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**Health Technology Clinical Committee Public Meeting  
May 17, 2013**

Craig Blackmore: Well good morning everyone. It's about five after, and there was an accident on I-5, so I think probably our northern committee members are stuck in traffic, but we have a quorum, so we can start to get organized and get started quickly.

So, we have a quorum, so I am going to call the meeting to order. This is the Washington State Health Technology Clinical committee meeting. Welcome to members of the public who have joined us. I am Craig Blackmore. I am the chair of the committee, and there are a few sort of minor housekeeping things before we start. The first is that the meeting is being recorded, so the committee members and others when you speak, please speak into a microphone and identify yourselves. Why don't we launch right in with updates, Josh?

Josh Morse: Okay. My name is Josh Morse. I am the HTA program director, and I'll give a brief presentation about the program and our plan for today. So, today's topics are cochlear implants this morning, bilateral versus unilateral, and this afternoon the committee will review ablation procedures for supraventricular tachyarrhythmia, including atrial flutter and atrial fibrillation.

So, a little background about our program. The Health Technology Assessment program is located within the Health Care Authority, an agency in the governor's cabinet in Olympia; 2006 legislation designed the HTA program to use evidence reports and a panel of clinicians, this group here, to make coverage decisions for certain medical procedures and tests based on evidence of their safety, efficacy, or effectiveness and the cost effectiveness, or value.

Some more background on the program. Multiple state agencies participate to identify topics and implement the policy decisions that come from this committee. These include the Health Care Authority, which manages the Uniform Medical Plan and the Medicaid Program, Labor and Industries, which manages the Worker's Compensation program, and Department of Corrections.

The agencies implement the determinations within their existing statutory frameworks. So, the purpose of this program is to pay for what works, work to ensure that medical treatments, devices, and services paid for with state healthcare dollars are safe and proven to work. We provide a resource for the state agencies that purchase healthcare. We develop scientific, evidence-based reports on medical devices, procedures, and tests, and we facilitate, we provide staff, for this independent committee to help determine which medical devices and procedures meet the test of safety, efficacy, and value. Our objectives, overall, are better health for our citizens. We strive for transparency. We work to minimize bias. We make efforts to be consistent in what we do. We evolve, as we need to, and we review old decisions, as new evidence becomes available or cyclic in that nature.

This is a high level overview of our process. Our technologies are typically nominated by our agencies, though anybody may nominate a technology for review through this process. The Health Care Authority director ultimately selects technologies that go through this process. We contract with evidence vendors, as we refer to them, or technology assessment centers, to generate technology assessments, or reports of the available evidence. To accomplish that, we developed key questions. We then publish a report and throughout that process, we publish drafts for public review. We then bring that information to this committee where we are today. Following this, we will have a set of draft determinations for another public review process and then the agencies will work to implement those decisions.

Our main key questions are, is it safe? Is it effective? Does it provide value? So, again, we strive for transparency. We work to identify the best evidence. We use a formal, systematic process for review of the evidence for the selected healthcare technologies, and the decisions come from this independent committee.

The decision basis includes: We look for objective factors for evidence consideration including the nature and the source of the evidence, the empirical characteristics of the studies or the trials on which the evidence is based, and the consistency of the outcomes. Additional factors may include the recency of the evidence, its relevance or applicability, and issues around bias.

Currently, this is our topic list for review in 2013: Following this meeting, the meeting in September, the next meeting of this committee, this committee is scheduled to review carotid artery stenting and cardiac nuclear imaging. In November, we are slated for a re-review of hyaluronic acid, which is an injection for knee osteoarthritis, and hip resurfacing. Those are both the first re-reviews

for our process. Beyond that, we have facet neurotomy scheduled for 2014 and not shown here along with that will be proton beam treatment.

How to participate with our program: We have a website where all of our work products are published, including the transcript from this meeting and prior meetings. The transcript from this meeting will be available in three or four weeks. You can join our stakeholder distribution list. The e-mail address is shown here. There is public comment on all of our deliverables, including proposed topics, those that are selected or proposed for review, key questions, draft and final reports, and draft decisions. One may attend these public meetings on the phone or in person. You can present comments to this committee, and you can nominate technologies for review. Thank you, very much.

Craig Blackmore: Thank you, Josh. Next item on the agenda pertains to previous meeting business, and first is to review the minutes from the last meeting. This has been provided to the committee members and is in the packet, and it is posted on the web. So, committee members, I will accept a nomination to approve the minutes or any comments.

Joann Elmore: So move.

Craig Blackmore: Do I have a second?

Seth Schwartz: This is Seth. I second.

Craig Blackmore: Alright, so please raise your hand if you favor approval of the minutes, which is all.

Josh Morse: Seven.

Craig Blackmore: Next item of business relates to the decisions that we made in the last meeting. Those decisions have been formalized into a document, a draft findings and decisions document by the staff, and again, this has been distributed to the committee members and our task, at this point, is to provide final approval or amendment, or whatever action we deem necessary at this point. So, starting with hyperbaric oxygen therapy, I will accept a recommendation for approval or further discussion.

Richard Phillips: Move to approve.

Craig Blackmore: Do we have a second?

- Michael Souter: Second.
- Craig Blackmore: Alright, so please show a show of hands for approval of our draft findings and decision on hyperbaric oxygen therapy. It's unanimous.
- Josh Morse: Seven.
- Craig Blackmore: The second decision we made in our last meeting pertained to cervical fusion for degenerative disk disease, so the same procedure. I am looking for a motion to approve or any other comments.
- Richard Phillips: Move to approve.
- Craig Blackmore: Do we have a second?
- Joann Elmore: Second.
- Craig Blackmore: We have a second, alright. Please, a show of hands for approval of the draft findings and decision on cervical spinal fusion, which is unanimous. So, that brings us to the agenda for the current meeting, and the first item is cochlear implants, bilateral versus unilateral, and we start the discussion of the topic by accepting public comments, both scheduled and unscheduled. Have we received any?
- Josh Morse: I believe we have four scheduled, and the first two will be via the telephone.
- Craig Blackmore: Okay, I am told we have four people who have signed up in advance, and each will be allowed five minutes to address the committee. We also have the opportunity for people who may not have signed up ahead of time to speak. If you wish to do so, there is a sign-up sheet right outside the door, and we will include you after we have gone through the people that have given us some advanced notice.
- Josh Morse: Okay, our first public commenter is Kathy Sie.
- Craig Blackmore: And the procedure, if you could please again identify yourself and tell us if you are speaking as an individual or if you are representing another organization or organizations, and please tell us also if you have any financial conflicts related to the topic under discussion. Thank you.
- Josh Morse: Dr. Sie, are you on the phone?

Craig Blackmore: Okay, we are a little in advance of our scheduled time, so we will circle back after we have heard some of the other comments and give Dr. Sie another opportunity.

Josh Morse: Okay, our second public commenter is John Niparko. This is also on the phone. Dr. Niparko, are you on the phone?

Craig Blackmore: Apparently not. So, we will move to number three.

Christine Masters: We are 15 minutes ahead of schedule.

Craig Blackmore: We'll circle back. We will give them another opportunity.

Josh Morse: Okay. So, the third, Douglas Backous. Do you have slides?

Douglas Backous: Uh, I have three slides, but you don't – if you don't show them, that's okay. Are you going to bring them up, or?

Josh Morse: Yes, momentarily.

Douglas Backous: Good morning, everyone. Thank you for hosting this discussion. We are talking today about cochlear implants, bilateral versus unilateral. Could you go to my second slide? I represent the Swedish Neuroscience Institute and my patients. I am on the cochlear surgical advisory board. Can we go to the next slide? Okay, so as far as the Swedish program, I have been in Seattle for about 13 years, and I did my first cochlear implant in 1993, so I have been in this industry for quite awhile, and there have been a lot of improvements in the technology over time. We started our program at Swedish where I changed jobs in town back in 2010. So, we started our program in 2011. I went back and looked at our data, and we have 11 bilateral implants that have been placed. Four of those are in adults, seven of those are in children, and when we talk about cochlear implants bilaterally, we talk about simultaneous versus sequential. The sequential patients are done not in the same setting. Some of these folks will actually have months to years in between their cochlear implants. The simultaneous patients are done in the same operation, which is much more cost effective but oftentimes with adults, we don't know whether they are going to benefit from a bilateral implant at the time of the first implant. Our seven children, they range from just under 23 months to 9 years of age. Three of those were simultaneous and four of those were sequential. We have had no surgical complications in that group. The average operating time is approximately 45 minutes more for a bilateral than a unilateral. All of them were activated between seven to ten

days of their implant, and one of those children we had device failure, which was a Nucleus 5 failure, and the Food and Drug Administration currently has the Nucleus 5 device on recall, and they are working out the bugs with that device. It turned out to be a hermeticity issue.

What is very important is all of our patients are using both implants. The sequential patients have each subjectively talked about an increased improvement in performance with their second device. A large group of those patients in the sequential group got their first cochlea implant, and when we put in implants, we are not exactly sure if we are implanting the better ear. There is no real test that can tell us that. When you put in a bilateral implant, you're always getting the better ear, because we're getting both of them, and each of those patients has shown a step in performance improvement, and that may be because we got the better ear.

One of the concerns is, when you put in a cochlear implant, can you actually damage the vestibular system or the balance system? None of our patients have had vestibular deficits from their implantation. Another thing I would like to suggest is that the National Institute for Health and Care Excellence, the NHS, the National Health Service in the U.K., underwent a multi-year project looking at bilateral cochlear implantation. They looked at all of the medical literature. It was woefully inadequate when it pointed to specific outcomes type of research, and as we all know in medicine, we are all striving for goals of good outcomes. We're not quite there yet, but they did come up with a core number of papers and made a very tough decision as a National Health Service where they approve unilateral implants for severely profound patients with hearing loss with no hearing aid benefit. That's a classic criteria for unilateral cochlear implant, but they have approved bilateral implants for all children, and I think a lot of that, which some of you are MHAs and outcomes people, so you're smarter than I in that category, but it definitely improves the cost utility of the cochlear implants when they are applied over a lifetime, as opposed to when they're put in later, but they also have approved it for adults who are blind who have other sensory disabilities and depends on hearing, and I apologize for the typo. It's not 'haring.' I have a problem with my own. People who really rely on hearing for their principle sensory contact with the world.

So, this is a very significant piece of work done by a large health system governing the entire U.K., and it is monitored very closely. The other part of their outcome was that the bilateral implants had to be negotiated to the best price and as an NHS, they have the ability to do that, and I don't know if the state of Washington wants to get involved with saying we're going to have a vendor for cochlear implants to make these accessible to people, but indeed

bilateral cochlear implants have made a significant step in improvement in our patient population, and I think the growing body of literature in the world is supporting that to the point where the largest health system in the world has actually accepted them. So, I am going to relinquish my last minute and just say thank you very much for hearing our arguments today.

Craig Blackmore: Thank you.

Josh Morse: Okay, Stacy Watson. If you could please state if you have any conflicts, thank you.

Stacy Watson: Thank you, very much, for allowing me to talk with you today. I am a cochlear implant audiologist here at Swedish Medical Center. I work with Doug Backous, and I am on the cochlear implant advisory board for Cochlear America. Slide two.

So, thank you for allowing me to bore you with some data today. I am going to start off talking about some of the numbers that we are going to be looking at today. I am just going to get a groundwork of what we're looking at. What number is actually better? What implies better performance? When we look at measures of hearing, we measure that in dB HL, or hearing level. The smaller the number, the better their hearing is. However, when we're looking at speech perception scores, whether they are understanding more in everyday communication, a larger number is what you want there. So, smaller and larger kind of keep track of all of those. Your speech perception threshold, again, smaller is better. So, we're turning down the volume to see how well they're understanding speech. At 50% of the level and how low we can go and they can still understand that. So, it is a little softer volume there, as well.

The signal-to-noise ratio is a lot of what we're going to be looking at today with you in my data sets, and it's a little bit difficult to understand. So, a smaller number, or a more negative number, is actually a better score. So, if we look at that chart on the bottom on the far left, my other right, it shows signal-to-noise ratio plus 55, meaning it's very quiet like we are in the room now, and there's no background noise going on. You can hear my voice comfortably. Now, on the far right, the signal-to-noise ratio of -12 is related to a noisy restaurant. So, you've got lots of background noise and maybe your speech signal is not as loud as that noise, and sometimes the noise is covering up that information. So, if we look at scores on the more negative side on the right side of the graph, it's better performance. So, you want a lower number in the SNR, or even a negative number.

So, what do we know is signal-to-noise ratio is unilateral versus bilateral? We have two ears, right? We're born with two ears. We don't go to the eye doctor and ask for a monocle. We need two eyes to see depth perception and give us some other information about the world around us. The ears are the same way. There are three things that the brain normally does that help us process out that information. It uses bilateral squelch information, pulling out and suppressing the background noise, binaural summation, getting two ears together is better than one. If you plug one of your ears, you will get kind of that concept of you've lost that binaural summation. The sound is very different, and we use the head shadow effect to tell – the head is going to block one ear over the other and give the brain a little bit more information about which side the sound is coming from.

Some of the research of, looking at the data out there on signal-to-noise ratios, there are a couple of different studies. One showed a 4dB signal-to-noise ratio improvement when they added in a second cochlear implant side. The other showed a 3dB improvement for bilateral compared to unilateral cases. So, there is definitely an improvement. Again, the smaller the number the better, so they are decreasing that performance.

When we look at how do we translate the signal-to-noise ratio into speech perception scores, there are a couple of studies that support that. The Mueller-Diele study out of 2009 illustrates that a 1dB improvement in signal-to-noise ratio improves speech perception scores by 8-11%, which is not a lot, but when you apply the study of Litovsky in 2006, a 1.5-3dB signal-to-noise ratio improvement could result in as large as a 33% improvement in speech understanding. That is a significant amount for somebody that only has one ear versus two. The Schoen study of 2002 also expected a 28% improvement, so it's supportive there.

When we look at pediatric cases, however, we have to look at learning environments. So, if we have someone in a classroom, we know the ideal signal-to-noise ratio in the classroom is +15. So, the speech is 15 decibels louder than any of the background noise. If anybody's been in a classroom lately, you know that there is a lot of commotion and stuff going on in the room. It's not always +15 signal-to-noise ratio. Another study illustrating 29 children found that unilateral cases were able to understand 21% to 78% correct in speech in unilateral implantation, but it improved significantly to 56 to 100% correct, and who doesn't want their child to understand 100% of what's going on in the classroom?

This is a graph of that same study set. The lighter colored bars are the bilateral cases of the test results in the bilateral condition, and the darker bars are the test results in the unilateral condition. So, what we know from research is that listening in noise is challenging. We all know that just from general everyday listening. The brain has normal abilities, normal natural abilities to pull out the speech from background noise, and bilateral implant users, adults and children, are able to take advantage of the natural processes if they have two ears. Thank you.

- Josh Morse: Should we go back to the phone? Dr. Sie, are you on the phone? Dr. Niparko?
- John Niparko: Well, good morning, everyone.
- Josh Morse: Good morning, Dr. Niparko. I'm Josh Morse, the program director. Do you have a slide presentation?
- John Niparko: I do.
- Josh Morse: Okay, we'll get that up and then we'll give you a signal.
- Joann Elmore: Hello, Dr. Niparko.
- John Niparko: Good morning.
- Joann Elmore: We were testing the sound. Go ahead.
- John Niparko: Yes, thank you. Shall I begin?
- Christine Masters: Yes.
- Craig Blackmore: We're pulling up your slides, so just give us one more second here. Alright, Dr. Niparko, if you could please just identify yourself and tell us if you are speaking as an individual or if you're representing other organizations, and if you have any financial conflicts of interest, please, and then go ahead.
- John Niparko: Yes, I'm John Niparko. I'm calling from Los Angeles on behalf of The American Cochlear Implant Alliance. I have to disclose to you that I do provide medical consultation to two of the manufacturers of cochlear implants, but I do wish for everyone to be aware that I receive no remuneration for that, and it is on a volunteer basis only that I provide that input.
- Craig Blackmore: Okay, Dr. Niparko.
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John Niparko: If the slides are queued up, I would appreciate it.

Craig Blackmore: Slides are queued up, and we are ready.

John Niparko: Thank you, okay. So we can go down to the first slide to provide a little bit of background on The American Cochlear Implant Alliance. We are a unique organization of members that are concerned with cochlear implantation and access to care. Our membership is comprised of providers, both medical and communication specialists, working with cochlear implant recipients throughout the United States. Go to the third slide please. The title is binaural hearing.

As we have just heard, this is fundamental to human perception. Two sets of Alliance comments to provide summaries of the literature on the benefits of bilateral cochlear implantation. As we've already heard, there is a summation effect that can improve detection and vocalization of sound, and this can result in enhanced accuracy in both production and perception of speech and signals. This carries functional benefits, reduced social isolation, and early [inaudible] with respect to development and learning. It can be absolutely a lifeline. Finally, there are no measurable health-related quality of life enhancements that are associated with such bilateral implants. I will move on to the fourth slide titled Effect of Unilateral Hearing Loss in Real World Environments.

We provide a couple of analogies, assessments, as well as the data to underscore the importance of binaural hearing, considerable effects of even mild unilateral untreated hearing loss are noted when we look at educational outcomes, somewhere between one and five and one in three children with mild untreated hearing loss will fail at least one grade. Permanent unilateral mild loss can impact a child's educational outcomes because of the challenging environment in which they are attempting to develop their scholastic skills. This can also affect their psychosocial well-being. The impact is only greater when the hearing loss is more significant. We'll move on to the fifth slide.

Minimal unilateral hearing loss references are provided here to give you a sense of scope of the problem. Again, the stakes are high when we deny the brain of bilateral stereo hearing. Going onto the sixth slide, Unilateral Hearing Loss in Adults.

The problems here are related to the loss of the summation effect and effective use of the head shadow, as you have already heard. Adults with normal hearing in one ear and un-aidable ear on the other side experience significant difficulty in the work place, social settings, and in many other aspects of daily life. The

problems of hearing speech, its localization, and hearing and noise are extensively documented. The impacts are far more significant for individuals who are bilaterally deaf and are able to only use one cochlear implant, because of the lack of input into that in an implanted ear, as well as the spectral limitations of the technology, which, fortunately, are becoming less and less severe.

Moving on to our summary slide, slide seven. Just as we use two eyes to develop our perception of scenes and landscape, binaural hearing is essential for spatial separation, salient speech from corrupting, background noise. That is, our ability to develop a sound state, if you will, and binaural listening is difficult to test in clinical settings, but it is essential in challenging listening conditions and those listening conditions, unfortunately, exist when our hearing should be at its very best, for example, in classrooms, workplace settings where people gather to learn new information and to maintain the social connectivity essential to cognition and to general health status. Thank you, very much.

Craig Blackmore: Thank you.

Josh Morse: So, our final scheduled commenter is Dr. Sie. Dr. Sie, have you joined us on the phone?

Kathy Sie: Yes, hi. I'm Kathy Sie. I am the director of the Childhood Communications Center at Seattle Children's Hospital, and I appreciate the opportunity to make some comments. First of all, I want to compliment the Hayes Group for their health technology assessment report on cochlear implants bilateral versus unilateral. I thought they did really a commendable job in synthesizing on a large body of literature to address some of these questions. As the director of the Childhood Communications Center at Children's, I would want to focus my comments on the pediatric group, and I will say that not all families would choose cochlear implantation for their children who are deaf, so our goal at Seattle Children's is to support families in whatever option they choose, with the focus of consistently exposing their children to language, but over 95% of deaf children are born to hearing families, and so these families often choose cochlear implants to help their children communicate in the hearing world. The improved speech perception and noise and sound localization was [inaudible] that I think is test and demonstrated in the data. It's very important to children, in the daily lives of young children, because they need to integrate large amounts of auditory information to acquire language and to me, the benefits will have a favorable impact on their speech and language development, as well as their safety. In addition to these benefits that can be demonstrated of auditory function and language, having two implants minimizes the chances the

child will be out of sound for any extended period of time. Kids have implant failures, hardware problems, and having a second side implant really helps them continue to function in all of the settings that they participate in.

The risks, I think, of having the second side implant are very low and they show this in their review literature. I will have to say that in the interest of responsible stewardship of limited healthcare dollars, I think one of the issues that needs to be addressed is taking [inaudible]. I think it is very important to have a carefully defined – patients undergo second-side implants. Some patients, such as those with severe developmental delay at the cochlear nerve, severe cochlear anomaly can be expected to get more limited benefit from a second cochlear implant. However, for those patients who can be expected to derive benefit from a second-side implant, perhaps we should be considering bilateral simultaneous cochlear implantation as the cost of bilateral simultaneous are less than bilateral sequential.

Unfortunately, I think there is little direct evidence by the cost effectiveness of bilateral cochlear implants compared to unilateral cochlear implants in the pediatric population, and part of this is that for the pediatric population the question is very complicated, because the potential impact of active auditory information on their language and cognitive development and optimizing a child's cognitive development will have trickled down to their academic performance and ultimately to their employment options. So, the potential economic advantages of optimizing a child's cognitive development are going to be difficult to calculate. So because of these long-term consequences, I fully support [inaudible] implant in carefully selected children with bilateral deficits.

Josh Morse: Thank you, Dr. Sie. Thank you.

Craig Blackmore: For clarity, we ask all of the presenters to the committee to tell us if they have any financial conflicts of interest. Do you have anything to share?

Kathy Sie: No. I have no financial conflict of interest.

Craig Blackmore: Thank you.

Kathy Sie: Thank you.

Josh Morse: And we have no day-of signups. Stacy Watson has spoken.

Craig Blackmore: Is there anyone else who is here who wanted to address the committee but did not have a chance to signup? Okay, then we will close the open comment

period, and we will proceed with the next item on the agenda, which is the agency utilization and outcomes.

Kerilyn Nobuhara: I'm Kerilyn Nobuhara. I'm the senior medical consultant with Washington Medicaid and will be presenting state agency data for bilateral versus unilateral cochlear implants.

Cochlear implants are intended to replace the function of an absent or nonfunctioning cochlea. This technology differs from amplification devices, such as hearing aids, the implanted bone conduction device known as the Baha and an auditory brainstem implant. Its use does require both surgical implantation, as well as an extensive post-implantation therapy in order to learn or re-learn the sense of hearing. In 2000, the FDA lowered the age of eligibility of cochlear implants to 12 months, and these devices are either on 510K or premarket approval with the FDA. I did include the FDA labels of the different devices in this slide set, primarily so that you had reference to the similarities and differences between the different devices available on the market. They all have a separation in terms of the adult versus the pediatric population of patients, and they all share a similarity in terms of the patients needing to fail a trial of amplification or hearing aids. There needs to be a confirmed diagnosis of hearing, severe to profound hearing loss, and that can vary depending on decibel levels or the type of functional tests, which are performed to elucidate that diagnosis, and you can see that there is a little bit of a difference in the language in terms of how, again, profound to severe hearing loss is defined in the pediatric and adult populations. So, here is the label for advanced bionics for cochlear, again, there is an age stipulation, a diagnosis of severe to profound hearing loss, a trial and fail of some type of amplification, as well as different functional hearing tests to kind of confirm that diagnosis of severe to profound hearing loss, and here is the Med El label.

So, for your consideration today and the director workgroup would like to thank you for taking this topic on. It is the question of whether or not the added costs for a second cochlear implant is offset in terms of clinical effectiveness and benefit versus a unilateral cochlear implant. There is a little bit of confusion in the public comment section about whether or not the question was bilateral cochlear implants versus no cochlear implant. That is not the question. The question is two cochlear implants versus one.

Current state policy for L&I and DOC, cochlear implantations are in prior authorization. For Washington Medicaid fee-for-service clients, presently prior authorization is required for clients 20 years of age or younger. Washington Medicaid only covers unilateral cochlear implants. There are no hearing

services or hardware benefit for adults in Washington Medicaid. For the pediatric population for the Washington Medicaid fee-for-service clients, there are a number of clinical criteria, which have been published in order for determination of a unilateral cochlear implant. The diagnosis of severe to profound hearing loss needs to be ascertained. The client needs to have both the cognitive ability to be a sufficient recipient for the cochlear implantation and needs to be able to participate in the extensive rehabilitation process after the implant is placed. There needs to be an anatomically accessible cochlear lumen in order for the child to qualify for this service, and there has to be no other contraindication to surgery.

