we're moving to a binding vote. So, these are the pink cards, or purple, or whatever they are, and you have three choices. Your choices are to not cover, which means IMRT will not be covered under any circumstance. Your second choice is to cover unconditionally meaning it will always be covered. Your third choice will be covered under certain conditions, and the conditions are those defined on the board, and we will have a vote, please.

Michelle Simon: Well, can we have a vote for cover with condition and then a vote for whether we approve the conditions? Because you may have some dissenting on the conditions.

Craige Blackmore: No. We did that. So you…

Chris Standaert: You can vote against them by saying no cover.

Craige Blackmore: You can choose another option or you can…

Michelle Simon: Because I don't agree with those conditions.

Craige Blackmore: Right. And that's... we know that.

Michelle Simon: Okay.

Josh Morse: 10 cover with conditions, 1 no cover.

Craige Blackmore: So, our enabling legislation requires us to determine if our decision is concurrent with existing national coverage decisions and I think... I believe we only have local coverage decisions. Isn't that correct? So, there is no national coverage decision. So, that is not relevant. And we are adjourned.