The Regence policy is very similar. Regence is our contractor for UMP, Uniform Medical Plan. Regence actually covers bilateral cochlear implants for both children and adults. They also have a number of clinical criteria published in order to qualify for this service. So, again, Regence covers ages 12 months or older. Their clinical criteria for the diagnosis of severe to profound hearing loss is by decibels. They also have some functional tests, which are required in order to establish criteria for cochlear implantation. Again, Regence covers bilateral cochlear implants for children and adults.

There is a Medicare NCD in place. This has been in place, since 2005. Medicare also covers bilateral cochlear implantations for their adults. They do have clinical criteria published in terms of who may qualify for this benefit. It includes having the cognitive ability to use auditory clues and a willingness to undergo an extensive program of rehabilitation following implantation. They need to have no contraindications to surgery, and the device must be used in accordance with the FDA approved label.

From the AMDG Workgroup perspective for the criteria ranking, safety was a high concern; effectiveness, medium; and cost also high for this technology. Some of the questions, which came up from the workgroup include those around safety, and those really were primarily based on what are the associated harms, and which of these result in permanent explantation and whether or not these harms are additive in the setting of a bilateral cochlear implantation. We also wondered about whether or not there is an established clinical standard in terms of sequential versus simultaneous approaches to bilateral implantation and what is the evidence basis for either method?

For effectiveness, one of the primary concerns was in the absence of true randomized control trials, what is the preferred study design, and you'll hear more about how our vendor actually delineated the different study designs for the cochlear implantation literature. Some of the other concerns that came up

from the workgroup are whether or not measured outcomes, such as sound localization, open and closed set speech perception tests, speech comprehension, and speech production tests serve as accurate surrogate markers appearing related function and overall health outcomes, and really the biggest question is whether or not there is any evidence for the contribution of unilateral versus bilateral cochlear implantation to neural development in children, return to work for adults, and prevention of dementia in older adults.

Cost was a high concern, primarily because of the present body of evidence, and the question is whether or not utility estimates derived from an adult experience really apply to pre-lingual children with severe to profound bilateral hearing loss, and I don't know if we'll be able to answer this question today based on the available evidence. The other question which came up for the workgroup was, what is the economic burden of hearing loss, whether or not this is actually known, and whether or not an ICER for unilateral versus bilateral cochlear implantation can actually be calculated in this context.

For the state data, this is from the PEBB population for years 2008 to 2011, there were 32 patients who received 36 cochlear implants. PEBB paid \$1.4 million for these 32 patients. The per-procedure-average was \$52,000 with the per-procedure-maximum of \$160,000.

For the Medicaid population, there were 79 patients who underwent 83 procedures over the four-year period. The agency paid \$1.9 million dollars. The per-procedure-average was \$23,000 and the per-procedure-maximum was \$74,000. We do have some bilateral implantation patients within our Medicaid population, and you can see that the costs really are not additive in terms of the unilateral versus bilateral cochlear implants.

For the populations for the PEBB cochlear implant patients, you can see that as would be expected, the PEBB population is an older patient set, so age 50 and older, and for the Medicaid population, the age of the patients, most frequently, are the pediatric.

Spread out by age for the Medicaid population, most of our clients are five years of age or younger at the time of their first cochlear implantation.

Facility fees. So, these are broken down by the facility and professional fees for PEBB for unilateral cochlear implantation, the per-procedure-average is \$67,000. For Medicaid, it is between \$28,000 and \$30,000, and you can see that the majority of the fee is actually the facility fee, which does include the cost of the implant, itself.

There are some batteries and other repair charges that are associated with having a cochlear implantation, and this is from the Medicaid population. So, on average, per patient per year, a battery claim, which is paid out, is approximately \$300 per patient, for service and repair \$1,600, and replacement of major components \$85.

Also from the Medicaid population, there are a number of rehab services and speech therapy services, which are involved in relation to having the implant device before implantation. Their per-patient average is \$1,400 and after implantation \$2,500, and that just reflects the training and reprogramming that is involved with the implantation service.

So, what are some of the agency considerations? As you will hear from our vendor, there are moderate levels of evidence demonstrating benefit for speech perception and sound localization in favor of bilateral cochlear implantation in the pediatric population. Very low quality evidence for speech comprehension and speech production in the pediatric population. For adults, there are moderate levels of evidence demonstrating benefit for speech perception in noise and sound localization in favor of bilateral cochlear implantation. The AMDG workgroup does understand that there are very unique challenges to testing the pre-lingual pediatric population, and that needs to be taken in to account, as these may have had adverse impacts on the quality rating of the evidence, particularly for the pediatric population of patients.

Overall, the workgroup impression was that there is inadequate evidence at present regarding addressing simultaneous versus sequential bilateral cochlear implantation.

So, the recommendation from the workgroup to the committee would be to cover with conditions for clients age 12 months or older, clients who have bilateral severe to profound hearing loss who demonstrate limited or no benefit from an amplification trial. These patients need to have the cognitive ability to participate in an extensive auditory rehabilitation program following their cochlear implantation. They need to have an accessible cochlear lumen and stimuable auditory nerve. There needs to be no other lesion present within the auditory nerve. No other contraindications for surgery, and the device must be used in accordance with the FDA label. Questions?

Craig Blackmore: Thank you, Dr. Nobuhara. So, at this point, we will see if there are any questions from the committee related to the agency presentation before we move on to the evidence presentation from the vendor.

- Male (50:44): I just had a quick question. When you were talking about the Medicaid coverage and you were talking about the cost of unilateral versus bilateral and you said there was no added cost. I have two questions, I guess. One is, my understanding was that you don't cover bilateral, so I'm curious how those patients got in, and then what I'm wondering is did they get in but then only one side was paid for or why was the cost no different?
- Kerilyn Nobuhara: The policy change happened in January of 2011. I think four of those clients had their bilateral cochlear implantations before that time. One of those clients had a bilateral implantation, which was done under the ETR process. That was a client who had the original cochlear implant, and he had a bilateral device failure. So, the request was made for reimplantation for both sides, and that was approved. The other two clients had authorization for unilateral implantation, bilateral implantations were placed, and they were actually paid by the agency.
- Craig Blackmore: Richard?
- Richard Phillips: Yes, I had a question regarding the last slide. It was just a clarification. You said that you recommended coverage above age 12 months and over. Now, is that just the pediatric population you're talking about, or is that everything?
- Kerilyn Nobuhara: So, presently for Washington Medicaid fee-for-service, there is no hearing benefit. So, as this would apply to our population of patients, it would apply only to the pediatric population.
- Richard Phillips: Only the pediatric.
- Kerilyn Nobuhara: But for the other agencies, it would apply for all ages.
- Richard Phillips: Okay.
- Craig Blackmore: Other questions? We'll have an opportunity to ask further questions as we move along. The next item is the vendor report, but before we get to that, I want to introduce – actually, I want to ask him to introduce himself, but that is our clinical expert. We have a clinical expert at all of these meetings because the topics under discussion may not be areas that are directly within the practice domain of the committee members, and we want to ensure that the decisions that we made are with an appropriate understanding of the clinical circumstances and context, which they would be applied. So, thank you, for being here, and I will ask you to introduce yourself and tell us if you have

conflicts of interest, as we do with all the speakers. Your role here is to be a resource, and we thank you for coming. We don't ask you to make a specific presentation, but inevitably we will have questions for you about the clinical domain, and I will point out that even in those circumstances when we have a committee member who works in the area that we are examining, we would expect the clinical expert to be our clinical resource to allow – to prevent having one individual from being in two different roles. So, thank you.

Jay Rubinstein: Thank you. My name is Jay Rubinstein. I'm the Virginia Merrill Bloedel professor of hearing science at the University of Washington. I'm the director of the hearing research center of the same name at the University of Washington. I am also a surgeon who does cochlear implants in adults and children and run an NIH-funded laboratory that studies hearing perception and technologies in cochlear implants. I also have conflicts of interest. I have received research funding from both Cochlear and Advanced Bionics over the course of the years. I am not currently receiving any funding from either company but have many times in the past.

Craig Blackmore: Thank you. So, the next item on the agenda is the evidence report.

Teresa Rogstad: Thank you. Today's presentation will follow the usual format by very briefly going through the background and the way the report was structured, and then proceeding to the findings, describing practice guidelines and payer policies and an overall summary at the end. If you are unfamiliar with some of these abbreviations and you have a copy of the slides with you, you may need to refer back to this slide, as we go through the presentation.

Joann Elmore: Thank you for doing that.

Teresa Rogstad: You're welcome. It's been estimated that about 5 per 1,000 children in the U.S. have some form of hearing loss, and 16% of adults. The type of hearing loss that is appropriate for cochlear implantation is called sensorineural hearing loss, and this entails a loss of the cochlear hair cells or cilia, and once they're lost they don't regenerate. Hearing loss can occur pre-lingually, before language development, or post-lingually.

Cochlear implants were developed for individuals with severe to profound hearing loss, which means that they have no residual hearing or nearly no residual hearing, which is sometimes measured by how much benefit they have from an acoustic hearing aid. Audiologists can measure hearing loss in terms of what's called the pure tone average. That's the minimum sound intensity that can be detected, averaged across a range of frequencies. The threshold for

severe hearing loss is 70 to 90 decibels hearing loss. The threshold for profound hearing loss is 95 decibels, and normal hearing individuals can generally detect sounds at 20 decibels or lower. The way cochlear implants works, in general, is that electrodes inserted into the cochlea deliver electric signals and perform the function of the missing cilia by stimulating the auditory nerve.

This slide presents the theoretical rationale behind two implants. As you have already heard, in normal hearing individuals there are measurable effects that occur from having two ears. So, the idea is that two implants might be better than one.

You have seen a slide also that shows the different components of the implant system. On the outside, that piece right above the ear is an external microphone that converts sound into electrical signals, and then sends those to an external speech processor, which is the part right behind the ear. That converts the electrical signals into radiofrequency waves that are then transmitted to the internal processor. That translates the coding strategies into very complex patterns that can be detected by the brain as speech. Those coded signals are then sent down through electrodes, which have been inserted into the cochlea, and they serve to stimulate the auditory nerve in the absence of hair cells.

This slide just shows that there are two external parts and then the two components of the implant itself.

The reason for addressing this issue is that a second implant, obviously, increases the cost and the risk, and the benefit is uncertain. It's a good time to do a report, because in the last several years, quite a substantial body of literature on bilateral cochlear implantation has accumulated.

The PICO specified that we look at both pediatric and adult populations and that we focus on comparing bilateral implantation with unilateral implantation. The outcomes ranged from detection of sound all the way up to more patient important, or especially patient important outcomes, like functional status and quality of life.

We also looked at complications. We identified some secondary outcomes that we would look at if they were addressed in the literature. One of those was tinnitus. That's a complication that sometimes accompanies hearing loss in adults. So, an improvement in tinnitus would be a potential benefit from an implant, and then things like employment, job performance, educational

achievement. The key questions followed the standard format of effectiveness, safety, differential effectiveness and safety, and cost implications.

We started by looking at systematic reviews that had been recently published. There were quite a number of systematic reviews, but most of them were missing a lot of studies, either because they were published several years ago and there has been a lot of research published since then, or they had inadequate search strategies. Some of them also had very little study detail, no quantitative data from the individual studies, for example. So, we chose to do a de novo approach and did a search for primary studies, and you can see when our last search dates were.

We also looked at the websites of professional associations and disease associations to pickup guidelines that didn't show up in our other searches.

Studies that were designed to compare bilateral with unilateral implants were eligible, if they included 20 evaluable patients who were assessed according to an objective measurement or a formal instrument. We also considered case series, if they provided extra data on treatment success predictors or complications.

The Hayes approach to quality assessment is very similar to the GRADE system, and it is outlined in Appendix III. We start with appraising individual studies focusing mainly on the risk of internal bias. So, can we believe the evidence produced by the study? When we evaluate the body of evidence for a particular outcome, we take into account not only the study design and weaknesses, but also whether the evidence that's produced actually matches the PICO statement, the quantity of data, and whether or not the studies were consistent in the direction of findings. Obviously, the best study design for addressing this question would be a randomized controlled trial where one group was randomized to receive two implants and one group received only one implant. There is only one such study in the literature. It was conducted in adults in 2006. The bulk of the studies fall into one of these four categories. We labeled them A, B, C, and D. That's not meant to convey any sort of hierarchal order. Design A is not the best and design D is not the worst. The designs A, C, and D are fairly familiar designs. They're observational studies, so they're subject to confounding.

The one that we labeled as design B is an intrasubject design, and I will get into that in a little bit more detail on the next slide. These labels of very poor, good, poor, and poor refer to the initial quality that we ascribed to a study based on study design, but then of course we took other things into consideration, such

as loss to follow-up and appropriate statistical analysis and so forth. So, looking at that study design that we call design B, in this type of study, all of the individuals had gotten bilateral implantation, but it was an experimental design, because the investigators manipulated the testing conditions. What they did was after the second implant, they applied their tests. This design was used quite frequently for measuring auditory outcomes. So, the tests were administered with both implants switched on and with one implant switched off. In the pediatric populations, usually the one that was left on for that monaural testing condition was the first implant, and in adults usually the comparison was made with the better hearing ear.

We considered this design to be subject to very little bias, because the patient related confounders were controlled. There also would be no temporal confounders, because both the binaural and the mononeural testing were done at the same point in time. Some of these studies did longitudinal assessments at different followup intervals. Some just reported testing at a single point in time. We considered whether that monaural testing condition of having one implant left on matched the preoperative condition of one implant, and we did not find any reason to believe that it changed. The studies that reported longitudinal data did explicitly report that the performance in that first implant remain stable over time.

So, the types of outcome measures, as you have already heard, are often reported in terms of the percentage of correct scores, or the mean percent of correct responses across several trials of a particular test for an individual. Some speech perception tests reported results in terms of a speech reception threshold, and that is the lowest sound intensity or the quietest sound at which an individual could perform at a pre-specified level, such as 79% of the responses being correct. You heard about the signal-to-noise ratio already, so that measures how quiet you can make the signal of interest in relation to the background noise before the participant can't hear it any longer, or cannot perform adequately on the speech perception test. Localization is measured in terms of the ability to distinguish between left and right sources of sound, and the studies either reported results in terms of the percentage of responses that were correct, or in terms of a minimal audible angle, that would be the minimal angle at which the participant could differentiate between two sources of sound, or the error between the true source of the sound and the direction identified by the participant. Functional hearing and quality of life were generally measured according to formal questionnaires. Most of them were disease-specific, but some generic questionnaires were also used. As far as we could tell from the literature, there is no standard test or protocol for measuring the auditory outcomes of speech and localization, and we really did not see that

there was a standard questionnaire for function and quality of life either, although some questionnaires do seem to be used more often than others.

As you can see from this slide, there was a large body of primary studies, both in adults and children. We relied on a technology assessment conducted in the U.K. for safety data, and then we found four additional case series published after that, that had safety data. Some of the studies selected for that key question #1 having to do with effectiveness also had differential effectiveness data, and we found some additional studies in children to help with that question. We relied primarily on a systematic review for covering the five economic evaluations that have been published on bilateral versus unilateral implants.

Before I get into the details of the findings, I am going to give you a preview, at least for those areas where the data is kind of complicated. For children, there was one poor quality study that evaluated sound detection and no studies that looked at neurocognitive development. So, we could not draw conclusions about those outcomes, and I won't be presenting any slides for those. The evidence was positive, and we considered it to be of moderate quality with regard to the auditory outcomes of speech perception and localization. Speech comprehension and production were assessed by some studies. The findings were completely mixed, so we could not draw conclusions there either. Evidence regarding functional and quality of life outcomes was positive, but we considered it to be of low quality, and the positive evidence only came when disease-specific scales were used, disease-specific functional hearing scales.

So, I will go into a little more detail now. I just wanted to point out, for those outcomes that are measured in terms of decibels, a decibel scale is logarithmic, so a 1 decibel improvement represents something like a 10-fold improvement in nature. I sought some guidance from Dr. Rubinstein about how to evaluate the clinical relevance of outcomes that were expressed in terms of decibels, and he advised that a 5-decibel improvement, when you are testing in noise, represents a large, clinically-meaningful benefit, and that a 2-decibel improvement is small but still noticeable to the participant. If you are testing in quiet, then these improvements would not be considered clinically meaningful. For tests of localization, or sometimes it's called lateralization, the studies generally looked at how well do people perform – or how much above a purely chance level of performance are the participants able to perform after the second implant? How well do they perform compared with a level that would represent pure guessing? Then, of course, oftentimes the outcomes were expressed in terms of the percentage correct responses. We don't have a way of mapping those to clinical or functional relevance.

The slides that look like this are taken from the summary of findings tables that you find in the evidence summary portion of the report. Each slide represents one row from one of those tables. It's been condensed a little bit to fit on a slide. The structure of these tables was patterned after the summary of findings tables that are currently being recommended by the GRADE system, and I understand the committee spent some time looking at those at a retreat in January.

I will take a minute to explain how the results section was set up. If we had been working with pooled data, what you would see here instead of all these numbers is a single event rate for the comparator and a single pooled event rate for bilateral implantation, and then down in the bottom section of that results section, you'd see a single-pooled relative risk, or you might see pooled means up above and a pooled effect size or something like that at the bottom, but we didn't have pooled data, so what we did was present ranges of results up above. These are all the results across all studies whether there was a difference and whether or not it was significant, and we had to present them in different sets according to how the results were expressed, and then down below, we described the number of studies that had positive significant findings, and we give you the absolute differences between groups or testing conditions, the range across studies. So, for children, the evidence was positive. We considered it to be of moderate quality. There were consistent findings across all eight studies that favored bilateral implantation. We don't know how to evaluate the magnitude of benefit. At the bottom part of this slide, there is some detail on mean age, the time between implants and followup. A piece of information that is missing from these slides is how long the participants had been using their first implant. In studies of children, for the studies that we rated as fair to good, children had been using that first implant from four to nine years at the time they underwent testing with their two implants.

For speech perception and noise, the results were also positive here, and we considered the evidence to be of moderate quality. The absolute differences in terms of the mean percent correct scores was 6 to 37 percentage points, a bit higher than what we saw in quiet, and for outcomes that were expressed in terms of a decibel difference, the differences were 4 to 6 decibels, so that's right around that value that was identified by Dr. Rubinstein as representing at least a clinically-meaningful improvement.

The next slide gives a lot of detail about the studies that were most influential in this body of evidence, and I won't take time to go through this right now, but we

can return to this if you have questions about how the studies were actually conducted.

The evidence was consistent and positive favoring bilateral implantation with regard to the ability to localize the source of sound. With performance in the comparator groups or conditions being close to chance levels and being considerably above that level with bilateral implantation. Again, we don't know exactly how to map these findings to a score on a functional or a quality of life scale.

Speech comprehension and production was measured by four very poor-quality studies. These were looking at things like the quality of the participants' spoken speech, for instance how hoarse their voice was. One study observed young children in a room with their parents, and the assessor looked to see if children turned their head appropriately when their parents were talking. We considered the studies to be a very poor quality, and they were completely split in terms of the findings, so we couldn't really draw any conclusions about this particular type of outcome.

Five poor-quality studies looked at functional and quality of life outcomes. The results consistently favored bilateral implantation if disease-specific scales or measures were used. When generic scales were used, no difference was detected. We considered the overall body of evidence to be of low quality. These underlined ranges here, those show you how large the scales were, what the perfect or maximum score was, so there was a lot of heterogeneity there, and when you look down here where we give absolute differences, they are all in different terms, but if you converted all of those scales to a 0-100 scale, then the differences would be in the range of about 12 to 21 percentage points.

So, to review, we could not draw any conclusions on an impact in sound detection, neurocognitive development, or speech comprehension and production. We did conclude that there was moderate quality evidence showing an improvement in speech perception and localization, but no studies have been done that map those kinds of outcomes to a score on a functional or quality of life scale. So, it is somewhat difficult to interpret those in terms of ultimate outcomes. For studies that did directly measure functional hearing and quality of life, outcomes were positive when disease-specific scales were used, but the evidence was considered, overall, to be of low quality.

In adults, we see a similar pattern of findings. No conclusions can be drawn about sound detection and neurocognitive development because there were no studies that looked at those in adults. There were also no studies that looked at

speech comprehension and production in adults. Regarding some of the secondary outcomes, there was insufficient evidence to draw any conclusion about those. There was positive evidence, as in children, regarding the impact on speech perception and localization, especially speech perception in noise, and there was positive evidence regarding functional hearing and quality of life measured according to disease-specific scales. We considered the evidence to be a bit better than in children.

So, going into a little more detail, 11 studies provided what we considered to be low-quality evidence, suggesting a benefit for speech perception in quiet. It was ranked as low quality because of some unexplained inconsistency in study findings. In noise, the evidence was more consistent. We considered it to be of moderate quality. Absolute differences ranged from 8 to 37 percentage points in terms of correct responses, and 0.53 to 11 decibels for signal-to-noise ratios, so that represents quite a wide range of findings. It does include that 5 decibels that we would consider to be clinically relevant. There is some more study detail.

Localization was consistently found to be better with bilateral implantation, and then, as with children, functional hearing and quality of life were found to improve with bilateral implantation, as long as disease-specific scales were used. If we converted all of these scales that showed positive findings to a common 0 to 100 point scale, then the differences would be in the range of 6 to 30-some percentage points. So, the magnitude of benefit here is somewhat uncertain.

So, to review, the conclusions that we could draw from the adult set of studies was that there was a positive impact on speech perception, at least in noise, and in the ability to localize sound and disease-specific function and quality of life improved with two implants. Major complications are possible with cochlear implants. Major is defined as anything that requires surgical intervention or is life-threatening, such as meningitis. Rates of major complications were estimated at 1.7% in the first year following the implant to almost 9% over a mean followup of four years. By the way, these data apply to any type of implant. We did not find any data that was specific to bilateral implants. The studies included a mix of both, and I assumed they were mostly unilateral implants. Also, the studies did not always distinguish between children and adults, so we're considering safety for both of those populations together. The types of complications that are possible in children and adults are the same. So, I read the rates of major complications. If you're looking only at explantation, which is usually caused by device failure, the estimates for that occurrence were from about 1% over the first two years to rates of 5 to 10% over a long-term

followup. Minor complications include things like wound infection or an increase in tinnitus. In the published studies, the estimates ranged from 1% in the first several months to 7.8% over a mean followup of four years. There was one estimate of 35% in the first year. This came from unpublished data submitted in 2001 to the FDA by one of the manufacturers, and we don't know how their inclusion criteria may have differed from what was used in the published studies.

Regarding the differential effectiveness and safety question, the only conclusion that we can make with moderate certainty is highlighted in yellow on this slide, and that is that the time interval between the first and second implant does not seem to make a difference regarding improvements in speech perception and lateralization. There was also low-quality evidence represented in that second row suggesting that age at the time of the first implant doesn't make a difference on outcomes. These findings were contrary to the expectations of the researchers, because of brain plasticity and an expectation that maybe older children would resist that second implant. They expected earlier age to be associated with better outcomes, but that wasn't borne out in the studies. For some of these factors, the evidence is of very low to low quality, so those conclusions could change in the future with accumulating evidence.

So, to recap question #3, in children the only conclusion that we can make with moderate confidence is that the time between implants does not seem to affect the bilateral impact, the bilateral effect. There was very little data on differential effectiveness and no data on a lot of the subpopulations that were of interest.

In adults, there was no more than one study for any particular factor of interest, just one small study, and for most of the factors that the PICO specified there was no evidence at all. So, we can't draw any conclusions on this question in adults.

For cost, we did find two very poor-quality studies that, not surprisingly, showed that the accumulative hospital stay was shorter when the two implants were made simultaneously rather than sequentially, but most of the cost data came from a systematic review that evaluated the cost utility studies that have been published to date, bilateral versus unilateral. One was conducted in the U.S. and four in the U.K. This slide presents the ranges of incremental cost effectiveness ratios that were calculated by the systematic review authors. They converted all of the individual study findings into U.S. dollars for the year 2009 and if you convert those further to 2013 dollars, you get ICERS ranging from about \$30,000 per QALY up to \$136,000 per QALY. These were for long

timeframes, 30 years to a lifetime. We do not have a lot of confidence in these estimates, and the next slide explains why.

The utility estimates on which the QALY estimates were based were quite variable. They were derived from scales that measure utility from 0 representing death up to 1.0, which represents perfect health, and for children, those estimates range from 0.03 up to 0.076. Keep in mind that one would be a perfect score. This data is missing from the slide, but in adults the estimates range from 0.03 up to 0.11. Of course, those estimates were multiplied by the timeframe of the study to get the total QALYs. The sources of those utility estimates were not very high quality, and indeed, the systematic review authors did find that when they did a study level sensitivity analysis that the ICERs were sensitive to the utility estimates. Other weaknesses in these data include using different sources of cost and utility data in individual studies, and no studies that used current U.S. specific cost data. The systematic review authors concluded that more empirical data are required to estimate cost effectiveness for bilateral implantation.

We found two relevant guidelines and a position statement, and I apologize. There is quite an error on this slide. For the Cincinnati Children's Hospital Guideline, they do not recommend sequential bilateral CI. I am not sure how that ended up on this slide. What they actually concluded was that there was no consensus on the ability of bilateral implants to improve quality of life. Their conclusion is consistent with the findings for our report, even though their methods were poor and the conclusions were based on a rather limited evidence base. In 2009, NICE produced a good-quality guideline that recommended bilateral implantation if performed simultaneously for children who have an inadequate benefit from a hearing aid and also for adults, as long as they also have blindness or another relevant disability. The NICE guideline recommends against sequential implantation. The American Academy of Otolaryngology and Head and Neck Surgery does not have an evidence-based guideline on the topic, but they do have a position statement that says that cochlear implants are appropriate for adults and children with severe to profound hearing loss.

For the payers that we were asked to look at, they all cover cochlear implantation for bilateral hearing loss. The private payers cover both unilateral and bilateral implantation, and they cover it both for children and adults, as well as without any regard to when hearing loss occurred in terms of language ability. The CMS policy, which you've already heard about, of course applies to adults only, and they do not make a distinction between unilateral and bilateral implants.

So, our conclusions regarding children are that speech perception, particularly in noise and sound localization, appeared to improve with the second implant. There is low-quality evidence that functional hearing improves as a result of a second implant. We do not know how to map those auditory gains to functional and quality of life scores. Serious adverse effects are possible. There is insufficient evidence to evaluate the impact on sound detection and neurocognitive development, and many of the factors that are important for assessing differential effectiveness and safety. No conclusions can be drawn about cost effectiveness.

This slide describes the population to which the evidence applies. It is not meant to convey any conclusion about effectiveness in patients who meet these characteristics, but these are the characteristics of the patients that were eligible for enrollment in the studies or this matches the baseline data that was reported. So, the evidence applies to children with pre-lingual deafness who had a good success with their first implant and undergo auditory and language learning, and who have no significant disabilities or structural abnormalities that would interfere with the success of that second implant. Also, almost all of the children receive their second implant before adolescence.

For adults, the conclusions are similar to children, moderate quality of evidence showing an improvement in auditory outcomes. Also, what we considered to be moderate-quality evidence showing an improvement in functional hearing and disease-specific quality of life. We do not know how to map those auditory gains to functional improvement and conclusions about safety and differential effectiveness and cost effectiveness are similar to children. For adults, the evidence applies to adults who have post-lingual deafness. We assume that it also applies to adults who do not have any concomitant disabilities. Two studies specifically excluded patients who did not have the cognitive ability to participate in testing or the training that was involved, and we assumed that probably other studies did, as well, but we do not know that for sure.

Gaps in evidence include the optimal age at which to do the second implant, bilateral implantation in several subpopulations, including adolescents, children with post-lingual hearing loss, and adults with pre-lingual hearing loss, moderate hearing loss, individuals with concomitant disabilities. More studies are needed to assess the impact on function and quality of life, especially over the long-term. Research is needed that could map auditory gains to a score on a functional or quality of life scale. The comparative effectiveness of different devices was not addressed in the literature. Safety specific to that second implant was also not addressed, and more work needs to be done to assess cost

effectiveness. We would also like to see more RCTs. Thank you, and I'd be happy to answer your questions, now.

Craig Blackmore: Thank you. Do committee members have questions for the evidence vendor at this point?

Richard Phillips: Yes, this is Dr. Phillips. I was questioning whether the – in terms of the safety I was more interested in the explant data. Of those explants, how many of them basically returned the patient back to their original baseline? How many of them really gave irreparable harm? For example, one of the things I would be concerned about would be vestibulitis or some vestibular function injury. Did that kind of serious injury occur? Or maybe our clinical advisor would be appropriate to respond to this, too.

Teresa Rogstad: Well, I will tell you what I know, and then Dr. Rubinstein can add to that. The explantations that were reported in the literature were usually because the device failed, and the technology assessment that was done in the U.K. looked at about 110 explantations over several studies and of those, seven of them resulted in permanent explantation. In other words, there was no reimplantation of a device, but they did not break it down according to the particular problem.

Jay Rubinstein: When you explant and reimplant for device failure, you can usually expect that performance will be at least as good as it was with the previous device. A lot of times, these explants and reimplants are done several generations of device later from the original implant. I actually published a paper over 10 years ago that demonstrated that with later technologies you actually get better performance from the reimplant than you do with the original one. In particular, vestibular injury is – significant vestibular injury is pretty uncommon either in primary or in revision cochlear implantation.

Joann Elmore: I had a followup question about the safety. The data that are described are in person years, and some of these are unilateral. Some are bilateral. I would be interested in the safety per ear. Can you help us with this question?

Teresa Rogstad: There was nothing in the literature to help with that. Some of the data were in person years. Some of them were just absolute – just simple rates over...

Joann Elmore: Well, if you know the underlying population, how many were bilateral how many were unilateral, and you know what the rates of bad outcomes were, you can kind of guess.

- Teresa Rogstad: I don't even know that. I looked at every single case series, even the ones that were covered in the technology assessment, and they didn't tell you. They would tell you – some of them did acknowledge that some of the implants were a second implant, but they did not present data – they didn't tell you how many and they didn't present data separately.
- Jay Rubinstein: Yeah. So, the reason for that is that you don't expect any interaction between the two sides in terms of complications. So, the risk of complication when you have two implants is twice the risk of when you have one implant.
- Joann Elmore: But I just didn't know whether the data that was presented were for patients that had a single side done versus patients that had both sides. I'm trying to guess what is the risk per ear.
- Teresa Rogstad: The way I interpret the data is that's the risk for either a first or a second implant. It's the risk for a single-implant surgery without regard to whether it's the first or the second one. There was no reason, as Dr. Rubinstein said, there's no reason to believe the risk profile changes with the second implant, unless the devices have become safer. They do make improvements over time in the safety of the surgical techniques and the devices.
- Joann Elmore: Unless you talk about two hospitalizations. With each surgery, there is the anesthesia risk and/or the infection rate.
- Teresa Rogstad: Right. You're exposing the patient to the same set of risks a second time. So, the risk per procedure doesn't change, but the total risk exposure of the patient, of course, is greater if they get a second implant.
- Joann Elmore: And a second surgery. With just the surgery itself, not the...
- Teresa Rogstad: Right. Either a second implant at the same time or a second surgery.
- Jay Rubinstein: So, if you're comparing simultaneous with sequential, the surgical risks are twice whether you do them at the same setting or in separate settings. What is different is that the overall anesthesia time is less if you do a simultaneous implant than if you do sequential bilateral implants, but one way or the other, the total anesthesia time for two implants is greater than one implant whether it's done in the same setting or in separate settings. You could talk about, well, the other hospital-associated risks of just being in the hospital after a surgery, and those are very small and typically not the issues that are addressed in the cochlear implants literature, because they don't end up being major issues that require revision surgery. The issues that require revision surgery are twice for

two implants as they are for one. If you have two implants, you are twice as likely to have one of them fail in your lifetime than if you have one.

Joann Elmore: So, the summary data that was presented on safety were in person years. The data that went into that, were most of those patients that had bilateral implants or were most of those data that went into the patients and studies that had single unilateral implants?

Teresa Rogstad: I believe they were mostly unilateral.

Joann Elmore: Okay, thank you.

Chris Standaert: Question. This is an outpatient procedure, or are people hospitalized for days? Is this like they get the procedure and go home?

Teresa Rogstad: No, it's inpatient. They stay in the hospital for two or three days, I believe. Is that right?

Jay Rubinstein: So, some centers will do it as day surgery. Patients will go home the same day. Other centers do it as an overnight stay.

Chris Standaert: Maybe one night sort of deal?

Jay Rubinstein: Yeah, so it's a 23-hour stay for other centers, and it's highly variable. I have patients in my own practice that don't want to stay in the hospital overnight. They want to go home the same day. Other patients want to stay in the hospital overnight and will.

Chris Standaert: Is there a life expectancy of these devices? Like, how long do they typically last?

Teresa Rogstad: It'll take me a minute to pull that up.

Chris Standaert: I mean, you can predict with like orthopedic implants you have some ballpark of how long you expect them to last. I have no idea what that expectation is.

Jay Rubinstein: The expectation is that it should not fail. This should be a lifetime device. The reality is it isn't always. What do we quote to patients? I typically would tell patients to expect a 1-2% failure rate per year. That actually varies dramatically depending on which generation of which manufacturer's device. There have been devices that have been recalled, because they have had very high failure rates. So, over the history of cochlear implantation, that number is a moving target, but in general, the failure rate is extremely low.

- Chris Standaert: They're built to last forever, essentially? That's the intent?
- Jay Rubinstein: That's the intent.
- Chris Standaert: Okay.
- Craig Blackmore: But there are maintenance costs. I mean, you change batteries and things.
- Jay Rubinstein: That's external.
- Craig Blackmore: That's external, okay.
- Teresa Rogstad: We're looking to see if we have data on the mean life of an implant. I am not sure if we do or not, but we are looking for it.
- Carson Odegard: Well, I can ask a clinical question, Carson Odegard. To our expert, or to our vendor, as far as this design, I would like to dig a little deeper on that design B intersubject comparison. You mention that it was adjusted for confounders. What are the weaknesses of that study? For example, I had one question that would kind of tune into, when you switch one of these off and both on and one off, when you retest it, or when you test that on/off situation, is there consistency amongst the studies in regards to the time that that's done, switch on and switch off? Is it – my question is, is there a catchup time that the brain has to take in order to respond to the test that would be consistent across the studies?
- Teresa Rogstad: Do you mean the time between having both implants turned on and only one implant turned on?
- Carson Odegard: Correct.
- Teresa Rogstad: That was done in the same testing session, so there was virtually no time, and the studies – some of them explicitly reported that they randomized the order of testing, you know? Whether they did one implant or two implants at first, but they were both done in the same testing session. The time since the second implant was inserted, that ranged from – in children, that ranged from four to nine years, and we only reported the latest data in the report. In adults, it had been six months or more since the second implant and Dr. Rubinstein indicated that adults acclimate to the implant much quicker than children.
- Carson Odegard: I see. So, when it is tested, it is done at the same time.

Teresa Rogstad: Yes.

Carson Odegard: When it's switched on and switched off, I mean, there's not like three minutes in between and then you test somebody else and it's one minute in between?

Teresa Rogstad: Oh, no. It's...

Carson Odegard: It's all done at the same time?

Teresa Rogstad: Yeah. Immediate.

Carson Odegard: Immediate, okay, thank you.

Jay Rubinstein: The better executed studies are random with regard to order, left, right, binaural.

Carson Odegard: I see. Thank you.

Chris Standaert: I had a question about quality of life measures and data, whenever you're ready.

Teresa Rogstad: I'm sorry, what was that?

Chris Standaert: I had a question about quality of life data, measures and data. It looks like there is data on hearing perception and language discrimination, but not much on quality of life, and I was curious as to the cause of that. Is it that there aren't well-validated scales correlating hearing to quality of life? There aren't good scales to measure quality of life or hearing perception, so they don't exist so they don't get studied, or that people didn't use them if they do exist in the studies?

Teresa Rogstad: I don't know why there are so few data. There are scales. There are scales that have been validated in individuals with hearing loss, and they look at things like if you're sitting at a table with several people, can you tell who's speaking, or if you're crossing the street and you hear a bus or a car, can you tell what direction it's coming from? So, those scales exist. They're pretty comprehensive. I don't know why more studies haven't been...

Chris Standaert: They just don't use them?

Teresa Rogstad: ...been using them. Maybe...

Chris Standaert: So are those – I mean, are those scales also then sort of – I hate to use the word scale, but those scales adjusted for use and cost utility data, like a number of quality of life scales have been adjusted into, or correlated into, cost utility scores. So, does the data exist and the people could have done better cost utility analysis if they had used these scales, and they just didn't do it, or we're not – the study – the scales aren't that advanced?

Teresa Rogstad: Well, I actually wondered that myself and wondered if it would be easier to demonstrate cost effectiveness if you used a disease-specific scale to measure utility, because the cost utility studies use generic scales, and that's a limited...

Chris Standaert: But those little – those differences make a whopping difference in quality.

Teresa Rogstad: They're not sensitive to the differences that you're looking for.

Jay Rubinstein: The other problem that the field faces is that the utility effect of a first cochlear implant is so large that the second implant disappears in the noise, unless you use a disease-specific measure. One of the things that this whole exercise has made clear to me is we clearly need a technique to map disease-specific measures that are sensitive to these effects.

Chris Standaert: So, this field just really doesn't have that at the moment. It's isn't in the literature at the moment to be utilized.

Jay Rubinstein: That's right, but to give you a simple – we talked about 5 dB being clinically significant. The person who is sitting directly in front of me, if he had a single cochlear implant, depending on his level of performance, we had an average level of performance with a single cochlear implant, he'd have a very difficult time understanding me talking behind him in a room that's reverberant like this. A 5 dB improvement in performance would mean that he'd be able to hear me talking behind him without turning around, just to put that into perspective.

Chris Standaert: Are those numbers, your perception of those numbers, are well sort of studied, accepted NCID sort of numbers that people have gone out and studied in patients and looked for minimal clinical important differences and try to quantify – are they quantified, or are you giving us your estimate?

Jay Rubinstein: No. I'm giving us examples.

Chris Standaert: So, we're still in the same dilemma in the field, that the field has not really gone that far into the literature and the research to get there.

Jay Rubinstein: And part of it is that it seems to people in the field that it's so self-evident that if we can double your performance and background noise, that's pertinent, and patients who get that benefit will very clearly state it. Hey, I can hear people talking behind me now. So, to people in the field, that's pretty self-evident until you engage in exercises like this when you have to say, how does this rate compare to coronary artery stenting? The need for it becomes much more clear.

Teresa Rogstad: We did find some data on how long the implants last. These are from some older studies, published like ten years or more, and they cover intervals of 11 and 13 years. One estimated an accumulative device survival of 90% or 13 years and the other one was 92% over 11 years. We don't have any longer-term data than that.

Craig Blackmore: So, the implants that were put in 20 years ago had a failure rate of a little under 1% per year, is what we're hearing?

Teresa Rogstad: Well, we don't know when they were.

Craig Blackmore: Well, if they've been in for 13 years and the paper was published...

Teresa Rogstad: Yeah, right. That's true.

Chris Standaert: Don't those papers assume 1%. We just don't know if it's linear once you break 13 years, because they don't have the data yet.

Teresa Rogstad: It was 11 years and 13 years at the time of the study was published.

Craig Blackmore: Other questions for any of our presenters? Okay, at this point in the schedule, we usually take a break, so why don't we do that and we'll return and have the committee commence its discussion towards discussion making. I've got 5 of 10, so why don't we reconvene at 10 after?

Alright, I'm going to call the meeting back to order. The next step in the process is deliberation among the committee members towards a decision having all of our resources here to continue to answer questions. In the past, we have found it useful for one of the committee members to start off by sort of summarizing where we are, not necessarily a final position on this is how I want to vote, but just giving us a framework to start with. So, I would like to call on the committee members, if I can have a volunteer, to kind of put where we are into

context, as a starting point for our discussion. Of course, if nobody volunteers, I will not be shy of appointing somebody. Alright, Joann, where are we?

Joann Elmore: I was looking for Chris. I think we need him here.

Craig Blackmore: Richard, are you ready to start us off?

Richard Phillips: Well, let me start from the very end of this then. I'm trying to figure out what conditions we wouldn't cover this for. Under what circumstances would we not cover it? Because I am really, my personal feeling looking at the data, is that there is pretty strong evidence it works for both adults and children. The question is, you know, the safety seems to be acceptable to me. So, where I guess I'm coming from is, you know, what conditions are we not going to cover as opposed to anything else? Are there any restrictions?

Craig Blackmore: Okay. Can I get somebody else to reflect on that? Agreement or disagreement, or? Kevin?

Kevin Walsh: I'm struggling with how to translate what are really surrogate markers into functional outcome, and this is similar to me to the using the computer to figure out the position of the holes for the knee replacement surgery versus doing it visually and realizing that there are two angles of – there's two degrees of improvement in accuracy, but there's no information on what functional benefit that means and deciding whether that's acceptable or not. So, this literature strikes me to say – I mean – I just don't know how much functional improvement there is. I struggle, as a provider who takes care of children, with the expectation that improved hearing translates into improved language development, which translates into a higher opportunity for success in school, but I don't see that reflected in any studies, and I don't know if that means that it's not been done, or it's not there.

Teresa Rogstad: Isn't it another body of literature, do you think? That you would look at hearing perception that has nothing to do with CI but has to do with...

Kevin Walsh: Well, no. I'm not talking – I'm talking about CI. I'm just talking specifically about CI. I mean, I understand that, in general, that's the tenet that we operate under in terms of doing hearing testing in children and doing speech therapy in children. So, I'm saying, okay. That's a given, but if that's a given, how come I'm not seeing any of that here? I don't know why, but I'm left – so I feel like I have the opposite position of Richard. Richard is saying, well, give me a reason not to cover it, and I'm saying, give me a reason to cover it, because I don't see it. The only thing I'm held back by is the fact that it's a child, and that I feel morally that

we probably need to give them every benefit we can, just like we decided that autism – that behavioral therapy for autism was going to be covered, because there wasn't anything else to give those kids. So, I'm okay with that, but that's not a scientific decision. If I have to make a scientific decision, I say, there's no evidence.

Seth Schwartz: I'd like to make a little response to that Kevin. I think we are looking at functional outcomes, but when you think about the measures of – the sound measures that we're hearing about, it's – you can kind of equate it to like a vision test. So, if you have a vision test and someone's got 20/20 vision versus someone who has 20/100 vision, you kind of know what that means. So, a lot of these are meant to be objective measures of what people are actually hearing. It's difficult to equate what that means in terms of quality of life when you're dealing with children. So, there's been kind of a surrogate measure with that looking at kids who – not who are implanted but just looking at the – what the impact of a unilateral deafness of unilateral hearing loss on kids is, and we heard a little bit about that before that in kids who have mild hearing losses, there is something like a 30% grade failure rate, which is huge, and they have not been able to show as clearly that if you put hearing aids on those kids and give them all the benefits that you should that they don't fail grades anymore, but that's sort of the empiric assumption, which is that if you reverse the unilateral handicap, then those kids are going to function more – or going to be less susceptible to that.

Kevin Walsh: So, is it naïve of me to think that should be able to be demonstrated?

Seth Schwartz: Well, I think there is some evidence of that, and there certainly is evidence of that and Dr. Rubinstein maybe you can kind of comment on some of what the evidence is, but I think there is some evidence that you can reverse the unilateral handicap by putting a second implant on these children. Do you want to comment on whether there is any evidence of that?

Jay Rubinstein: There's more evidence for that in mild hearing loss but I'll give you an explicit example. One of your pediatric patients who is riding a bicycle with a unilateral cochlear implant has no idea where the car honking at them is coming from. If you have got bilateral cochlear implants, they know where the car honking at them is coming from. That's one of the things that you – part of why we measured these – do the measures we do is that it's something we can hang our hat on and statistically measure a clear advantage, and there's no question that bilateral cochlear implants provide better sound localization. So, it's very important in a variety of situations that children, and adults, encounter. So, if you're looking for a single reason to cover it, that's it.

Craig Blackmore: So, we've heard the evidence about sound localization, but to get back to the question of grade failure and school outcomes, if you will, can you just tell us in terms of the evidence reviewed, I mean, did you seek those out? Was that part of the scope? What did you find? I mean, we've been through it, but I think we need to sort of hear that clarification.

Teresa Rogstad: School performance was one of the outcomes listed in the PICO. So, if it had been there, we would have reported. I mean, we looked for virtually any and all outcome measures. There was a single study in children. It wasn't – I think we rated it as poor quality, that borrowed some questions from a particular functional scale, one of which included the participation in a mainstream classroom, and they showed that after the second implant, significantly more children were participating in a mainstream classroom than before. Of course, there was a time lapse in between. So, we don't know whether they improved because they were just maturing or because they got the second implant. That is the only thing of that nature that I came across.

Craig Blackmore: So, I'm – if I may – in terms of grade failure, which we heard a lot about, you're saying that there was simply no evidence?

Teresa Rogstad: Correct.

Kevin Walsh: And then, I guess, to speak to adults, I'm left with the same thing but even less outcome measures that show functional benefit, return to work. I mean, I saw – I heard all the implications that were made, and they all make sense to me, but I don't see it demonstrated in any studies.

Chris Standaert: That seems to be one of the problems, yeah. They didn't take that next leap into saying, does this really matter regarding job performance and job retention and all this.

Kevin Walsh: Right. And part of me wonders, well did they look and didn't find anything, so they didn't publish, or did they not look?

Joann Elmore: Well, it looks like in children, the function quality of life outcomes was positive and the quality of the – so the types of studies that were done were low. So, it looks like there is some evidence, not RCTs, but in functional and quality of life outcomes in their summary on page...

Kevin Walsh: Quality of life outcomes are often self-reported.

- Joann Elmore: Right, so you're looking on functional outcomes that are more...
- Kevin Walsh: That can be demonstrated, yeah.
- Chris Standaert: Was it just scores and dropout rates and things that are sort of more externally valid?
- Craig Blackmore: Yeah, I guess it depends on what constitutes a surrogate, if you will, and what constitutes a true outcome, and is improvement in hearing a true outcome? I mean, it's certainly more of true outcome than a blood glucose level or the diameter of an artery. If one is doing research, does one have to show that equates with educational gains, or is it sufficient to say that kids can hear better, we achieved our goal? I mean it seems to me that there is some value in hearing better, and I don't know if – is that – I don't know where the bar should be in this one, because it has face validity as an important outcome, but we haven't seen that it translates to more global outcomes.
- Michael Souter: Given that the country spends a lot of money in screening newborns for hearing deficit and given the other educational interventions that are focused on a hearing-impaired child, it seems entirely logical to me to support that very point you make, that hearing gained is an end in itself, and I think that there are a lot of other factors that come into what use you make of that hearing. That depends on the child's own intellect. It's volition to study the supportive social backgrounds, etc. There are a whole lot of other factors there that would play into those circumstances that would probably make it a very large and very complex study to do. Nonetheless, it would be nice to see something, but I do think that as – if you look at what our society is placing priorities on, it's clearly identified that hearing loss in children is an important goal to recognize and to do something about.
- Joann Elmore: I agree with that.
- Richard Phillips: I had a question for the – maybe for the state agencies. I saw that this was identified as an issue of high interest of cost. Cost was a big issue here, and yet we only have a hundred cases that have been done in the last four years between Medicaid and the PEBB and is it the cost per case that is the concern, or is it the overall cost to the state?
- Kerilyn Nobuhara: We came up with that high concern before we actually pulled all of the cost data. The question was whether or not the bilateral cochlear implants would double the cost to the state agencies and that obviously is dependent on whether or not they are done in a simultaneous fashion versus a sequential.

- Richard Phillips: In that regard, is it not reasonable that if the state can somehow either provide discounts or mandate that they be done simultaneously, or is that extending beyond your authority?
- Kerilyn Nobuhara: I think that would extend beyond what we would usually publish in terms of a coverage policy.
- Craig Blackmore: Can I just drill down on the numbers a little more? I mean, we heard 100, but I think that's the unilaterals, right? I mean, I'm looking at this and I'm seeing what looks like eight over four years?
- Chris Standaert: When I look at the Medicaid data, you have seven bilaterals and you have almost 70 unilaterals.
- Craig Blackmore: Seven under Medicaid and one under the PEBB?
- Chris Standaert: That's only maybe 10% or so that are actually bilateral. Most of them seem to be unilateral.
- Richard Phillips: Under Medicaid?
- Chris Standaert: Yeah, Medicaid.
- Richard Phillips: That would have been almost all unilateral.
- Chris Standaert: Agency slide 9. They have a few older people for whatever reason, but it's seven.
- Craig Blackmore: Slide 15, it looks like you did one under the PEBB and it looks like you did seven over four years under Medicaid on slide 16.
- Teresa Rogstad: What page?
- Craig Blackmore: Page eight, slide 15 and 16. So, bilateral I would agree with your question. Bilateral is very uncommon in this state it looks like.
- Jay Rubinstein: So, not every person who's a candidate for a unilateral cochlear implant is in fact a candidate for bilateral cochlear implants. So, the cost, even if you did them all sequentially, is not double unilateral implant. There are many patients who have one cochlear implant who can make effective use of the hearing aid in the opposite ear. Hearing aids in people who have significant loss of hearing

can provide complementary information to a cochlear implant. So, some people are better off with a hearing aid and a cochlear implant than they are with two cochlear implants. Other people hear better with two cochlear implants than with a hearing aid on the other side. So, you can't just take the unilateral numbers and double them in order to figure out what it would cost if bilaterals are covered.

Joann Elmore: But you did say earlier that you see the need for more specific criteria and specification of when you would do bilateral.

Jay Rubinstein: I mean, I – we do pretty elaborate evaluations, both in adults and children, and when a patient or family is seeking out advice on whether they should get a second cochlear implant or not, we assess their implant and their hearing aid and the two together in order to determine, do we want to put a cochlear implant in the opposite ear?

Chris Standaert: So, while we're on that, I have a question on the decision making between simultaneous and delayed implantation. I assume there are all sort of patient variables that come into play when you decide that, and you may put one in somebody may actually have declining hearing in the other ear and become a candidate later down the road, so they become delayed, even though that wasn't the initial plan. I assume some of those you have no idea how somebody is going to even respond to one and so you put one in and see if they get anything out of it whether they have the cognitive, neurologic to work with it and then you put the other one in before you put them both in. I assume all of these things come into play. So, it's not an easy – it's not purely an economic decision to say unilateral versus – simultaneous versus delayed.

Jay Rubinstein: That's absolutely correct and there are also families where you would expect them to want to do the second cochlear implant who will take years before deciding to have the other procedure because they're doing so well with the first one. They don't feel the need to do the other for extended periods of time.

Chris Standaert: So you're finding that incremental benefit in the patients for whom their incremental benefit is of sufficient value to them and is probably very challenging given the magnitude of the benefit of one.

Carson Odegard: I have a question about the cost analysis that we get at the end of some of these reports and the thing is that it comes down to a similar conclusion that – for example, this report states what society can bear, and I'm not sure what that even means. So, when we get these figures, we really don't know how to use

them properly. So, does anybody have an idea of what – we've had a \$50,000 range in this country per QALY, so...

Chris Standaert: Well, I think we have problems with our QALY because they don't have good quality of life data from which to estimate cost utility. Therefore, the cost utility data are next to meaningless, because you just don't have the data from which to – so even if you can say there are 30 to 150, you have no idea, really.

Carson Odegard: Yeah, that's my concern.

Chris Standaert: Yeah, I don't know how much value you can ascribe to the numbers we have, because none of these studies actually measured the true health quality utility of these devices, and since they haven't measured it, how do you calculate it?

Carson Odegard: So, it's hard to put into our discussion that kind of data to evaluate that.

Craig Blackmore: So, who have we not heard from? Joann?

Joann Elmore: I don't have anything else to add.

Michael Souter: I have one more technical question, I suppose. Once the internal implant is in, is that – will that work with other devices, external devices, in the future or are you thereafter tied to one proprietary manufacturer? Is there any interchangeability between the internal and the external devices?

Jay Rubinstein: So, you can't interchange a cross-manufacturers, but all of the manufacturers strive to have their newer external devices be backward compatible with their older internal devices.

Michael Souter: When you say strive, are they successful in that regard?

Jay Rubinstein: For the most part, yes. In certain specific situations, no.

Craig Blackmore: Other questions or comments?

Richard Phillips: An implant from one company can't be used with another.

Craig Blackmore: Okay, well, I think we're going to have to work our way towards a decision here, and we have three choices. As always, we can cover without limitation. We can not cover under any circumstances, or we can define some limited circumstances in which we can go for coverage. Sometimes when we go through this exercise, it is fairly apparent that the committee is sort of drifting in

one direction or another, and in this one I think it's a little – maybe there's a broader range of opinion at this point, but I would like to try to narrow things down a bit if I could, and I think maybe the way to do that is to turn to our tool, our HTCC Coverage and Reimbursement Determination Analytic Tool and the committee members are all familiar with this tool. It's to help us work towards a decision by making sure that we are considering all the outcomes in terms of effectiveness, safety, and cost effectiveness, and we work towards our nonbinding initial voting.

So, the first issue is, have we listed and delineated the safety outcomes that we believe to be of concern, and staff has prepopulated the document with outcomes of relevance, surgical complications, device failure, reoperation, revision, wound infection, tinnitus, etc. Are there are other safety outcomes that the committee should be noting that are not included on this list? Any of the committee members want to add? I'm sensing that we're fairly comfortable with that.

In terms of effectiveness, we had talked about outcomes related to hearing, sound detection, perception in quiet and noise, localization, and we had talked about sort of more global outcomes, like neurocognitive development, quality of life, functional outcomes, etc. Are there outcomes that aren't on this list that we should be considering?

Chris Standaert: Functional outcomes is a huge range. I think our problem is that we don't have any data on any of them, to any great degree, so I don't know if we have to break that down more. You could break it down by all sorts of things if you had data on again job retention, school performance, and grade progression and all that, but we don't have it. So, if we don't have it I don't know if it's worth. In abstract, it would be nice to be able to subcategorize it thinking that we might have that data, but we don't.

Craig Blackmore: Unfortunately, in the reality of the HTCC, we never have all the data we want. Then, in terms of cost, we talked about both fiscal cost and cost effectiveness. We haven't talked a lot about special populations. We have heard from our evidence vendor about certainly the age and differences between the pediatric and the adult age groups, and we haven't heard a lot about some of these other factors, but I think we have heard what is available. Are there other populations that should be on our list as considerations that we have not touched upon that are of concern to the committee?

Carson Odegard: In response to that I raised the question about the national coverage decision. They have a lot of restrictions in the way that they apply – or they have not a lot

but they have some restrictions that they apply. I don't know whether that has an effect on the way we make our decision or not. I mean, we have to be at least compliant with them or not go against what they say, but we can obviously be more liberal than what they ask. That may be something we want to incorporate.

Craig Blackmore: So, when we get to the point about talking about potential conditions, we will come back to that.

Carson Odegard: Fair enough.

Chris Standaert: I find it sort of interesting that NICE covers for adults with other impairments, yet I didn't hear you talk about studies of cochlear implants in people who are deaf and blind versus people who have eyesight and are deaf only. I didn't hear that, so I wonder how they came up with that.

Teresa Rogstad: I don't know. There wasn't any evidence about that in the technology assessment that guidance was based on. I think they had a lot of expert testimony.

Craig Blackmore: So, you looked for that and were unable to find the evidence? Okay, thank you.

Carson Odegard: So, it's my understanding that the national coverage, they are recognizing speech perception as the outcome and not localization, is that correct?

Craig Blackmore: We have a copy of the national coverage decision. It's in the tool that we're just working on, page three of your decision tool is, I believe, the national coverage decision. Yeah, national coverage determination is on page three.

Josh Morse: It's also in the agency slides.

Craig Blackmore: It might be a little easier to understand in the agency slide.

Josh Morse: Carson, there are no criteria other than speech understanding that are used for cochlear implant candidate assessment, and there is no criteria that separate unilateral from bilateral. All the programs have their own methods for differentiating candidates for unilateral or bilateral, but the actual coverage decisions are simply based on the same criteria for unilateral implantation.

Carson Odegard: Great, thank you.

Craig Blackmore: Okay, I'm going to move us on. Anything else the committee members want to weigh in on at this point? Okay, I'm going to move us on to the first voting question, and the purpose of the first voting question is not to be binding. It's not to commit the committee members. It's not even necessarily to lead directly to our binding vote, but rather to serve as an anchor so we can understand the range of understanding across the committee and that we can use that for further discussion as needed and refinement as needed. Nonetheless, it is a good sort of starting point.

So, the way we structure this is, we vote separately on effectiveness, safety, and cost effectiveness, and the choices are unproven, equivalent, less effective, or less whatever and more, and it becomes very relevant what the comparator is, and the comparator in this case is unilateral. So, for effectiveness, the first question is, is bilateral cochlear implantation – how does the effectiveness compare to unilateral cochlear implantation, and you can vote that you don't know, it's unproven, that they are equivalent, that bilateral is less effective than unilateral, or that bilateral is more effective than unilateral, and effectiveness would be based on the criteria that the individual committee members believed to be most relevant. We understand where we want to get?

Josh Morse: I see eight more, one unproven.

Craig Blackmore: Okay. The next piece is safety, and again, so this would be the safety of bilateral implantation versus unilateral implantation.

Marie Brown: Sequential or at the same time?

Craig Blackmore: Not otherwise stated. So, generally we talk about some or all situations. So, in this case, I guess it would be we can't have some or all can you? It would have to be all. So, do you think it – okay, if you think under any situation – no, you can't do that. It's got to be all. It's either always safer, always less safer, equivalent, which might mean better under some circumstances and worse under others, or you don't know.

Carson Odegard: Can I ask for some clarification here, because it seems to me that if we're going to be comparing against unilateral, then basically the safety concerns have to double, because the safety concerns have to double, because it is basically going to be double whatever is over here. On the other hand, if we say per ear, I would say equivalent.

Craig Blackmore: Well, I don't think you can say per ear, because this is what happens to the patient. So, it's per patient.

Carson Odegard: So, it's per person?

Craig Blackmore: It has to be per person.

Carson Odegard: Okay.

Craig Blackmore: Is your chance of having a complication if you have two of them versus one. This is the nonbinding vote. It's just a starting point.

Josh Morse: That's eight less and one unproven.

Craig Blackmore: And then finally cost effectiveness.

Josh Morse: Nine unproven.

Craig Blackmore: Okay. So, where we are in the majority at least is that we have something that is effective, at least under some circumstances based on some outcomes, and it has risk in terms of safety. It is an invasive procedure, it has to have some risk, and we have unproven cost effectiveness. So, I think most of us are heading down a path towards either coverage or coverage with conditions, although that's not 100%. Do I need to confirm that, or is that evident? Maybe I'll confirm that.

Joann Elmore: You're correct.

Craig Blackmore: So, what we often do in this circumstance, which I think makes sense, is to define the conditions under which the group that believes we should cover with conditions, what conditions that would mean, and that group might be all of us or it might be a minority, and then we would subsequently have a vote on covering under all circumstances or covering on this predefined set of conditions that leaves open the possibility of voting for noncoverage at the end, but we are going this path, because we believe that's where we are. Is that consonant with everyone? Is that reasonable?

Joann Elmore: Mm-hm.

Craig Blackmore: Okay, so we'll do that. So, then what we do is we have Margaret or Christine put up a piece of paper and we start to write on it.

Marie Brown: Could we use the medical director's recommendations? They had a list of conditions to work from.

Craig Blackmore: We can start with that. We can start with a coverage decision. We can start with whatever we want to start with.

Joann Elmore: Start with the recommendations.

Craig Blackmore: Start with the recommendations?

Chris Standaert: We have the NCD, too, so.

Craig Blackmore: Okay, I think the committee wants to start with the agency medical director's recommendations as a starting point, and it's coming up on the screen. She's got it down already. It's coming on mine. You're looking at almost identical to the...

Joann Elmore: Yeah, I would recommend two edits here under the cognitive ability, what about a willingness?

Chris Standaert: You probably need both.

Joann Elmore: In other words, you know, they have to be willing to undergo rehab, so cognitive ability and willingness to participate.

Chris Standaert: Yeah, I'd go with that.

Joann Elmore: And willingness. And then under the accessible maybe and structurally suitable. In other words, you can access it, but it has to be structurally suitable, and our clinical expert can advise us if my wording isn't appropriate, but you say accessible cochlear lumen, but it has to be accessible and structurally suitable.

Seth Schwartz: Dr. Rubinstein, do you want to make any comment about that statement, because I find that a little bit problematic, because what we're talking about is, some children may have a cochlear that's effected and might make the surgery more difficult, but the implant may still be their only option for hearing improvement, and there may be opportunities to help those children anyway. So, maybe Dr. Rubinstein, could you talk a little bit about that situation?

Jay Rubinstein: So, as Dr. Schwartz was just implying, this is a very, very complex question, and structurally suitable and accessible depends a lot on the surgeon involved and what their experience is. There are many children, and adults, who have cochleas that would not classically be called structurally suitable, yet we now

know are entirely structurally suitable and that the patients can do quite well, may do very poorly, we just don't know in advance.

Joann Elmore: Then maybe delete what I just suggested and it's covered under our nice and vague no other contraindications to surgery and leave it up to the surgeon.

Chris Standaert: I mean, the language you took is from the Medicare NCD that says accessible cochlear lumen that is structurally suited to implantation. So, is that problematic? I mean, it's – these are very vague terms. I don't know what accessible means and I don't know what structurally suited means, so there's no definition of either. So, it's sort of what you think.

Craig Blackmore: Does it add anything?

Seth Schwartz: Well, Dr. Rubinstein can talk about this as well, but I think part of what this comes up with are there are two scenarios that I think are most commonly referred to is, one is some children are born with a malformation where they have no cochlea, and that is a situation where an implant is generally not a good option for them. The other circumstance is that children and adults can both develop meningitis or a few other conditions which can lead to ossification or deposition of new bone into the cochlea, which can make implantation more difficult, or impossible if you're not skilled at accessing a cochlea in that circumstance, and yet there are some opportunities in those patients where you can actually do drillouts or other surgical procedures but you can still get the implant in effectively. There are some questions about whether the performance is equivalent. Some of those patients will do very well, as Dr. Rubinstein was saying. Some won't do very well, but to have it be an across-the-board just if you have something wrong with your cochlea you don't get one I think is a little bit restrictive. When I think about what Joann said about allowing the surgeon or the team in a discussion with the family to have that be a potential option is, I think, is more suitable.

Jay Rubinstein: That same question actually applies to the following line. Historically, we never put cochlear implants in anybody who had any lesions of the auditory nerve, but now we've actually found that there are patients who have neurofibromatosis type 2 who have a vestibular schwannoma that is either not growing or has been radiated, and they have no hearing in that ear, and they will, in fact, get substantial benefit from a cochlear implant. So, that's an old criterion that really is not followed in the field anymore.

Joann Elmore: I think we should delete that part, the lesions in the auditory nerve. Just delete that. Leave it up to the surgeon with no other contraindications for surgery.

- Teresa Rogstad: Well, I don't think that was discussed in the evidence anyway.
- Carson Odegard: I have a question about audible frequency. Some of these guidelines mention the frequencies involved. The agencies didn't mention this. What is the importance placed on the frequencies? In the field if that's just self-evident, I mean that's just something that everybody knows about. Do you even need to include it?
- Michael Souter: You do have a threshold of loss defined. That's probably enough supportive criteria.
- Carson Odegard: I don't think we see it here in his, but in the study there were.
- Seth Schwartz: I'm not sure what that was referring to. I think that there is a pretty acceptable frequency range, over which impact hearing and function. In other words, the ultra-low frequencies or ultra-high frequencies are not important for this. So, I think there is just the general speech frequencies that are likely to impact patients and the outside frequencies, we aren't concerned with those.
- Carson Odegard: That's what I figured.
- Michael Souter: I have a question on cost implications. I understand that there are now newer generations of implants that are MRI compatible, is there much of a price difference in those compared to the older established models?
- Jay Rubinstein: Well, I mean, each later generation of cochlear implant device costs more than the previous generation.
- Michael Souter: I mean, what's the typical variation in price that we see?
- Jay Rubinstein: When I first started in this field, I think a cochlear implant probably cost about \$15,000 for the device itself, and now I'd say it's about \$30,000. That's over a very long period of time, 20 years. But...
- Michael Souter: Is there uniformity across the different manufacturers in terms of within a fairly tight price band or is there a great variation?
- Jay Rubinstein: Yeah, there is, and there's also – there's not a lot of uniformity across centers, because every center negotiates their own price with the different manufacturers. But yes, across the manufacturers it's pretty uniform. There's not that many.

- Marie Brown: Am I correct that the age 12 months and older is because that's when they did the evidence on children, it is on children 12 months and older?
- Jay Rubinstein: The evidence actually has now come out in the last few years that less than 12 months actually does result in more rapid improvement in outcomes and better outcomes and safe surgeries. The 12 months comes because that's the sort of earliest FDA criteria is 12 months, but in fact, many children now are getting implanted at 8 months.
- Craig Blackmore: But the data that we saw was all from children who were over 12 months, right?
- Jay Rubinstein: There is no bilateral data comparing bilateral to unilateral for less than 12 months that I'm aware of.
- Teresa Rogstad: I'm not entirely sure, but we looked to see. Since the FDA labeling requires a minimum of 12 months, basically the U.S. studies would do studies on children older than that.
- Jay Rubinstein: Actually, many of the U.S. studies would have children who got their first implant before 12 months and their second implant after 12 months, which is a very common clinical scenario. You have a child, you have very good data about their degree of hearing loss. They get a first implant that's nine months and then they get another implant six months later.
- Carson Odegard: Could you comment upon the first criteria there? The age of 12 months or older? Is that restrictive? Can that decision be made at six months, for example, from your perspective, or is that?
- Jay Rubinstein: So, I find 12 months to be highly restrictive, and we frequently find that we're needing to explain that this is a child that we know will benefit from an implant at an earlier age, and we now have very good language outcome data for unilateral implants only that are earlier than 12 months, at least in the short term, does significantly better than later than 12 months.
- Chris Standaert: But this doesn't restrict a unilateral implant at all. This is only you can't get the second one before you're 12 months.
- Jay Rubinstein: So, that I do not find restrictive at all, because I don't commonly perform simultaneous bilateral implants under 12 months because of concern about the accuracy of our hearing measures in very young children.

- Chris Standaert: So, as 12 as a bilateral restriction would be different?
- Carson Odegard: That makes sense.
- Chris Standaert: Do we need to specify sensorineural hearing loss, Seth, do you think?
- Seth Schwartz: I think it does make sense to have that say sensorineural hearing loss. I think the only concern about the 12 months, I think, and I would clearly agree with Dr. Rubinstein that the data that exists is in unilaterals. The only question is, if we're talking about the potential cost advantage of doing simultaneous bilateral versus sequential, it could be restrictive, even though it may be the choice of the clinician and the family not to do bilateral simultaneous in younger children, there's a question of whether we should make that comment at all.
- Michael Souter: I think there is always the opportunity, as more evidence emerges, to justify the evidence that we could see the benefit derived from the unilateral, that this decision could always be revisited at the 18-month cycle.
- Craig Blackmore: Yeah, I have trouble proving something where we have no data, and it's not FDA approved.
- Chris Standaert: Right, I do too. Yeah, we don't have data on bilateral in under 12 months.
- Carson Odegard: The thing that's happening here, it's not like you're not going to do it, it just means it's the timing in which it's going to be done. You're going to wait for four months before you do it or something like that.
- Chris Standaert: You can do one in an 8-month-old, see how they do with it, see how they grow.
- Carson Odegard: Well, it doesn't make any difference in cost is what I'm trying to say. The state's not going to save any money. They're just going to dictate that it's going to be done at time A rather than time C or whatever.
- Seth Schwartz: Well, currently Medicaid, for unilateral still has 12 months as the limitation.
- Craig Blackmore: Other comments?
- Seth Schwartz: Just about the accessible cochlear lumen and stimuable auditory nerve, whether that's still – people like the way that's worded.
- Craig Blackmore: So, the studies that we have, the studies that are on the better side, there were some that were moderate evidence, do we know the inclusion/exclusion criteria

for who got bilaterals? Do we know if these were people who had accessible cochlear lumen, or is this anybody? Do we – can you help us with that?

Teresa Rogstad: Some of them did specify no structural abnormalities that would interfere with success, but they were not any more specific than that. Some of them just said severe to profound hearing loss.

Craig Blackmore: So, my advice would be to go where the data from the studies leads us rather than where the surgeons believe they can have technical success, but that assumes that we know where the data from the studies leads us, because we know what the inclusion and exclusion criteria are, which they may not have been terribly explicit about.

Teresa Rogstad: I can do a quick check to see how many...

Craig Blackmore: Thank you. Other comments? What does device used in accordance with the FDA label mean?

Chris Standaert: I guess that should be FDA-approved labeling, but...

Craig Blackmore: Yeah, but what does that mean, practically? I don't know.

Chris Standaert: It means it has to be used as approved by the FDA. The FDA has conditions on their approval.

Craig Blackmore: What are those conditions?

Joann Elmore: Those are in the slides.

Craig Blackmore: Alright. Help me out.

Joann Elmore: They depend upon a manufacturer, so I wonder if we're requiring that, then?

Craig Blackmore: So, where?

Joann Elmore: Page three, slide three, four, and five.

Craig Blackmore: Page three of the agency's...

Joann Elmore: ...of the HCA. You know, slide three for Clarion. Like an adult has to score less than 50% on a test of open set hearing and noise test.

- Craig Blackmore: So, this is a trial of hearing aids and that sort of thing.
- Chris Standaert: Those are payers though. Those are payers.
- Joann Elmore: No, this is the FDA label.
- Craig Blackmore: The FDA labeling is on slide three.
- Joann Elmore: But Craig is asking a good question. By adding that final sentence in, are we then forcing additional criteria that is manufacturer specific?
- Craig Blackmore: Which might not be a bad thing. I don't know.
- Joann Elmore: But, you notice how it varies by each manufacturer?
- Jay Rubinstein: And each manufacturer varies over time, as new studies are done of technologies that they develop.
- Chris Standaert: Yeah, it does not seem like we have any data to supercede FDA labeling on where it's approved and not approved, and there are going to be different circumstances and populations for which specific devices are approved. This is the way the FDA works. So, I think it is very reasonable – we've done it before. Like BMP we did the same thing. We basically matched the FDA approved indications. It depends how we say it. The FDA label doesn't quite sound right either. It's either FDA-approved indications or FDA-approved labeling or something like that.
- Craig Blackmore: I mean, I struggle to be less restrictive than the FDA if I don't have evidence. If I have evidence, I have no trouble saying this is where the evidence takes me, but when the evidence gets weak, which is generally the case, I have a little more trouble going beyond where things have been approved.
- Chris Standaert: So, you're saying you don't like that or you do like that?
- Craig Blackmore: I like keeping it in.
- Chris Standaert: I do, too.
- Craig Blackmore: Even though it does assign restrictions, which vary, etc.
- Joann Elmore: Even though it's variable across manufacturers?

- Craig Blackmore: I mean, the devices are variable across manufacturers, too.
- Joann Elmore: That's what I mean.
- Craig Blackmore: And, you know, I don't know if that's the – if the devices are sufficiently similar that it makes sense that be harmonized, but I'm not going to know that without a bunch of data from the manufacturers that I don't have.
- Seth Schwartz: Just as information, I mean, Medicare sort of made their own determination, and they sort of disregarded the FDA approvals and made their own determination.
- Craig Blackmore: So, you think the Medicare is in conflict with the FDA? Is that what?
- Seth Schwartz: It is, for better or worse, but it is.
- Craig Blackmore: Alright, we should look at that.
- Seth Schwartz: And I'm not saying we should go with that. I'm just saying that it's...
- Craig Blackmore: No, I didn't understand that.
- Joann Elmore: Medicare national coverage is used in accordance with FDA-approved labeling, slide 10.
- Seth Schwartz: Their speech criteria are more restrictive than the FDA speech criteria.
- Joann Elmore: Oh.
- Craig Blackmore: When the FDA says you have to use - sorry – Medicare says you have to follow the FDA-approved labeling and it has further restrictions, is that?
- Seth Schwartz: Less than 40%.
- Craig Blackmore: Yeah, that's on the top paragraph of that slide.
- Jay Rubinstein: Whereas, FDA was 50% for the ear to be implanted and 60% in the contralateral.
- Carson Odegard: Oh, okay.

- Craig Blackmore: Okay, so our charge, our legislation, says that we have to be able to explain why we differ from Medicare national coverage determinations, if we do, and again we don't hesitate to do that if we believe the evidence supports it, but we have to decide, as a committee, if the evidence supports having different criteria.
- Joann Elmore: Perhaps the populations are different?
- Seth Schwartz: I'm not saying that we disagree. I'm just saying we have to decide that explicitly.
- Chris Standaert: I mean, the trouble is that different devices have different FDA-approved criteria and there are different thresholds for the different devices. So, either we're going to arbitrarily pick an average or some number and apply it to all devices, or we just make people follow the specifications of the device, as approved by the FDA.
- Seth Schwartz: But there's conflict in the CMS decision.
- Chris Standaert: I know, so we either replicate their conflict or we...
- Seth Schwartz: But if we differ with their decision, don't we have to say why?
- Chris Standaert: Yeah, we say we found it conflicting with the FDA and we opted for the FDA requirement.
- Craig Blackmore: I mean, I don't think there's conflict. The Medicare coverage decision explicitly says you have to follow the FDA and you have to meet these additional criteria.
- Joann Elmore: And the additional criteria was just the most stringent of the manufacturer FDA labels, which was less than 40%. Some of the others were less than 50%.
- Craig Blackmore: This would be in addition, or would sort of trump the FDA, but you still have to follow the FDA. So, it begs the question, if the coverage decision has criteria for percent improvement from – actually I have to read this again to understand it.
- Seth Schwartz: It's not...
- Joann Elmore: It's less than 40%.
- Seth Schwartz: What your speech discrimination score is at baseline.

- Craig Blackmore: Oh, okay. So, your score, right. So, if your score is less than – so, if the national coverage decision has a criteria for what your score has to be, do we wish to replicate that in our decision, or do we believe the evidence tells us otherwise?
- Joann Elmore: Or do we believe that there's inadequate evidence?
- Craig Blackmore: Yeah. I mean, we can say that too. We can say we disagree with Medicare because we don't think there's enough evidence to agree with them. We just have to be explicit. I'm not pushing one or the other. I just want to make sure that we have done what we are charged to do.
- Chris Standaert: So, if we go back to our inclusion criteria, was our inclusion criteria be this cutoff by Medicare for our studies or were they typically the manufacturer specifications and FDA approval for the devices?
- Craig Blackmore: So, the inclusion criteria for the better quality evidence studies, right?
- Chris Standaert: Yes.
- Craig Blackmore: Have we made any progress on that, or?
- Chris Standaert: Because that would help us.
- Teresa Rogstad: Yes, in terms of the anatomical contraindications, only two pediatric studies address that issue in their inclusion criteria. They excluded individuals, one said no anatomical contraindications to implantation, and the other one just said radiographic evidence of normal cochlear anatomy. Those were both good quality studies, and there were only two good or fair-quality studies in the adult set that address that issue, and they said no malformations that would interfere with the success of the surgery. They were not any more specific than that.
- Craig Blackmore: Okay.
- Teresa Rogstad: If you – you were discussing the thresholds for performance on speech tests and in adults only, only a handful of studies define the inclusion criteria in those terms and the threshold ranged from 30 to 50%. There weren't enough data in any one threshold to form conclusions. In fact, the ARC did a technology assessment in 2011 on behalf of CMS in order to determine whether that 40% threshold level could be supported by the evidence, and they concluded that there was insufficient evidence to justify that or rule it out.

- Craig Blackmore: Okay, to get back to the list, we have been talking about this anatomic criterion, accessible cochlear lumen and stimuable auditory nerve. Are we happy with this? Do we wish to get rid of it? Do we wish to make it more restrictive? I'm looking for input from the committee.
- Michael Souter: Well, it's also in the Medicare coverage, as well.
- Craig Blackmore: So, is that similar language?
- Michael Souter: An accessible cochlear lumen that is structurally suited to implantation. They also mentioned freedom from lesions of the auditory nerve, as well.
- Craig Blackmore: Okay. So one choice is to basically pattern after that language. Another choice would be to leave it at the discretion of the surgeon, if the surgeons believe they can technically succeed in people that would not necessarily meet these criteria. Committee members? I'd like to go with a show of hands on the restrictive versus less restrictive. Go ahead.
- Chris Standaert: I mean, I'd go with less restrictive to a degree, but given the – we always have to match – we always have to explain our differences from the CMS if we have them, and frankly we didn't come up with this language. The medical directors came up with the language. We have no idea where it even came from. They just sort of picked it.
- Craig Blackmore: It comes from the national coverage decision.
- Chris Standaert: No, it doesn't. It's different than the national coverage decision. They don't mention anything about a stimuable auditory nerve.
- Chris Blackmore: Alright, I stand corrected.
- Chris Standaert: But that's not from the national coverage decision, and that's not any of the inclusion criteria in our studies, so where did we come up with that?
- Carson Odegard: The agencies did.
- Chris Standaert: The agencies did, but that's – we're not the agencies. So, I don't think we have a basis for coming up with something different. I think we can look at what CMS said and then say based on a rational discussion of this, that might be overly restrictive for the patient population, but I don't know that we can add restrictions that don't exist in the CMS thing or that we found in the literature. Does that make sense?

Craig Blackmore: I agree. If stimulable auditory nerve is not in either of those sources, then it might not be the best choice.

Michael Souter: And again, while I understand our clinical expert saying that the threshold is shifting in terms of freedom from lesions in the auditory nerve, I think we need to see data on that before we could actually justify.

Craig Blackmore: I think the choices are going with, and tell me if I'm wrong, but going with the national coverage determination, which is more restrictive, and which is at least close to what limited information we have on the inclusion criteria for the studies or going with a less restrictive model that is based on basically opportunity for technical success, and you can defend either of those. My bias would be, you know, our charge is look at the evidence and this is what we have evidence on. It's not great evidence, but I find it convincing for benefit, but I only find it convincing for benefit in the people that they study, and if there were people that were clearly excluded, I have trouble making statements about that.

Joann Elmore: I agree.

Craig Blackmore: But, that's an opinion.

Seth Schwartz: I'm not sure of this so I'll ask, but was the national coverage decision, did it include evidence for children, or was it focused on mainly adults?

Craig Blackmore: They don't give an age. Well, we don't have an age on this slide. I don't have a – you should probably go to the source.

Seth Schwartz: For [inaudible] on the ARC report, what they looked at, I think it was just adults, but can you confirm?

Teresa Rogstad: Correct.

Seth Schwartz: Yeah. So, the reports they commissioned for making their determination was adults only.

Craig Blackmore: But the evidence inclusion criteria for children we've heard, and it was you have to have a lumen.

Seth Schwartz: But that's for Medicare, not for...

- Craig Blackmore: No, but I mean for the studies that we've heard that provide evidence of effectiveness in children, the inclusion criteria for those studies, as best can be determined, were restricted to similar to this.
- Chris Standaert: So, you said the ARC report was 2011, and the coverage determination we're looking at is from 2005. Is there a new coverage determination for Medicare?
- Teresa Rogstad: No, and I couldn't find any indication on the website that it was on a Meg-Cac agenda or anything. So, I think since the ARC report didn't find anything to suggest a change in the policy...
- Chris Standaert: Although the ARC report also didn't find any justification for their inclusion criteria of hearing perception.
- Teresa Rogstad: That's true. They didn't find anything to disprove it either. So, I mean, I don't know what the reasoning was. All that I know is there no evidence that the policy is going to change.
- Craig Blackmore: The report was consonant with the inclusion criteria for the adult study you just told us. Some of them were 30% or 50%. I mean, it was somewhere in that range, but it wasn't absolute.
- Teresa Rogstad: Right. Most of the studies actually didn't express inclusion criteria in those terms.
- Jay Rubinstein: We recognize that a lot of these bilateral studies are done in countries outside of the United States where national coverage decisions or FDA criteria don't apply, but it is safe to say that if I were doing a large scale study of bilateral versus unilateral cochlear implants I would focus on people with normal anatomy and people who do not have structural anomalies of the auditory nerve either.
- Craig Blackmore: It's also safe to remember that patients with other conditions that would not meet these criteria would still be eligible for implantation potentially if they were enrolled in a study to answer those questions. So back to the sheet. We need a decision on inclusion or exclusion of basically the third bullet point of the national coverage decision on slide 10 of the AMDG presentation. So, this is what the coverage decision – the wording we have here is freedom from middle ear infection, an accessible cochlear lumen that is structurally suited to implantation, and freedom from lesions in the auditory nerve and acoustic areas of the central nervous system. So, include such criteria or not include such criteria.

- Joann Elmore: How about include something but a little bit more general?
- Craig Blackmore: What do you have in mind?
- Joann Elmore: I don't know. Anatomy suited to implantation, I mean, something basic. I mean it seems self-evident that if they've got middle ear infections they're not going to implant.
- Chris Standaert: I think that's in the contraindication to surgery, right?
- Joann Elmore: Right, one would hope.
- Chris Standaert: Again, do our inclusion – do we have exclusion criteria from the studies that mimic these, or no? I figured I would ask, because I had a feeling. The exclusion criteria of the studies, do they help us at all with structural deformities, or no?
- Teresa Rogstad: To the extent that was addressed, as an enrollment criteria, they seem to support excluding structural abnormalities, but only four of some 35 or more studies mentioned that as a criterion. So, it's a little bit hard to know whether – so most of the evidence does not have that as a criteria. It doesn't state it as a criterion. It may be that this is considered standard practice, or like Dr. Rubinstein said, if you wanted to show effect, you probably wouldn't enroll patients you suspected might not have a good outcome. So, I think probably the evidence generally applies to no structural abnormalities.
- Jay Rubinstein: As I'm thinking about it more, structural anomalies are not discrete. There is a continuum of structural anomalies of the cochlea from very mild anomalies that have no impact on outcome to very severe anomalies that have profound effects on outcome, and there are minor anomalies of the cochlea where I would include them in a study like this, and presumably some of these studies do have those patients in it, because most surgeons would look at that ear and say, well that's this particular mild anomaly, say a Mondini deformity of the cochlea, and it's not going to affect the outcome of the implant. So, it's a mixed bag. There are probably some minor anomalies in these studies.
- Joann Elmore: Which is why the national Medicare is too restrictive when they say freedom from lesions in the auditory nerve and acoustic areas. It's almost too restrictive.
- Craig Blackmore: Well, I assume they mean tumors when they say lesions.

- Chris Standaert: Well, I think they're talking about anything – so, sensorineural hearing loss, but if the sensorineural hearing loss is from a more proximal lesion in the central nervous system, it doesn't matter what you do to the cochlea. That's what they're saying. So, if you have a brainstem lesion and that's why you – then – but as he is saying, there may be some lesions in that pathway that really aren't the cause of the hearing loss. You could have a neurofibroma that isn't – or a schwannoma or some other thing that isn't structurally impairing the neurological function that one would still consider a lesion of the nervous system that isn't really a structural problem, in terms of impairing hearing. So, I guess that's where it gets tricky, and again, we have no data. I think that little phrase kind of covers it actually, because if you had a destructive lesion of some sort in the auditory nerve, that would not be an anatomy suitable to implantation, I would think.
- Craig Blackmore: We can do this. My bias would be to use the language of the national coverage determination, because I don't see any compelling reason not to. Again, whatever the committee.
- Richard Phillips: When you're talking about the national coverage decision, are you trying to apply those data to children, too, because the testing, for example, it says testing at 40%. You can't test some of these kids, can you? So, I mean really, it's almost like it doesn't apply to a portion of our population.
- Craig Blackmore: I don't know, maybe the 40%...
- Chris Standaert: That's 40% on test of open-set sentence cognition, which you can't do...
- Jay Rubinstein: Those are adult tests.
- Chris Standaert: Yeah, you can't do that in a 12-month-old.
- Craig Blackmore: That wouldn't work in a 12-month-old.
- Chris Standaert: Personally, I would say you leave out the preamble, take the other pieces, and then use the FDA labeling as a way to restrict it based on testing.
- Craig Blackmore: So, the FDA labeling has adult and pediatric conditions that might supercede this 40%, because this is adult specific, I think is what we're hearing.
- Teresa Rogstad: The FDA labeling generally describes the eligibility criteria for children in terms of no evidence of improvement in language skills, as assessed by an audiologist

or other healthcare professional, because they can't take those tests, but there does have to be an assessment that they're not making an improvement.

Craig Blackmore: There's an assessment in the trial.

Chris Standaert: So, we could leave out some preamble on the explanation that this does not necessarily apply to children, so we don't think we should have it and we'll just go with the FDA labeling.

Craig Blackmore: So, we have the last two paragraphs or bullet points here that are options, and we should choose one of those two. So, I'm going to ask for a show of hands on option one, which is simply stating anatomy suitable to implantation, and then I will ask for a show of hands for freedom from etc., etc. from the coverage decision. So, the anatomy suitable to implantation group, please give me a show of hands. And the group who would choose the national coverage language freedom from, etc. There are some abstentions, which is fine, too, but most of us favored the bottom bit, so can we please remove the anatomy suitable to implantation. Are there any others up here that deserve further discussion?

Okay, then we will press on, and I think the next step in this process is for a binding vote, so this will be for coverage or noncoverage or cover with conditions of bilateral cochlear implantation. These are the pink cards, and your choices are to vote for coverage without conditions, which is self-evident, noncoverage, which is again easy to understand, or cover with conditions and the conditions are predefined on the slide there. So, may I have votes, please?

Josh Morse: Nine cover with conditions.

Craig Blackmore: So, it is our job to determine if there is a national coverage decision and if our decision is consonant with it, and it largely is with some areas of clarity that we felt the evidence supported, and that concludes...

Josh Morse: There is also a consistency with expert guidelines to be checked, as well.

Craig Blackmore: Consistency with expert guidelines. Well, we looked at the payment decisions.

Josh Morse: They're included in the decision document.

Craig Blackmore: They are included in the decision document.

Josh Morse: Actually, it's in your decision tool discussion.

Craig Blackmore: We included discussion of the NICE and the Children's Hospital in our presentations, and we have also seen the AAOS guidelines, so I think the committee is aware of those guidelines in making this decision. That was part of the discussion, and we relied upon the best evidence from the best trials and the inclusion criteria there.

Alright, we charge staff with formulating a draft coverage decision for final approval and discussion at the next meeting, and that concludes cochlear implants.

Lunch is not here, so we will continue. Next, let's make sure our vendor is here. We can go with agency utilization and outcomes.

Seth Schwartz: Craig, since we've been doing it at the end of the meeting, you know, we've been talking about the upcoming key questions. Do you want to take a little time now and do that so we don't have to do that later, or is that?

Craig Blackmore: We have to be in the window of time here.

Seth Schwartz: I know, but that's not – isn't that separate. That's not part of the meeting.

Craig Blackmore: It's not on today's agenda. We don't have any that are at that point in development. So, we're going to continue. Are the agency – are you guys ready for the next topic? We're a little ahead of schedule, but if you're here and willing to present, we could move on with that before lunch. So, we're going to start into our second topic of the day, which is catheter ablation procedures, and in the interest of scheduling, we're going to have the agency medical directors provide their comments to us first.

Steve Hammond: My name is Steve Hammond. I'm a chief medical officer of the Department of Corrections and here to present the Agency Medical Directors Comments on catheter ablation procedures for supraventricular tachycardia.

So, a little background. Catheter ablation for supraventricular tachycardia is intended to control or cure various types of cardiac arrhythmias originating above the ventricles. It is an alternative to medication and surgical treatment. What brought this up as a suggested topic of review is some uncertainty about benefits of catheter ablation in various types of supraventricular arrhythmia. There are a number of types. The safety of the procedures was uncertain. Cost was a serious consideration. Billed charges from outpatient hospital facilities

where these procedures are performed can be quite high, exceeding \$100,000 for an outpatient procedure, and I will stop and comment.

There was a – I remember one sentinel case in which an individual was sent for a second attempt at an ablation to treat sinus tachycardia, again with very high charges, and so it was cases like this that brought the topic up for consideration. Also, catheter ablation needs to be compared to alternative management strategies, which could include medication treatment or antiarrhythmic drugs, surgical treatment, or no active treatment. So, at the time of the initial topic selection, the AMDG rated the concerns as high for efficacy and really the concern being in what conditions is this an effective treatment. Safety concerns were medium, and cost was high.

After review of the evidence report, the concerns were modified to some extent. The concern about efficacy remained high for some arrhythmias, but was less of a concern for others where there is more evidence to support efficacy or effectiveness.

So, from our point of view, we wanted to know when catheter ablation is the procedure of choice to manage different supraventricular arrhythmias. We wanted to know how management by catheter ablation compared to management with antiarrhythmic drugs or even no treatment, and in what patients catheter ablation procedures are appropriate. For example, is this appropriate for highly symptomatic patients, for patients who have failed medication treatment, and again, is it more appropriate in the setting of particular types, subtypes of supraventricular arrhythmia and tachycardia than in others. Again, we wanted evidence on the safety of these procedures and to the extent available for the cost effectiveness.

These are the current coverage policies in the four agencies participating in the review. Labor and Industries does cover this, although it is rarely required under L&I. It is covered, but prior authorization is required. PEBB-UMP, the state employee's plans, require no prior authorization and cover. Likewise, Medicaid covers without prior authorization. The Department of Corrections does require prior authorization.

So, looking at the utilization data, I will use the pointer at the screen at the front of the room, or the room near the refreshments table, the screen there. We see that for the public employees, plans over a four-year period, expenditures were \$9.7 million and for Medicaid \$2 million. We see that the average payment per procedure is substantial. It is higher for PEBB-UMP than for Medicaid, and we

also see some evidence of rising utilization, more pronounced in the Medicaid population than in the public employee's population.

Looking at the age distribution of these procedures, we see in the PEBB a concentrated, perhaps not surprisingly, in the middle-aged and elderly groups, age greater than 50, somewhat less askew towards the higher age ranges for the Medicaid population. Again, likely reflecting the age distribution in these covered populations. Slight predominance of males over females.

Now, the cost data we looked at previously were for amounts paid. This is a look at amounts allowed. In other words, sort of the negotiated price under the different plans, but this may include copays by patients, but in any case, I mention the billed charges in excess of \$100,000 by hospitals, but these are negotiated, allowed amounts here, and we see considerable variation between UMP, as the primary payer, versus for reasons I'm not really clear on, UMP Medicare allows considerably higher. We also see that the great preponderance of the charges come from facility fees, which would include equipment, also. Okay, I think that's enough for that slide.

There is no national coverage determination under Medicare for catheter ablation procedures. So, the evidence report, this is the summary from the agency perspective. For atrial fibrillation, catheter ablation, may be more efficacious than antiarrhythmic drugs in preventing recurrence of atrial fibrillation, although question remains is this in those failing antiarrhythmic drugs and is it most suitable for symptomatic patients? In the case of atrial flutter, catheter ablation does appear to be more efficacious than antiarrhythmic drugs in preventing recurrence, although the questions remain would this be after failure of attempts at cardioversion.

In a couple of subtypes of SVT, supraventricular tachycardia, the atrioventricular nodal reentry tachycardia and atrioventricular reentry tachycardia, there is some data that suggests efficacy of catheter ablation greater than antiarrhythmic drugs, but really not sufficient to determine that with confidence, I should say greater efficacy than drugs and surgery or no treatment. For Wolf-Parkinson-White syndrome, there does appear to be evidence of superior efficacy for catheter ablation treatments, again in reducing recurrence rate, and for the remaining subtypes of SVT listed here, sinus tachycardia, atrial tachycardia, focal junctional ectopic tachycardia, and nonparoxysmal junctional tachycardia, there is no evidence of efficacy specific to these types. So, in summary, the evidence best supports efficacy and symptomatic drug resistant atrial fibrillation, atrial flutter, and WPW syndrome.

There is sparse evidence to support efficacy in AVNRT and AVRT and really evidence is lacking to support efficacy for the remaining listed arrhythmias.

Safety appears to be equivalent to interventions other than catheter ablation. Cost effectiveness, there have been some studies. I would suggest, the medical director suggests, that it really can only be argued for in the setting of symptomatic drug-resistant atrial fibrillation, atrial flutter, and WPW syndrome where efficacy is reasonably well established.

So, our recommendation is that catheter ablation be covered with conditions, those being as shown here for atrial fibrillation, atrial flutter, WPW syndrome, and AVNRT, AVRT when symptomatic and resistant to drug therapy and that catheter ablation not be covered for, I'll just read them off one more time, sinus tachycardia, atrial tachycardia, focal junctional ectopic tachycardia, and nonparoxysmal junctional tachycardia. And that concludes the agency presentation.

Craig Blackmore: Thank you. Questions? Richard?

Richard Phillips: Steve, on some of your cost data, when you're doing ablations, do any of these cost data include the cost of pacemakers that are sometimes added in?

Steve Hammond: Yes, I believe so. Now, Margaret can correct me if I'm wrong, but what we tried to do was just look at all of the costs surrounding the procedure done on the day of the procedure. Is that accurate, Margaret?

Margaret Dennis: Yeah. Related by diagnosis [inaudible] for the duration of optimization or the [inaudible].

Richard Phillips: So, it's possible that over-extends the cost, because sometimes these patients are treated with pacemakers in addition to medications. So, in a sense, it may – the cost may not really reflect comparators. Does that make sense?

Steve Hammond: The cost could include a pacemaker being inserted as part of the procedure.

Richard Phillips: Yeah, and the other part was is that even if they didn't get the ablation, they might get a pacemaker anyway. That was my point. So, in other words, as a comparator, the pacemaker costs may not – may not be a comparable kind of comparison. That's all I'm getting at.

Steve Hammond: The entire cost might not be avoided if the ablation procedure...

- Richard Phillips: Yeah, that's my point. That's what I was trying to clarify.
- Steve Hammond: Okay.
- Richard Phillips: And it sounds like that might be the case.
- Margaret Dennis: I'll verify that.
- Chris Standaert: Many times I've seen patients who have been hospitalized and had a couple of ablations and a catheterization and all sorts of stuff done during one stay. So, if you add all those up, it gets very expensive, but that's not just the cost of one ablation.
- Craig Blackmore: So, I am struggling with the cost data, and I hope you can help me out. When I look at slide 6, it says that per procedure average, and this is a UMP, is somewhere on the order of \$17,000. When I look at slide 8 for UMP, it says the average is \$31,000 or \$55,000, and – just help me understand the difference here.
- Steve Hammond: Okay. That's the difference between what was paid on the previous slide versus what is allowed. So, when - an allowed cost is the negotiated cost and that can include a secondary payer or a copay.
- Craig Blackmore: So, secondary payer meaning there's another insurance company that's chipping in? I mean, I don't think the patients are chipping in \$30,000 here, but somebody is paying that, even if it's not the state. Is that fair?
- Steve Hammond: That's my understanding, and Margaret would you agree with that?
- Margaret Dennis: Right. Either Medicare or a secondary, another – they have another primary coverage.
- Craig Blackmore: Okay. Thank you.
- Steve Hammond: So, we tried to show both because we want to show what the actual financial impact on the agencies is, but we also want to talk about the more – the actual cost of the procedure.
- Craig Blackmore: No, I think that's great. I just wanted to understand it. Thank you.
- Joann Elmore: I had a few questions also. I think we're always intrigued by the cost information. It seems that you basically took the day of the procedure, but

there's a lot of cost associated with the EP testing that includes the echo and the event monitor and other things. So, those really aren't bundled into this the way you calculated it. I'm assuming that's correct, although if you took all of the costs on the day of the procedure, if they zapped things and they had to put in a pacemaker, then that would be included here.

Steve Hammond: Yes, and it's my understanding if EP testing were done on the same day of the ablation procedure, that would also be included.

Joann Elmore: Okay, and then my other two questions. Do you have any idea how many patients come back for repeat?

Steve Hammond: That's a great question, and I think we did look at that, but I – Margaret is nodding affirmatively.

Margaret Dennis: Yeah, we looked at that and we took it out of the data because it is very rare that we had repeats.

Joann Elmore: Over this couple of years?

Margaret Dennis: Yeah.

Joann Elmore: Over the four-year period, it was low numbers.

Steve Hammond: Infrequent.

Joann Elmore: Okay, and then my final question is, what percentage of these ablation cases were for AVNRT or AVRT?

Steve Hammond: I can't tell you that. I'm not sure that we broke that down. We did look at diagnosis codes. I can tell you just in general, atrial fibrillation is the most common. Atrial flutter, WPW are also fairly common, but I am actually getting beyond having the data right in front of me, so.

Richard Phillips: One other quick question. Do you have any restrictions, as to which technology can be used? As example, the cryo versus the radiofrequency ablation?

Steve Hammond: We did not suggest that. It did not look to me as if the evidence really strongly would indicate one direction or another. So, we just decided to address them as catheter ablation procedures in general, but certainly open to suggestions from the evidence or our expert.

Richard Phillips: And then the other thing was is that a lot of these procedures are done with transesophageal echos and all that, and those costs are all involved in that, too?

Steve Hammond: Again, they would be included, just all the charges for the day of the procedure, at least for the outpatient procedures.

Craig Blackmore: Any other questions? So we're – it looks like our vendor is not here yet, but our lunch is, so that makes it pretty easy. We're going to shoot for 12:15, but that assumes everybody is here. At least until 12:15, let's eat.

Craig Blackmore: I'm going to call the meeting back to order. I have, I think, 7 committee members present. So we have a quorum. We're going to rearrange the schedule a little bit. The goal is to try to keep the public comments within the pre-scheduled window in case somebody were calling in. We wouldn't want them to miss the opportunity.

So what we're going to do next is we're going to go — in just a minute we're going to go to our vendor evidence report, but first Dr. Hammond wanted to respond to some of the questions that were raised earlier during his presentation.

Steve Hammond: Thank you. Yeah. Over the break Margaret was able to pull up some of the payment data and details to address, to some degree, some of the questions Dr. Phillips was raising. This is just from the PEB data that was I think 559 cases over four years and among those she found only seven pacemaker insertions involved in what we counted as procedures on the day of the ablation. So that didn't amount to a great number and the payout for that was modest, \$2,600. And the amount allowed was also modest at \$11,000.

She was able to pull up diagnoses and among that group of patients the most common diagnosis was atrial flutter at 185. There were 176 cases of atrial fibrillation and 151 of paroxysmal atrial tachycardia, which I believe is a fairly non-specific diagnosis. And then 71 diagnoses even less specific cardiac dysrhythmia. So again atrial flutter ended up being the most common diagnosis, but very close to the number that had a diagnosis of atrial fibrillation.

Craig Blackmore: Thank you. Robin, are you presenting or who? Okay. Thank you.

Robin Hashimoto: Just give me a second. Okay. Everybody ready? So I'm Robin Hashimoto. I'm here from Spectrum Research and I'm going to present our evidence report. Okay. So the term supraventricular tachyarrhythmias encompasses a variety of diagnoses all of which lead to a rapid heart rhythm, and all of them have the

arrhythmia originating above the ventricles. So I'm going to give you a brief background on how the heart beats.

So of course you can see the upper two chambers of the atria and then the bottom two are the ventricles and the heart's electrical conduction system is what makes it beat. And it's made up of tractive modified cardiac muscle that doesn't contract but instead generates and conducts action potential through the heart. So you can see the sinoatrial node up there at the top left. And this is a group of pacemaker cells in the right atrium that spontaneously initiates the action potential and thus the contraction of the heart, and it does this at regular intervals. So the action potential spreads from the SA node across two fibers at the same time. It moves across the interatrial fiber transmitting the impulses into the left atrium and then at the same time it transmits the impulses to the atrioventricular node or AV node. The AV node then acts to slow the impulse down and that allows the atria to contract before the impulse moves into the ventricles.

And then the impulse goes ahead and moves into the ventricles through the left and right bundles of His and this causes the ventricles to contract. During and after this process the atria and ventricles repolarize and the process begins again.

Okay, so supraventricular tachyarrhythmias are caused by disorders in this electrical track system either with the initiation of the impulse or within the conduction system. And the causes and severity of the disorder vary with a number of factors including age, sex and comorbidities, and supraventricular tachyarrhythmias are characterized by their origin. The main categories of course are atrial fibrillation, atrial flutter, and supraventricular tachyarrhythmias or SVTs. And I'm going to talk about each of these briefly.

So atrial fibrillation is the diagnosis for which the bulk of the evidence was found for the report. It's the most common form of supraventricular tachyarrhythmia that accounts for about a third of hospitalizations for cardiac dysrhythmias. It has an estimated prevalence of 0.4 to 1% of people in the United States and the risk of developing AFib increases with age.

Other risk factors include male sex, obesity, smoking, diabetes and hypertension. Having AFib increases a patient's long-term risk of stroke, heart failure and all cause mortality and it can also impair a patient's quality of life. It's considered recurrent once a patient has had two episodes and it is described as paroxysmal if it self-terminates, persistent if it lasts more than seven days or permanent. So atrial fibrillation is characterized by uncoordinated atrial

activation with consequent deterioration of the atrial mechanical function. And the disorganized impulses that cause the heart to quiver very rapidly during AFib are thought to originate in the pulmonary veins.

So the report included a summary of all identified guidelines and here I've only included those guidelines for which the class of recommendation was reported. So first off the 2011 American College of Cardiology, American Heart Association, they do recommend antithrombotic therapy to prevent stroke in all patients except, of course, if it is contraindicated, and that's a Class 1 recommendation. So in general antiarrhythmic drugs are given a Class 1 recommendation. It's also recommended that patients with long standing permanent or persistent AFib be given rate-controlling drugs such as beta blockers or calcium channel antagonists to control the resting heart rate.

In patients who are refractory to at least once antiarrhythmic drug, ablation is recommended, and it was given a Class 2A recommendation.

The 2012 Heart Rhythm Society, European Heart Rhythm Association, European Cardiac Arrhythmia Society guidelines recommend ablation for symptomatic atrial fibrillation that's refractory or intolerant to at least one antiarrhythmic drug. For paroxysmal AFib, and that's a Class 1 recommendation, persistent AFib and that's a Class 2A recommendation, and then they gave a Class 2B recommendation for ablation for patients with long-standing persistent AFib. Prior to the initiation of drug therapy ablation is considered reasonable for symptomatic paroxysmal AF and that's a Class 2A recommendation. And we didn't identify any specific guidelines for cryoablation with classes of recommendation. Though NICE Guidance from 2012 does state that there is adequate evidence on the efficacy and safety of cryopulmonary vein isolation for AFib to support its use if patients have failed medical therapy.

So atrial flutter is another type of supraventricular tachyarrhythmia and it is characterized as a reentrant tachycardia where the impulse moves in a self-perpetuating loop through the atria. Symptoms include acute palpitations, fatigue and chest pain and the risk increases with age and male sex. Treatment options include antiarrhythmic drugs, cardioversion and ablation.

So many guidelines including the 2003 guideline from the ACC and AHA strongly recommend ablation for the long-term management of atrial flutter, especially when it's recurrent or doesn't respond to drugs.

They also give a Class 2A recommendation for ablation in patients with the first episode of well tolerated flutter. Antiarrhythmic drugs were given a Class 2A or B recommendation in patients with recurrent and well-tolerated flutter.

The 2003 Heart Rhythm Society guidelines give a Class 1 recommendation for ablation to be used as an initial therapy for typical flutter and then a Class 2A recommendation for patients with atypical flutter who are refractory to antiarrhythmic drugs.

So there are a number of different types of supraventricular tachycardias, and in the interest of time I'm just going to focus on the couple of types for which the most evidence was available. So the first of these is atrioventricular reentrant tachycardia or AVRT and it's characterized by the presence of an additional pathway that can conduct impulses. One type of AVRT is Wolff-Parkinson-White Syndrome, which is characterized by pre-excitation combined with tachyarrhythmias. The second type is atrioventricular nodal reentrant tachycardia or AVNRT, and this is the most common form of the SVTs and the irregular conduction leads to an almost simultaneous conduction both up the atria and down the ventricles.

So treatment options for the SVTs also include antiarrhythmic drugs and ablation and the 2003 ACC AHA guideline was the only guideline for which the class of evidence was reported. And because there were so many diagnoses within this category, I've only listed the Class 1 recommendations. So as you can see ablation was given a Class 1 recommendation for the treatment of AVNRT, Wolff-Parkinson-White Syndrome and AVNRT.

So catheter ablation is a technology of interest, of course. And it's performed in a catheterization lab. It involves guided insertion of the catheters from the arm, groin or neck into the heart. Radiofrequency energy is sent to the point in the heart that's believed to be the source of the arrhythmia and these areas vary by diagnosis and patient. Another form of ablation that's been developed more recently is cryoablation, which uses pressurized refrigerant to freeze the focal point. In either case the energy that's applied destroys or ablates very small areas of tissue and eliminates the disruption of the heart's electrical circuit. And catheter ablation may be used in conjunction with antiarrhythmic drugs and anticoagulants.

So this image just shows some catheters being used to ablate areas around the pulmonary veins, which is the primary focus target area of ablation for AFib as the pulmonary veins have been identified as the source of triggers that initiate and or perpetuate AFib.

And then various additional approaches can also be used in addition to pulmonary vein isolation, or PVI, to treat AFib. For atrial flutter the target is typically between the tricuspid annulus and the inferior vena cava, and then the target for the SVTs varies by diagnosis.

As of the writing of the report, the FDA had approved 18 radiofrequency ablation devices and 3 catheter ablation devices. Approval of these devices began in 1994.

So the most frequently used comparator in the studies we identified was antiarrhythmic drugs. And I'm not going to go over each one specifically. They are organized into classes and they have a variety of potential side effects, which may include cardiac complications. Typically if a patient is getting treated with antiarrhythmic drugs only, then it's probably going to be a long-term treatment for that patient. Surgery was reported in a handful of trials, but it's less frequently used. Cox maze surgery is an open heart surgery. It involves placing the patient on cardiopulmonary bypass and making incisional scars to block the abnormal electrical circuits.

So these are the five key questions that the report addresses. We evaluated the efficacy and effectiveness of catheter ablation, whether there was evidence of differential efficacy of different types of ablation, the efficacy of different PVI approaches to treat AFib, safety of catheter ablation, and whether there was evidence of differential efficacy or safety in subpopulations, and finally we evaluated the cost effectiveness of catheter ablation.

We included studies that enrolled adults with the various types of supraventricular tachyarrhythmias that I discussed who were treated either with catheter ablation, and for AFib we only considered studies that used pulmonary vein isolation because it's the current standard of care. Comparator treatments included medical therapy, surgery, or other strategies to control rhythm.

Outcomes of interest for efficacy and effectiveness – the primary outcomes were freedom from recurrence as well as mortality, stroke, or congestive heart failure that was not caused by the procedure. And we reported a number of secondary outcomes as well, as you can see. For safety we reported procedure-related mortality, stroke and congestive heart failure and we also reported any other complications or adverse events that were reported in the studies.

This is the result of our literature search. So you can see that for key questions 1 through 4 we started out with over 4,200 studies and after applying the inclusion/exclusion criteria from our PICO table we ended up with 88 publications to be included for key questions 1 through 4 and seven for key question 5.

So I'm going to present my results today in terms of the overall strength of evidence and so I just wanted to give you a brief background on that. We determined the overall strength of evidence for individual outcomes and this was done separately for each comparator group and for each diagnosis. And the way in which we grade the SOE is based on our application of grade and AHRQ's recommendations. So we start grading the strength of evidence for each conclusion based on the quality of the studies available. That baseline strength of evidence can then be downgraded due to the risk of bias, inconsistency, indirectness, imprecision, or publication bias. After taking all of these factors into consideration we then arrive at a final strength of evidence rating. Okay? So these are the four strength of evidence ratings that are possible. An SOE of high indicates that we have high confidence that the evidence reflects the true effects. An SOE of moderate indicates we have moderate confidence that the evidence reflects the true effect and that further research may impact the results. Strength of evidence of low indicates we have low confidence that the evidence reflects the true effect and that further research is likely to impact the results. And a strength of evidence of insufficient indicates either that the evidence does not permit a conclusion or is unavailable.

So moving into the results, again, key question 1 asks about the evidence of efficacy and effectiveness of ablation for the various supraventricular tachyarrhythmias. And for the talk I'm going to focus on summarizing the evidence for the primary outcomes when it was available and also on summarizing the highest quality of studies that were available.

So I'm going to start with radiofrequency pulmonary vein isolation compared with antiarrhythmic drugs for patients with atrial fibrillation. So the eight RCTs listed here met our inclusion criteria and they enrolled between 30 and 198 patients each. Most of the studies specified that they included symptomatic patients. The first study listed there by Wazni and colleagues evaluated PVI and antiarrhythmic drugs as first line therapies, and the mean duration of symptoms in these patients was less than half a year. The remaining studies evaluated PVI and antiarrhythmic drugs as the second line treatments and patients had been symptomatic for a range of approximately three to six years. The symptomatic status of patients wasn't clear in the Pappone study. The way that they wrote it

implied that patients were symptomatic, but it's not definitive. And then in general patients included in these studies were refractory to at least one antiarrhythmic drug, though all but one study gave patients in the antiarrhythmic drug group a drug that they had not previously tried.

So in these studies, cumulative freedom from recurrence of atrial fibrillation or atrial arrhythmia was described as the primary outcome of interest. That being said the definition of freedom from recurrence varied by study in terms of whether or not it had to be documented, symptomatic or how long it lasted, etc. And the full definitions are in the report on page 146.

So I'm going to present the results in terms, again, of the overall strength of evidence for that outcome whether results favored one treatment over the other and on the slides you'll see the effect size and the number of studies.

So there was moderate strength of evidence that there were significantly greater freedom from recurrence following PVI compared with drugs between 6 and 12 months follow-up based on data from seven RCTs of 714 patients, and a similar effect was found at 48 months based on data from 1 RCT.

So this is a meta-analysis that shows the results from freedom from recurrence that I just discussed in the short term. So the six studies that were included in the meta-analysis all employed a blanking period, which is a period of time that ranged in the studies from about one week to three months following ablation during which recurrence is not evaluated. And this is used because it does take some time for the scars to form and completely eliminate the disruptions of the electrical conduction system. So you can see that when ablation was used in these patients as a second line therapy, which is up here, that all five studies favored ablation. Basically you can see that all of the diamonds and lines are to the right of the middle line. One study used ablation as the first line therapy to treat AFib and similar results were found, and that's right here. So overall, patients randomized to PVI were nearly three times as likely to have cumulative freedom from recurrence than those patients randomized to receive antiarrhythmic drugs.

There was low strength of evidence based on data from one to two RCTs that there was no difference between treatment groups and the incidence of mortality, stroke, or congestive heart failure that wasn't related to the procedure. Unfortunately, mortality and stroke were not consistently reported for both treatment groups for the majority of the randomized controlled studies, and this did affect the overall strength of the evidence grade. Also note that because these were all rare outcomes and because there weren't very

many patients with available data that there wasn't enough power to detect a difference between treatment groups. In addition, this isn't on the slide, but one perspective and two retrospective cohort studies reported that death was less common following ablation compared with medical treatment and these results were shown to be statistically meaningful in the two studies that did statistical analysis. One of these in the prospective cohort study had over 1,100 patients and they reported that death unrelated to the procedure occurred in 6% of PVI patients compared with 14% of antiarrhythmic drug patients and that difference was statistically significant.

So we included data from one FDA summary of safety and effectiveness pivotal trial and it compared cryo pulmonary vein isolation with antiarrhythmic drugs in patients with AFib. Patients were followed for one year and we found low strength of evidence that there was greater freedom from recurrence following cryo PVI compared with drugs. There was low strength of evidence that there was no difference between treatment groups and the incidence of mortality, stroke, or congestive heart failure not attributed to the treatment.

Only one comparative study met our inclusion criteria that compared radiofrequency PVI to Cox-Maze surgery and it was a retrospective cohort study. And there was insufficient evidence regarding the outcome of freedom of recurrence in the patients who are treated with antiarrhythmic drugs and then in the absence of antiarrhythmic drugs there was low strength of evidence that patients had greater freedom from recurrence following surgery compared with ablation.

Finally, we found low strength of evidence that there was no difference in the incidence of procedure unrelated stroke between treatment groups.

For atrial flutter one RCT met our inclusion criteria. It compared radiofrequency ablation with antiarrhythmic drugs and patients were at least 70 years old and were followed for a mean of 13 months. We found moderate strength of evidence that ablation provided significantly greater freedom from recurrence when compared with drugs. And there was low strength of evidence that there was no difference in the incidence of mortality not attributed to the treatments given. Again, in reality there was not enough power to detect a difference between treatment groups for this rare outcome.

So moving into the evidence on the efficacy and effectiveness on catheter ablation for the SVTs. I'm going to start with AVNRT. Overall, four cohort studies met our inclusion criteria. One of these compared ablation to antiarrhythmic drugs; two compared ablation to open paranodal dissection

surgery, which from my understanding isn't really used anymore; and then one compared ablation to no treatment. Overall, the strength of evidence from these studies was insufficient making any conclusions uncertain.

For AVRT one small retrospective cohort study met our inclusion criteria and it compared radiofrequency ablation to antiarrhythmic drugs and to surgery in terms of symptom improvement. And again the strength of evidence was insufficient.

And so finally for key question 1 we included one RCT that compared radiofrequency ablation to no treatment for patients with Wolff- Parkinson-White Syndrome and there was moderate strength of evidence that ablation resulted in a 55% lower risk of recurrence at 24 and 48 months compared with no treatment. And there was low strength of evidence that there was no difference in the incidence of mortality between treatment groups with no treatment-related deaths reported for either group.

Key question 1A asks whether there is differential efficacy between the different types of ablation. All the studies we identified for this key question compared radiofrequency ablation to cryoablation. And we did not identify any RCTs that evaluated these different types of ablation for atrial fibrillation. So we'll go right to flutter. So for atrial flutter four RCTs met our inclusion criteria. These studies followed patients for 3 to a mean of 15 months. There was low strength of evidence based on data from three RCTs so there was no difference in freedom from recurrence between treatment groups. There was also low strength of evidence from one RCT that there was greater persistent bidirectional conduction block, which was the primary outcome for that particular study following radiofrequency ablation compared with cryoablation.

For the SVTs the only studies that we identified evaluated AVNRT. So four RCTs were identified that compared radiofrequency to cryoablation. And there was moderate strength of evidence from three of these RCTs that there were significantly greater freedom from recurrence following radiofrequency ablation compared with cryoablation at 6 to 12 months follow-up.

Key question 2 asks about whether there is evidence regarding the comparative efficacy of various approaches to radiofrequency PVI for AFib. Overall, the key question included data from 35 RCTs, but I'm going to focus on the approaches for which we had the greatest amount of evidence. So we found low strength of evidence based on data from five RCTs that wide area circumferential ablation resulted in greater freedom from recurrence than PVI alone. We found moderate strength of evidence that there was no difference in treatment from

recurrence following PVI compared with PVI plus additional left or right sided lines. And we found moderate strength of evidence based on data from six RCTs that there was greater freedom from recurrence following PVI plus complex fractionated electrograms or CFE, which involves ablation of sites thought to be critical for the perpetuation of AFib.

Key question 3 asks about the comparative safety of catheter ablation. So we evaluated the safety data from all of the comparative studies included in key question 1. And then in the report we supplemented this information with data from large case series, which I'll touch on a little bit later.

So for atrial fibrillation we found low strength of evidence from one RCT that there were no differences in the incidence of procedure-related mortality with no cases being reported from the RCTs. There was also low strength of evidence from three RCTs that there were no differences in the incidence of procedure-related stroke, which was 0.7% in the PVI group and 0.6% in the drug group. Similarly, there was low strength of evidence that there were no differences in the incidence of pericardial effusion or cardiac tamponade or pulmonary vein stenosis between treatment groups.

Data from one RCT that compared cryo pulmonary vein isolation to drugs for treatment of AFib provided low strength of evidence that there was no difference between groups in the incidence of pericardial fusion or cardiac tamponade or in the incidence of pulmonary vein stenosis. No cases of procedure-related stroke occurred following cryoablation. That data was not reported for the antiarrhythmic drug group.

For atrial flutter there was low quality evidence from one RCT that there were no differences between treatment groups and the incidence of treatment-related death with no cases of death occurring. For AVNRT there was insufficient evidence from one cohort study that suggested that there might be a higher incidence of persistent AV node block following ablation than that which occurred after open paranodal dissection surgery. And then there was no difference between groups in terms of pacemaker implantation.

Key question 4 asks whether there is any evidence of differential efficacy or safety for catheter ablation compared with other treatment groups in subpopulations. So although we evaluate all subpopulation data from the comparative studies included in key question 1, we found no evidence on the differential effectiveness of catheter ablation versus a comparator group for any subpopulation.

Finally, key question 5 asks about the cost effectiveness of catheter ablation and we only included formal economic analyses for this key question. So we identified five cost utility analyses that evaluated atrial fibrillation, none for flutter, and one for specific SVT diagnoses. So starting with AFib of the five cost utility analyses that met our inclusion criteria, three evaluated the cost effectiveness of catheter ablation compared with antiarrhythmic drugs for a five-year time horizon and then there did this evaluation for a lifetime horizon. And I'll talk about that on the next slide.

So for the five-year time horizon the populations included hypothetical cohorts with paroxysmal atrial fibrillation who are resistant to antiarrhythmic drugs. One study was conducted in the US, another in Canada, and the third was conducted by the NHS in the UK. So two studies found that the incremental cost effectiveness ratio was \$51,000 to \$59,000 per quality adjusted life year. And then one found that the ICER was \$33,000 to \$44,000 per QALY and that decreased with increasing stroke risk. We concluded that there was moderate quality evidence that PVI may be more cost effective than antiarrhythmic drugs depending on how much society is willing to pay per quality adjusted life year.

For the lifetime horizon the population was hypothetical cohorts of patients with paroxysmal or persistent AF with low to moderate risk of stroke. Again, one study was conducted in the US and the other two were done in Europe. So for the lifetime horizon the ICER ranged from \$12,000 to \$29,000 in two of the studies and then the third study reported that PVI dominated antiarrhythmic drugs meaning that PVI was both more effective and less costly. So we concluded again that there's moderate quality evidence that PVA may be more cost effective than antiarrhythmic drugs depending on how much society is willing to pay per quality adjusted life year. And in general ablation seems to be more cost effective in the lifetime horizon due to the long-term costs associated with long-term antiarrhythmic drug use.

For supraventricular tachycardias, we identified one diagnosis-specific cost utility analysis that met our inclusion criteria. The population was a hypothetical cohort of 40-year-old patients with Wolff-Parkinson-White Syndrome and it was conducted in the US. And the study found that ablation dominated drug therapy. So we concluded that there's low quality evidence that ablation may be more cost effective than antiarrhythmic drugs.

So I'm going to end the presentation by going over the findings with the strongest evidence for each of the diagnoses. So for AFib we found moderate strength of evidence that radiofrequency PVI led to greater freedom from recurrence compared with drugs in both the short and the long-term. We found

low quality evidence that cryo PVI results in greater freedom from recurrence compared with drugs in the short-term. We found low strength of evidence that patients treated with radiofrequency or cryo PVI have low rates of mortality, stroke, and congestive heart failure similar to that of antiarrhythmic drugs and that's those things related to the procedure. We found low to moderate evidence that different approaches may be superior to PVI alone though the addition of left or right sided lines had no impact on freedom from recurrence.

For safety we found low strength of evidence that there was no difference in procedure or treatment-related mortality, stroke, or other complications following PVI versus antiarrhythmic drugs. Data from cohort studies supported this conclusion and data from large case series of at least 1,000 patients each, these were prospective case series designed to evaluate adverse events, and they supported this very low incidence of complications following PVI.

For cost effectiveness we found moderate strength of evidence that PVI may be more cost effective than antiarrhythmic drugs though this, again, depends on how much society is willing to pay per quality adjusted life year. We also found that PVI was more cost effective when evaluated for a lifetime horizon because of the long-term costs associated with drug use.

For atrial flutter we found moderate strength of evidence that catheter ablation results in greater freedom from recurrence than antiarrhythmic drugs in the short term. And we found low strength of evidence that radiofrequency catheter ablation results in greater freedom from recurrence compared with cryoablation in the short term.

For safety we found low strength of evidence that there was no difference in procedure or treatment-related mortality following ablation versus drugs. And then data from prospective case series of at least 100 patients support this very low incidence of complications following ablation. We didn't identify any studies that evaluated the cost effectiveness of atrial flutter.

Moving into the SVTs we found moderate strength of evidence that catheter ablation resulted in greater freedom from recurrence in the short and long term compared with no treatment in patients with Wolff-Parkinson-White Syndrome. We also found moderate strength of evidence that ablation results in similarly low rates of procedure unrelated mortality when compared with no treatment. And we found low strength of evidence that ablation may be more cost effective than antiarrhythmic drugs.

Lastly, for AVNRT we found moderate strength of evidence that radiofrequency catheter ablation results in greater freedom from recurrence in the short term when compared with cryoablation. So I think we're going to do...

Craig Blackmore: Yeah, thank you. The schedule is a little awkward, but we're going to juggle things a little bit and I'm going to ask the committee members to hold questions at this time so we can get the public input in the window that they might have been expecting to sort of give everybody an opportunity. So thank you. We'll be right back to you. And at this point I want to open the discussion for public input.

Josh Morse: We have two public commenters. Dr. Poole? Do you have slides?

Jeanne Poole: No.

Josh Morse: Okay.

Craig Blackmore: So we ask that you introduce yourself and you tell us either — tell us who you are and if you're speaking as an individual or if you're representing a group and if you have any financial conflicts of interest, please.

Jeanne Poole: My name is Jeanne Poole. I am the director of the electrophysiology labs and service at the University of Washington. I've been an electrophysiologist since the 1980s. In terms of conflicts of interest, none in the catheter ablation space. I do with other aspects of what we do.

What I wanted to be able to do was step back and give you a little bit broader picture of these arrhythmias. I think Robin Hashimoto did a great job summarizing all of the clinical trial data that does or does not exist. I think what doesn't come out very well in such a summary is that to a large extent catheter ablation, in terms of its application to the variety of rhythms that you just heard about, parallels very much the technologic advances and discovery of using ablation as a technique to actually cure certain kinds of arrhythmias. So for instance atrial fibrillation is a rhythm that probably 70% of us will experience as we all age and it's found most often in the setting of comorbid conditions— underlying coronary artery disease, congestive heart failure, whereas the other types of rhythms that we'll refer to as the supraventricular tachycardias. They came under some acronyms that you saw, ADRT, AVNRT, those rhythms are very, very different from when we consider atrial fibrillation. Those are rhythms that we considered congenital. They occur most often in younger individuals; frequently presenting as children, teenagers, 20 year olds with heart rates that are approaching 200 beats per minute. They don't happen every day. They

don't happen even sometimes once a month. These individuals may or may not have a trigger for those arrhythmias, but without a doubt the majority of these rhythms are going to impact that young person's life in a significant way. They won't be able to play sports, they won't be able to drive if they are highly symptomatic. And so very early on in the evolution of electrophysiology as a specialty it was very clear that antiarrhythmic drug therapy for the majority of such young people was a very poor option. You can't take a young 20-year-old man and put him on a beta blocker. They become impotent and they really don't like you as a physician any longer. For young women they are going to gain weight and they also aren't going to like you very well. It just doesn't make any sense to give a young person a daily antiarrhythmic drug that has significant side effects if you can actually cure that arrhythmia. And so those rhythms were studied extensively. As soon as this technology of catheter ablation became apparent, it was just simply clearer that that was a much superior approach to these people and you could do — what we can hardly do in medicine at all and that is actually cure a potentially either life-threatening or life-significant problem. And so there's not a lot of randomized clinical evidence as you saw because that kind of arrhythmia, that kind of medical problem doesn't lend itself well to the clinical trial process. The clinical trial process when you're looking at outcomes, especially the big outcomes like mortality, require a lot of years if you're talking about a 20-year-old with an event happening once a year or twice a year. You would have had to follow those patients for 40 or 50 years and then it wouldn't make any sense anyway because by then they are going to have their other comorbid problems. So there isn't a lot of trial evidence. I think those rhythms nicely fall into an example of medicine where we do something because it simply is what works.

And then you move up from those rhythms into atrial flutter. And atrial flutter is you've got one foot in both camps if you will. Atrial flutter can be similar to the rhythms I just described in a young person where that's the only problem that person has. And again it makes sense to cure a problem because atrial flutter and the rhythms that I presented earlier are ones where you can target a specific area in the heart and go after that and cauterize or ablate that area. And so for a lot of patients with atrial flutter also that's what made sense for the same reasons versus taking an antiarrhythmic drug. There's a different group of patients with atrial flutter and then you cross over into atrial fibrillation. Now we're talking about older age individuals, underlying cardiac or pulmonary disease and the question becomes a different question than that younger group of patients. And that's where issues of overall mortality, survival, risk really lend themselves to the clinical trial process, which is why there's this wealth of data that has evolved over the last decade as we've applied the technology of catheter ablation to a very different sort of beast. Now we're not targeting just

a single little spot in the heart. You're talking about trying to isolate large areas of the left atrium and protect that patient.

Also in terms of why randomized clinical trial data is important is because these patients have coronary disease, they are going to die of heart failure, die of a heart attack, and you really do want to ask the question, "Is that little bit of higher risk that we thought might exist with catheter ablation going to outweigh the risk for the antiarrhythmic drug therapy?" And as you saw actually what's evolving through the clinical trial data is that this is a very good approach for even this older age population. With that I will wrap it up. I'm getting the signal to wrap it up and turn it over to my colleague for a few further comments. Thank you very much for your time.

Josh Morse: Thank you. Actually, we have one other scheduled commenter. Dr. Muelheims? Is he — can we unmute the phone and see if he —

Jeanne Poole: He was going to fly in today.

Josh Morse: Okay. We'll check the phone after. Dr. Viswanathan?

Mohan Viswanathan: Actually, I prepared a document, which I have sent electronically to the SHTAP as well. So this is for the committee's—

Woman: You can give it to me.

Mohan Viswanathan: Oh sure. So just in terms of introduction my name is Mohan Viswanathan. I'm an electrophysiologist at the University of Washington. I do perform catheter ablation for all these different arrhythmias. In terms of conflicts I have filled out the form. I am a site investigator for the Cabana trial, which is the first — or one of the largest outcome studies for atrial fibrillation ablation versus medications, which is an ongoing trial. So it is our goal with that trial to really ultimately get some more hard outcomes in terms of atrial fibrillation ablation.

I feel that Dr. Poole has really nicely summarized the difference in these arrhythmias and the appropriateness of use of catheter ablation for these arrhythmias. If you don't mind, I may go through some of these points here, which I feel make our point well in that — and I'll take one each at a time. So supraventricular tachyarrhythmias you've heard about the various ones — AV nodal reentrant tachycardia, AVRT Wolff-Parkinson-White Syndrome, and atrial flutter. They are abnormal arrhythmias that affect many patients of many ages, but largely seen in young individuals. Many of these individuals are unable to tolerate medications for many years given the side effect profile of the

medications as well as some of their effects, which are actually beneficial, but ultimately may result in life-threatening bradycardias meaning a slow heart rate of proarrhythmic effects such as ventricular arrhythmias. And in some cases of antiarrhythmic drugs, namely amiodarone, which is widely used, unfortunately, some non-cardiac side effects such as liver, lung and thyroid toxicities really do limit our use of that medication. So catheter ablation procedures for the supraventricular tachycardias, namely AVNRT, AVRT, WPW, and atrial flutter have become the standard of care for treatment and they, in many cases, result in about 90 to 95% success in terms of a curative treatment, which is, as Dr. Poole had mentioned, rare in any field of medicine.

Catheter ablation for atrial fibrillation has also been applied over the last 15 to 20 years and has resulted, as Ms. Hashimoto had demonstrated, a significant reduction in morbidity associated with atrial fibrillation, namely a reduction in recurrent hospitalizations due to the need for cardioversions due to the associated congestive heart failure that may be seen with atrial fibrillation and devastating stroke. The majority of patients who have received catheter ablation for any of these arrhythmias do report an improved quality of life as we've seen with the data due to freedom from arrhythmias and reduced need for antiarrhythmic drugs and any medications in the future.

Finally, there has been a significant cost savings incurred with an earlier approach involving catheter ablation for SVTs as compared to medical treatments due to the costs associated with the recurrent need for hospitalizations when medications are used, primarily due to the marginal efficacy of medications. We've observed, many times we initiate medications but they work for one or two years but ultimately patient's symptoms breakthrough medical treatments and we do have to look at these types of treatments. So due to the, as Dr. Poole has mentioned, the underlying mechanisms of the subset of supraventricular tachycardias that do affect younger individuals, namely AVNRT, AVRT, Wolff-Parkinson-White Syndrome, and partially flutter, catheter ablation has become the standard of care because of its high effectiveness in abrogating the re-entry loops so to say in the muscle of the heart that results in these arrhythmias.

And finally, catheter ablation procedures for SVTs are really associated with a minimal procedural risk in the patient on the order of 1% or less of any adverse outcomes. So this makes this type of treatment a palatable and very reasonable option for a lot of individuals to actually achieve a cure in many cases. So the take home point that I would like to leave you with is that catheter ablation for SVTs and atrial fibrillation continues to be highly effective and has become the standard of care in the majority of these supraventricular tachyarrhythmias

including atrial fibrillation in that it has little associated procedural risk. It uniformly provides the patient an improvement in quality of life and is associated, in some cases, 90 to 95% cure rate and in the case of atrial fibrillation significant morbidity benefit in terms of recurrent hospitalizations for congestive heart failure, stroke and recurrent arrhythmias. So with that I will leave you with the document and take any questions.

Craig Blackmore: We don't usually ask questions of public presenters, but would you mind just sharing with us what the Cabana trial is and what that's all about.

Mohan Viswanathan: Sure. So the Cabana trial is a multi-center NIH sponsored randomized controlled trial of individuals with some risk factors associated with atrial fibrillation. So the initial group is individuals who are 65 years of age who have paroxysmal or persistent atrial fibrillation. If you're less than the age of 65 you have to have one or more risk factors such as hypertension, prior stroke, diabetes, congestive heart failure, or an increased size of the left atrium. If you're younger you have to have some predilection to a higher rate of atrial fibrillation. So these individuals are randomized to the use of antiarrhythmic drugs or upfront catheter ablation. Some of these individuals may have already been on antiarrhythmic drugs. That's okay. And so once they get randomized they are — so you have to be prepared to undertake a catheter ablation if a patient is contemplating that. And what we're trying to find out is, there's a heart end point of mortality. There are secondary endpoints of stroke, recurrence of atrial fibrillation and one of the nice things about this trial is there's very strong and very robust monitoring of patients for recurrent atrial fibrillation with a weekly monitor that is given every so often. So it's one of the largest trials to look at a hard endpoint of mortality with antiarrhythmic drugs versus ablation.

One caveat is if antiarrhythmic drugs result in certain cases intolerable side effects or recurrent atrial fibrillation that is debilitating the patient they can be crossed over at a certain point to the ablation arm as per the physician's who are evaluating the patient.

So we are really excited. It's in the process. As of right now there's near 1,000 patients who have enrolled. The goal is about 3,000. So we're on our way, but probably in the next three to four years we should have an answer. But in the interim preliminary data has not been released. Actually, the wealth of evidence already is in favor of catheter ablation and we'll see if that is borne out in the long run.

Craig Blackmore: Thank you.

Mohan Viswanathan: All right.

Craig Blackmore: This is the public comment period of the HTCC discussion of catheter ablation. Is there anyone who called in who wishes to address the committee at this time? Okay, we'll close the public comment period and move on in the agenda and — so we'll circle back now and, you know, Robin, you don't have to get up, but I just want to take this time to return and see if there's questions of the presentation we heard from our evidence team.

Seth Schwartz: I just have one quick question about the outcome. So for the patients who have successful ablation are we to assume that they no longer required anymore medical therapy?

Robin Hashimoto: In the majority of the studies, we only have follow-up for 6 to 12 months, most of them were 12 months. Most of those trials the patients did get antiarrhythmic drugs for a period of time. I want to say 1 to 3 months and then it was discontinued. But after that, you know, we don't have evidence to answer the question.

Seth Schwartz: Okay. And the other question — I'm not sure who to ask this one to but I'm just curious about the cost difference. So how much do — because I mean presumably if this works and they don't have a recurrence and they don't need meds for the rest of their life then that's interesting. And then we have patients who are on drugs for the rest of their life. I'm curious, do we have any idea what those drugs cost like monthly, annually? Is there anyone?

Robin Hashimoto: That's not a question for me.

Seth Schwartz: Does the agency maybe have an idea?

Craig Blackmore: I have been remiss in not introducing our clinical expert. So Dr. Reddy has joined us from Oregon. Thank you for being here and if you could just take a moment to introduce yourself to the committee and also tell us if you have any conflicts of interest.

Ramakota Reddy: Yep. Hello. I'm Dr. Reddy. I'm a practicing electrophysiologist now in Eugene, Oregon. I've been practicing for about 16 years as an electrophysiologist. I don't have any conflicts of interest in the electrophysiology/catheter ablation realm. Like Dr. Poole I'm in another field in electrophysiology.

Craig Blackmore: Would you share those with us, please?

Ramakota Reddy: I do a fair amount of research using implantable devices—defibrillators, pacemakers and that sort of thing. As far as the question on the cost of medications, that's one of the questions that patients ask me all the time and I don't know exactly how to answer that in most cases. Usually I think about the cost to the patient, which is different than the cost to the whole medical care system. But some of the drugs that are used, and Ms. Hashimoto did a list of them, are trade medications that are in the range of \$300 to \$400 a month. For example Dofetilide, which is the only one that's approved for atrial flutter, is still a relatively expensive medication. Most of the antiarrhythmic medications, because they don't have a lot of patients on them tend to be expensive even when they're generic. And another set of medications that tend to cause a lot of side effects are blood pressure medicines like beta blockers or calcium channel blockers that don't work that effectively, but do have the benefit of being relatively cheap.

As far as your first question goes in terms of after an ablation if you expect people to not be on medications, that gets into which types of ablation you're doing. If you're doing an ablation for an ordinary SVT or for, in most cases, atrial flutter, we consider patients who are ablated, particularly the young patients who are ablated for WPW or for an SVT, really to be cured. I would not give them a medication. I don't even see them after a year. They say you're done, you're 21 years old, you had a small congenital problem. We fixed it. You're done. Go live a normal life. You don't have heart disease anymore. So they almost universally, if it's a successful procedure, and it is successful 95% of the time, don't have to take medications ever until they get new heart disease later on in life.

For atrial fibrillation it might be a different story. You know, atrial fibrillation it is the case that people will sometimes recur later on and they will have a period where they might be antiarrhythmic drug free, but it's managing more of a chronic problem as opposed to curing a congenital problem. So it's not - whether they'll have 20 years being drug-free is sort of an open question at this point. It does depend on what arrhythmia you are talking about.

Chris Standaert: I have a question. One issue with our follow-up in the complications and things really is the time. Twelve months is not very long when you're talking about cardiac issues; especially in 20-year-olds, much less even 60-year-olds is not very long. And so you have the whole constellation of, well, if you cure the thing then there are no problems. If you don't cure it then you might actually have higher mortality rates if you don't do it. But we don't — we don't have any studies tracking any of this. There's no data from Framingham, there's no data

somewhere else that really tracks mortality over decades for some of these issues that would help us sort through that a little bit. Again, 12 months is really almost — it's just not very helpful to tell us one way or the other for most of these conditions, frankly; especially for big things.

Robin Hashimoto: Yeah. So from the randomized controlled studies we don't have long-term data. Let me take a couple minutes and make sure that I can give you the correct answer for the cohort studies and see what case series data we had as well, so I don't answer you incorrectly.

Chris Standaert: Okay. And my other question is in the cost. When you have cost there you used the phrase hypothetical cohorts. So hypothetical cohorts mean these aren't actual data from actual people with actual numbers. These are — I mean what does hypothetical cohort mean?

Robin Hashimoto: Um, it varied by economic study. But the rates of stroke, the rates of complications, the rates of recurrence, etc. were taken from literature reviews. Some of them were just taken from RCTs.

Chris Standaert: So these aren't actual populations being studied. They are estimates of—

Robin Hashimoto: In general, yes. Yes. Unless, you know, if the information was taken—

Chris Standaert: Even the cost data then is all hypothetical too?

Robin Hashimoto: Yes, yes.

Chris Standaert: So lots and lots of assumptions in there.

Robin Hashimoto: Yes. And the assumptions are all documented in the Appendix tables.

Chris Standaert: Okay.

Michael Souter: I'm interested in that question of the longer term effect in this as well. I mean as far as I can see, the reports seem to concentrate on randomized controlled trials for the longer term outcome. But there are several national registries in existence. You made reference to some of them in your evidence tables, the Spanish registry, you do talk about the German registry there, there's an Australian registry, etc. I don't see any of that data in the report with regards to those longer term questions that you're bringing up. I'm just wondering, have I missed it?

Robin Hashimoto: So in general registries are, you know, they are going to be case series data. They provide low quality of evidence. We really limited — typically we don't even include data from case series unless we have to.

Michael Souter: But when you're talking about clinical effectiveness versus efficacy then I think that we'd be looking for registry data as opposed to—

Robin Hashimoto: I'm sorry. Can you say that again?

Michael Souter: When you're talking about clinical effectiveness as opposed to efficacy I'd be looking for registry data to contribute to that.

Craig Blackmore: She did give us safety data from the registry.

Michael Souter: Yeah, but the question that Chris asked with regards to long-term outcome from the recurrence of arrhythmia.

Craig Blackmore: I think we're waiting to see the results of the Cabana trial and others to know what the long-term outcome is.

Chris Standaert: I think I would also disagree with the statement of the registry as being low — it depends on how you're looking at them. As cause-effect data they are very low quality, but as complications and long-term efficacy and survival rates and all of that there... we don't have a better way to do it. So in terms of just disregarding registries as a useful source of information for our process I would disagree with your statement.

Woman: We generally do not disregard registries if they are comparative. With regard to the exclusion, which usually is at the level of case series because you have questions compared to what? And so there was a large volume of studies, as you saw, and so we needed to make decisions on what would be the highest quality of evidence to present to folks. We fully understand that, yes, for efficacy these are great. For effectiveness then we will need to look at the other things. And Robin is looking up some of the information for the comparative cohort studies that we do have. But that is a problem that we have across the evidence based practice evaluation field is that the case series provides some information. But in the absence of a comparator it's difficult to understand how those data are really [inaudible].

Marie Brown: What data would contribute to the clinician's confidence that this is a cure?

Ramakota Reddy: [not talking into mic]

Well, clinicians [inaudible] so for many of these arrhythmias there's a—patients are having very, very frequent problems and then after you do the procedure they have essentially none or [inaudible], so it's more of a . [inaudible] cure for and that applies to almost everything in medicine. Some of the arrhythmias that we're talking about, as in WPW, it's pretty clear what the arrhythmia is caused by. By repairing the cleft palate, you repair the cleft palate and you look at them a year later and they don't have a cleft palate because they have been cured and you can look at them 10 years later or 100 years later and they still don't have the cleft palate. You can say that it's been cured because you know what the underlying problem was and you fixed it. Some of these arrhythmias are so well defined that you cure it because you fixed what the problem is.

Atrial fibrillation is different than that, and it's not as easily well defined what the underlying problem is. So that's where we start getting into the — if you haven't studied that don't [inaudible] — aren't based on the study you do to yourself. And that ends up being how do you [inaudible]? The type of study that have already been presented like the Cabana trial [inaudible] fully randomized patients for various case series where you look at patients compared to how [inaudible]. Those studies have always, you know, take a cohort [inaudible] subjected to catheter ablation compared to a [inaudible] out in the world. You run into an enormous number of [inaudible]. It's really hard to interpret whether the patients with [inaudible] are the ones that are healthier [inaudible] better to begin with or they are the more sicker ones. [inaudible] compared to a population that's more controlled with a really [inaudible]. I have a hard time as a clinician interpreting [inaudible] study myself. Does that answer your question?

Craig Blackmore: Other questions from the committee?

Robin Hashimoto: Can I go back and answer this?

Joann Elmore: I don't think your microphones are on.

Woman: Can you hear me?

Richard Phillips: No, not very well. I can't hear anybody.

Robin Hashimoto: Okay, this is working. So to answer the question about long-term — is it long-term complications? So for case series most of the outcomes were 30 days. If they weren't 30 days the case series didn't report the length of follow-up. For the comparative cohort studies, and I'm speaking about AFib here, we don't

really have any data on mortality past about 30 months. And that's, you know, related to treatment-related stroke. And then, you know, part of the problem is that with complications if you want to say that mortality for example is related to the treatment it typically occurs, you know, within 30 days after the procedure. Otherwise it's not considered to be a complication. So that really gets into the question of efficacy or effectiveness and in that case we have — let's see here. I have far too many tabs in here.

So I mentioned in my talk some data from some cohort studies that compared PVI to antiarrhythmic drugs. And I think the follow-up for those, you know, was again relatively short. So we don't have 10-year data and this is, you know, for mortality that is not related to the treatment. There was one large, as I had mentioned, prospective cohort study that enrolled 1,170 patients and this was a Pappone study done in 2003, and the follow-up was a mean of 30 months. In that study mortality not related to the procedure was 6.5% following pulmonary vein isolation and then 14.3% following antiarrhythmic drugs plus or minus cardioversion. And that result was statistically significant. And, you know, mortality was caused by stroke, congestive heart failure, MI, sudden death, and then a variety of other causes. Does that answer the question?

Craig Blackmore: I have another question which relates to the duration of symptoms and maybe I missed this or maybe you didn't talk about it. I don't know, but did you encounter any data on the comparison? Basically on the differential effectiveness of catheter ablation immediately at the onset of symptoms versus some period of time later?

Robin Hashimoto: Right. So we would only have data for atrial fibrillation to even talk about this question. So for that one if you remember in the slides we had one study in which patients were treated with first line therapy and they had only been symptomatic for a mean of about six months. So that's the closest that we have.

Craig Blackmore: So there's no direct comparison?

Robin Hashimoto: There's no direct comparison.

Craig Blackmore: One study seemed to have similar results with immediate, which was defined as up to six months. Is that right?

Robin Hashimoto: That's the closest I can come to that. And then otherwise patients received a second line therapy and they had been symptomatic for three to six years on average. In all of those studies the results were statistically significant in favor

of ablation. So we don't have differential efficacy data per se to answer that question.

Craig Blackmore: And all of those—I mean they were randomized, but obviously they weren't blinded. There were no—

Robin Hashimoto: Right.

Craig Blackmore: But the outcomes were measured and they were presumably objective measures of—

Robin Hashimoto: The primary outcome, again, was freedom from recurrence and it's a little bit messy. It's very consistently, across the trials that we included, it was described as the primary outcome of interest. How it was defined really varied. I can't say that there was one definition. In a couple of cases the studies didn't even report how it was defined. Like how long does the occurrence last? Like how many minutes or seconds, does it have to be recorded or not?

Craig Blackmore: Symptomatic versus asymptomatic?

Robin Hashimoto: Yes, exactly.

Craig Blackmore: What the surveillance was and if it was equal surveillance in both arms?

Robin Hashimoto: Exactly. There was variance. So keep that in mind.

Chris Standaert: I have a question that may be for you, it may be for our clinical expert. So at the start of this you guys broke this down by a whole bunch of different — the SVT question is my question. You broke it down by different types of SVT. But when it came down to it you had studies on one or two of those. But looking at it — so when I think about the SVTs and our process and whether we start breaking this down by different versions of SVT we don't have a lot of data on most of them. I assume in some because the frequency is relatively low in the population. So we're not going to find them. I assume some is — the clinical diagnosis of SVT and then what type it is and what subtype it is, I assume in part can be even determined electrophysiologically. So it's not so overt. And when the state gave us data they just said SVT. They didn't break it down. So I don't even know if there are codes when you diagnose these things. I don't know if there are codes in the billing sheets for all the different types of SVT or do you just check SVT. You know? So I'm wondering about the granularity in that and whether we really have any basis for becoming granular and SVT are what we think about as a bigger thing.

Robin Hashimoto: Right. Well, one thing to consider is I had a slide with the guidelines on it. Let me see if I can just go to that. These are just the guidelines but these, from what I can tell, are the most — I went way past it — cited guidelines from the American College of Cardiology and American Heart Association and they were done in 2003. But the strongest recommendations were given for some specific diagnoses. It's not a broad, you know, all SVTs should get ablation or all SVTs should get antiarrhythmic drugs. So from my perspective at just looking at the evidence that's the only answer to your question that I have. There is not a lot of evidence from these studies. Dr. Reddy, you might want to—

Ramakota Reddy: SVT is really an unfortunate term. It's become a little bit of a wastepaper basket term. It is rare that you'll find an electrophysiologist who will talk about doing an AFib ablation as doing an ablation for SVT. You always separate out atrial fibrillation and that's a [inaudible]. And SVTs from an electrophysiologist's perspective when we're going in for an ablation generally refer to the—basically the curative type procedures, the ones that are, you know, find one location that is the cause of the SVT as a well-defined mechanism and they will find where that location is, is what that diagnosis comes from. Whether it's called WPW or AVNRT.

Chris Standaert: Do you know this before you go in?

Ramakota Reddy: Occasionally. Sometimes you'll know if someone has WPW before you go in. But sometimes—

Chris Standaert: But other times you just know they are going into ventricular tachycardia—if they go into tachycardia and you go in and—

Ramakota Reddy: Right.

Chris Standaert: Right. So it will be determined while you're in the midst of the procedure.

Ramakota Reddy: Right. But you're not going to go in anticipating doing an atrial fibrillation ablation. In that case atrial fibrillation—

Chris Standaert: No, you can sort those out.

Ramakota Reddy: An atrial flutter, as Dr. Poole pointed out, is sort of in between. When you're going in to cure atrial flutter it is generally well known what it is when you're going in. The problem is that SVT can, properly speaking, be applied to all of the method group including AFib and A flutter even though I would not refer to that

when they are all supraventricular. We think as electrophysiologists and perhaps it could be—the guidelines sort of reflect that. Atrial fibrillation is one completely separate category than all the rest of the ablations, and all the rest of the ablations, atrial flutter included, are in the sort of curative arrhythmia type of category and they are thought about differently. You know, nobody feels the need to do big studies on any of the other arrhythmias because, you know, again like I said it's like you're born with six fingers and you take one finger off you're cured of having that congenital abnormality. You don't have to look 10 years later to see if it grew back. You kind of fixed the problem and you're done. AFib is a much more chronic thing. It's more like chronic arthritis where you do want to look later on to see what you're doing, whatever it is, is effective because it's not—we're not sure how curative our procedures are going to be. So it's really AFib versus non-AFib ablations. That's really the break point and you'll find much more data on atrial fibrillation. Not because it's a better ablation, but because we don't know as much so we're studying it more. The rest of the ablations you'll find very little data and I would be surprised if you find any new data on any of the other arrhythmias because no one is interested in studying them. It's a foregone conclusion everything short of atrial fibrillation.

Chris Standaert: Right.

Ramakota Reddy: So perhaps we're not, as doctors, as careful as we should be in coding SVT. I won't code—

Chris Standaert: Are there codes for all these other things like codes for—

Ramakota Reddy: Yeah, there's a code for WPW. I don't even know if there's a code for AVNRT. I'm sure there's a new code for it.

Chris Standaert: It might not even be there.

Ramakota Reddy: Yeah.

Craig Blackmore: Joann?

Joann Elmore: I had two questions. One for the vendor and one for our clinical expert. For the vendor, actually, I want to thank you for giving the amount of detail that you did. The 300 pages report plus the 150 pages of appendices because this way we were allowed to go in and see what was in some of the studies. So thank you.

Robin Hashimoto: Yeah.

Joann Elmore: In our last review this morning we came up with a cover with conditions. One of them being, you know, whatever the FDA label was. And I just looked quickly at the FDA labels this week and it seemed like most of them were for AFib, A flutter and I didn't see them for many of these other things. And so I'm just wondering. It seems like there has been the treatment creep where we're sort of using it where it seems to be working, but it seems like it is off label and I wanted to see whether that was a correct interpretation.

Robin Hashimoto: Let me look on my computer if you want to—

Joann Elmore: In the meantime I'll ask the clinical expert. I had a hard time with your three quick slides of safety. I kind of want to know, you take a bunch of people and you put them through this procedure versus you take them and give them the drugs for a few years. Tell me, you know, what percent die, what percent have strokes, what percent, you know, have heart block. Is it 1%? 2% have heart block? And there was no mention of radiation exposure. And so I'm just wondering if our clinical expert would say a little bit about the two comparators.

Ramakota Reddy: Oh, between drugs and catheter ablation?

Joann Elmore: Uh huh.

Ramakota Reddy: Well, I can tell you what I tell my patients, which is that a catheter ablation, even for an SVT, is in fact an evasive procedure and one could expect an occasional complication. It is in the grand scheme of cardiac procedures a very low risk procedure, but it is a procedure where we're putting catheters into the heart and I quote in the range of about 1 in 500 to 1 in 1,000 chance of some important and potentially dangerous complication. And maybe a 1% chance of a minor complication something like bleeding in the groin or something that doesn't even keep you in the hospital another day, but it is something that you notice from pain or bleeding. Radiation exposure is probably something that we as physicians don't pay attention to the risk of in any of our realms, you know, whether it be imaging or any other—in terms of a lot of procedures. If the patient needs a procedure and it involves radiation we tend to go ahead and do it. But I can tell you the amount of radiation from doing an EP study is considerably lower than that from say a CT scan; an ordinary CT scan or any other—most of the radiological procedures. It's more than a chest x-ray, but it's lower than say a CT scan. So it is always a consideration that I've heard estimates on how many cancers are caused by medical radiation. So it is one of the things that causes medical radiation, but it's not a big consideration in the

decision with the exception of women who are lactating that I personally avoid doing radiation procedures on.

The radiation exposure from catheter ablation is going down because of even newer technologies, you know, fluoro-less types of procedures. So there's some sensitivity to it but it's not a reason not to do the procedure.

Now as far as drugs go most of the antiarrhythmic drugs carry a risk and some of them are very well documented risks. And again what I tell my patients is that if you take an antiarrhythmic drug you are approximately doubling your risk of having a cardiac arrest. And that's close to what the studies show. Most people don't have a very high risk of a cardiac arrest. So doubling that risk is perhaps acceptable for controlling of their arrhythmia. But it is increasing your risk. You're not making people live longer when you prescribe them an antiarrhythmic drug and there has not been really any study that shows that antiarrhythmic drugs improve mortality. They might improve symptoms, but they don't improve mortality. So there is a risk to an antiarrhythmic drug as well and over the medium term it's—the risk of both antiarrhythmic drug or an ablation are relatively low, but the curves will cross over at some point assuming you live long enough.

Chris Standaert: That's where longer term stuff would have helped us.

Robin Hashimoto: Okay, oh, this is working. Great. So first off regarding radiation exposure the reason that I didn't mention it is because we couldn't find any evidence on it. So that being said regarding the FDA approval or the indications for the various devices. So again there was, what did I say, 18 radiofrequency catheter ablation devices that are approved and 3 cryo. So they started getting approved in 1994 and if I'm remembering correctly they weren't used to treat atrial fibrillation until the year 2000 or so. Is that correct?

Ramakota Reddy: Roughly.

Robin Hashimoto: So just glancing cursor, you know, doing the cursory glance through the different FDA indications, and these are all listed in the appendix starting around page 134 or so, you know, there are so many different devices and some of them are indicated for specific diagnoses—AVNRT, flutter, AFib and it's really, you know, across the board. So I wouldn't say, you know, I can't speak for a physician and know which ones that they are using to treat which diagnosis. But there are a number of catheter systems that are approved for a variety of the different diagnoses.

- Joann Elmore: I didn't see — are any approved for like atrial tachycardia? I didn't—
- Robin Hashimoto: Yeah and we didn't really have any evidence for atrial.
- Joann Elmore: What's being used. Okay, thank you.
- Robin Hashimoto: Right. And I mean as you can see right here on the guidelines for the regular tachycardia, you know, the ACC recommends first off antiarrhythmic drugs for treatment. So we don't really have a lot of evidence on that.
- Craig Blackmore: Other questions? Richard?
- Richard Phillips: This has more to do with the long term—what are the—do you know the number in most of these studies, the number of procedures, EP studies, and/or ablation procedures that are required for the patients? Or was that ever looked at in the studies?
- Robin Hashimoto: Um, in maybe half of the studies patients underwent re-ablation. I would say two to three procedures. Just a second.
- Ramakota Reddy: I can speak to that a little bit I think. I don't have the exact number that she might be able to come up with, but for atrial fibrillation ablation, at least historically, there's been a fair percentage of repeat procedures to get a good effect and I think the preferred average is quoted in the range of 1.8 procedures per patient to get the efficacy that we're talking about for atrial fibrillation. For atrial flutter and the other SVTs, for the non-AFib arrhythmias, it is quite rare, maybe 1 in 20 or 1 in 30 people that would need a re-do procedure and that would just be because the one area that you try to ablate you didn't quite get and you have to go in at it again. So the average in that case would be something like 1.05.
- Richard Phillips: Is it fair to say that the frequency is changing as time goes by? I mean are you getting better at it?
- Ramakota Reddy: Yeah. The number of redoes—
- Richard Phillips: Assuming the number of repeat procedures in 2013 might be less than in 2008 or something?
- Ramakota Reddy: Perhaps.
- Richard Phillips: Perhaps?
-

Ramakota Reddy: For atrial fibrillation what—people live longer and, you know, we're treating someone who has had a little bit of a chronic disease. As time goes on it might start recurring again despite kind of getting rid of the triggers that you got rid of the first time and as they are continuing to be sick and having multiple comorbidities and new parts of the heart are becoming arrhythmogenic, you might do procedures that you wouldn't have done before because they were left in atrial fibrillation and you failed the first time. So sometimes as you keep people healthier you end up doing more procedures just like what we see in coronary disease. If you make people live longer they are going to have more stents put in.

So I don't know if that—to get the success that we get the number of procedures we need is lower, but the patient might end up with more procedures because we've been successful and we may need to do something on them later on for atrial fibrillation. And again this applies only to atrial fibrillation, not to the only ablations.

Richard Phillips: I have another question too and that has to do with this potpourri, this pot of SVTs. You don't really know what those diagnoses are until you do an electrophysiologic study, do you?

Ramakota Reddy: In many cases. We won't know precisely where the abnormal tissue is until you actually go and map it out. You can give a pretty good guess in many cases from the EKG of their SVT of where it is and depending on what the arrhythmia is you can be better or worse, but you won't know for sure until you actually do the—

Richard Phillips: The reason I'm asking is because I'm wondering, you're going to end up having to do electrophysiologic studies on these people anyway, are you not, in order to establish the diagnosis? The question is, are we going to cover the, you know, the ablative procedure to treat it when, you know, it seems to me if we're already covering 80% of the cost is that something we should be considering or not? Does that make sense where I'm coming from there?

Ramakota Reddy: Well, it is incredibly rare to do an EP study now for an SVT just for the purpose of precisely knowing what the diagnosis is without going through an ablation afterwards, you know, basically most of the diagnostic EP studies are done for the purpose of ablation and if you don't attempt to ablate the patient, in other words the patient says, I don't want a catheter ablation, I'd rather be treated in a different way. I'd rather be treated with medications. That's acceptable. It's okay. That's an acceptable choice on their part. It's not—they have to put up with the side effects and risks of medication, but we'll treat with medications.

In many cases you can base your decision on what medication to use without doing an EP study. So you won't need to do an EP study to make your decision on what medication to use. And if you do an EP study, it's in almost all cases with the intent of doing a curative ablation.

Seth Schwartz: Are those separated or do you do the EP study and the ablation at the same time?

Ramakota Reddy: Same time.

Robin Hashimoto: Can I answer the previous question really quick just to give you the evidence that we had? Six of the RCTs, the patients were permitted to undergo re-ablation and it was 6 to 43% of patients did undergo repeat procedures. And then—

Craig Blackmore: I'm sorry, that's for AFib or that's for—

Robin Hashimoto: AFib. This is all AFib, yeah, because that's what we have the most evidence for. And I also wanted to note that in about half of the RCTs patients were allowed to go—were allowed to cross over to the other treatment. And so in about half of those studies, patients who were randomized to receive antiarrhythmic drugs eventually did cross over and receive ablation and it was about 42% to 77% of patients in the controlled group eventually received ablation.

Craig Blackmore: So how many in the intervention group actually received the control intervention, which is antiarrhythmics?

Robin Hashimoto: It—most of the studies they received antiarrhythmic drugs as part of the treatment for a relatively brief period of time. Crossover was pretty low. I'm only seeing one study here where patients in the PVI group crossed over. It was 9% of patients, so not very many.

Seth Schwartz: Did it say what the determination was for why they crossed over? Was it progression of—

Robin Hashimoto: Recurrence.

Seth Schwartz: Recurrence? Even - failure of drug therapy and that sort of thing?

Robin Hashimoto: Yeah.

Ramakota Reddy: That's almost always why.

Robin Hashimoto: You know, and again the exact definition of why that might have occurred, you know, would vary.

Seth Schwartz: And for our expert I'm just trying to understand clinically how this goes. I mean we're talking about—in the majority of these—some of these conditions obviously like the congenital conditions there may or may not be a medication trial first, but for these AFib patients presumably most of these patients will undergo a medication trial or be treated with medication for a period of time. And it seems that a lot of those patients go for this procedure when they have failed medical therapy. And when we look at the criteria were some of them were having failed one drug. And so I'm just sort of curious how that goes. Are there a number of drugs which are effective? Is that just a point at which there's an opportunity to discuss this as an option? How does it go clinically when you're working with a patient who has atrial fibrillation?

Ramakota Reddy: By and large in my practice I think what the guidelines suggest is to try an antiarrhythmic drug to see if it gives you a good result with someone who has atrial fibrillation first. Now the intent of the Cabana trial incidentally is to see whether even that is appropriate, whether we should maybe use catheter ablation as a first line, like we do for all the rest of the arrhythmias. But failing having that data—most clinical practice is to use one antiarrhythmic drug because if an antiarrhythmic drug works for atrial fibrillation given the uncertainty of how well the ablation is going to work and that the success of ablation for AFib is not anywhere near as good as it is for the rest of the arrhythmias, drugs don't look so bad in comparison. You know, you use a drug and after—if a drug fails then you have a choice as to whether to continue on with other medications. But, you know, when one drug fails it is less likely that another drug is going to work. Most of the drugs have perhaps in the range of 60% success rate. So if one drug doesn't work you say, well we can try something else. If it's in the same category of drugs it's likely it's not going to work. You might try a different category of medication and you might get some to work. And I actually like to try two, you know, I like to try a couple medications before doing an atrial fibrillation ablation and if the medications don't work then you reach for something beyond medications to treat it. In a sense it's like treating somebody who has knee pain. You give Tylenol, might use Motrin, might use something a little bit more potent, but if that doesn't work you say, okay we're going to do a knee replacement or we're going to do a knee surgery on you. It's generally in that progress. And it is—I would consider it appropriate to have at least been on one medication before considering a catheter ablation. I think with the data right now it might be okay to do it as a first line treatment, but I think it probably is better to try a drug—a drug if it

works really well for the patient is, you know, it's cheaper and it's easier and potentially as safe as an ablation. But if a drug's not working it's likely another drug is not going to work and it is perfectly reasonable to go to an ablation then. It's also perfectly reasonable to give another drug a shot. That's sort of a clinical decision. It's made with the doctor and the patient.

Craig Blackmore: Is there a role for cardioversion in that sequence or am I outdated?

Ramakota Reddy: A cardioversion does not, you know, the whole idea of both medications and catheter ablation is to keep from going into atrial fibrillation or into the arrhythmia in the first place. Cardioversion only gets you out of the arrhythmia. So essentially 100% of people who would get cardioversion, maybe not quite 100%, but most people get cardioverted from atrial fibrillation will recur. Now whether they recur five minutes later or five days later, five months later, or five years later, you don't know, but they probably will recur because all you're doing is resetting it and the idea of the ablation or medication is to make that time longer or to make it so they don't recur. So cardioversions are involved in all of these things. It's a rare patient who is not going to need a cardioversion even as part of the ablation and certainly with the antiarrhythmic drugs they get cardioverted along the way. Cardioversion is in the spectrum of things you do just to get them out. The idea is to keep them from going in.

Seth Schwartz: And then one other question—we're lacking long-term data on efficacy for fibrillation. So in other words we don't know—we know that some patients are going to recur and they are going to require repeat treatments, and we don't know what that period of time is from the data. I'm curious if you have any clinical sense of what that time period is? If you do ablate somebody what do you tell them is the expected duration of effect of that treatment?

Ramakota Reddy: Well, I hope for as long as possible. Although I do tell people that it is much more common to make people dramatically better than it is to cure them for a decade. Most people, what they're looking for is to have a lot less atrial fibrillation. They feel lousy when they have atrial fibrillation. If they are in atrial fibrillation 50% of their life and you do an ablation and they have AFib maybe two days in a year they are dramatically better. That would be considered a failure by all these trials even though the patient is clinically dramatically better than they were before. And I try to get my patients to expect that. To, you know, expect to have an improvement, but maybe not to have complete elimination of atrial fibrillation, which makes it seem like it's more successful at the end because they are generally more satisfied with it.

But, you know, if you want to say, what would I expect as a clinician if we do an AFib ablation, what percentage of patients would I expect to have to be completely free of AFib 10 years later? It's less than half. Like I say it's a progressive disease. How many people do you expect who get knee replacement to be completely free of arthritis 10 years later? It's really—that's not really what you're necessarily shooting for. If you get it, it's great. But that's not what you're shooting for all the time.

Seth Schwartz: And part of where I'm going with this, you know, we're looking at potential costs of medications is very expensive and the cost of the intervention is expensive. But if the intervention keeps you off medications for 10 years then that—it may look better. So the other—I guess along those lines if a patient still may have a few episodes of AFib are you going to have those patients still on medication?

Ramakota Reddy: Not always. Sometimes they don't, you know, the decision whether they be on medication or not, again, is based on how much atrial fibrillation you might be having.

Man: Okay.

Marie Brown: Okay. And when you say fail medication you mean side effect—you mean intolerable side effects?

Ramakota Reddy: No. Or the medication is not working, you know, atrial fibrillation does not lend itself to treatment with medications very well. There's patients who we give them our most potent medication that we have that can cause long-term lung problems, liver problems, eye problems, a huge number of problems. Even that if you give it at high doses to people for atrial fibrillation perhaps as at best 70%. And that might even be generous in terms of how well it is in keeping people out of AFib. So medications can fail because they actually fail to do what you want them to do. They don't have any effect on...

Marie Brown: So there are lab studies showing liver disease?

Ramakota Reddy: Uh, or they start having side effects or intolerability to it. So it fails for both reasons. Most of the time they fail because they just don't work. In my experience, you know, the medications just don't control atrial fibrillation, you know, sufficiently, and that's a failure.

Craig Blackmore: Go ahead.

Carson Odegard: I have just one other question, you know, a little data on the use of cryoablation and—other than it was comparable to RF ablation. What's your experience with the cryoablation?

Ramakota Reddy: For SVTs, for the, you know, single freeze SVTs I think you don't quite damage as much tissue I think with most cryo balloons and that's part of why it might be used. You know, there's some suggestion it might be safer and that you don't get as much collateral damage so you might not cause as much other damage. But if you don't burn as much tissue you might have a lower chance of for sure getting the one that you want. And I think there's maybe a couple percent increased risk of having a recurrence say for an SVT. And a recurrence for an ordinary SVT is because you haven't completely eliminated the pathway and then can have a recurrence. It almost always happens within a few months. You know, if it's gone for six months it's gone for their lifetime. But to be incomplete is probably a little bit more common with cryo, not dramatically so. And I use both partially depending on how high up of a risk I think it is.

Carson Odegard: There's a chance of having a cryo and then come back and do an RF after that?

Ramakota Reddy: Yes, that can happen. Yes.

Carson Odegard: Okay.

Ramakota Reddy: It's not common. I usually—what I quote my patients for recurrence rate for doing an ordinary SVT ablation is perhaps in the range of 3 to 5% and that's not because it grew back, but because we didn't complete the ablation to begin with. With cryo, I'll say it's maybe like 5 to 8% or something like that. It's still better than 90% success.

Now for AFib there are a lot of different technique as Robin sort of pointed out. There are a lot of different techniques that are being used for atrial fibrillation. We're still sort of looking for the one that turns out to be the very best, which is why there are a lot of studies in that. And the cryo balloon, which is a considerably different type of cryo than the point-to-point cryo is a way to do pulmonary vein isolation differently than sort of cauterizing around the circles. That's the understanding as far as if you do an SVT ablation where you're trying to get to one area, in many cases you burn one time with a catheter about that big. You just burn one location about that much and it's gone. Maybe two or three. For atrial fibrillation you might be burning 70 or 80 areas to get those veins isolated. So it's considerably more ablation for atrial fibrillation because you're trying to isolate a vein and many of the technologies that are being developed now, cryo balloon is one of them, and there's various other

technologies are designed to kind of get those veins isolated in a more efficient manner. That's more of a technical improvement. It's not really a different nature of procedure, but it's trying to kind of find the best way to accomplish pulmonary vein isolation and a cryo balloon, you know, many would argue that it's a better way to accomplish pulmonary vein isolation than radiofrequency. Just from my own personal bias is that I prefer using a cryo balloon for achieving pulmonary vein isolation, but radio frequency is the way it's been done for the last 10 years and that is very successful too. It's a risk benefit thing ultimately and there will be studies—there will be comparative studies on those as the technology evolves.

Carson Odegard: Great. Thank you.

Craig Blackmore: So it's just about 2:00 and we're due for a break. So let's take a break. I will ask the committee to reconvene at 10 after 2:00. Thank you.

All right. We have a quorum so I will call the meeting back to session. So it's time for the committee member deliberation on where we're going with this. I'd like, again, to invite to a member or members of the committee to summarize where we are. Do I have any volunteers? Well, let me back up a little since nobody ever volunteers for anything. So I think we're probably in agreement, and tell me if this is not so, we're really dealing with basically three broad categories – we have atrial fibrillation, we have atrial flutter, and we have this package of what we're calling SVT although we know that's not a great term, but encompassing WPW and some of the others. And I propose to treat them separately and then maybe they will reconverge or maybe they won't. Does that seem—

Group: Yes.

Craig Blackmore: Okay. So why don't we start with—we can go in historical order here as I understand it and start with the WPW SVT family and now I can solicit somebody on the committee to summarize where we are in terms of that group. Kevin, can you help us?

Kevin Walsh: Well, I thought there was evidence that WPW was different than the other SVTs in terms of success or effectiveness?

Craig Blackmore: You are saying we should treat that one differently than—

Group: Yes.

Craig Blackmore: That's fine.

Kevin Walsh: You're grouping them maybe physiologically together. I'm saying there's more evidence that WPW responds than there is that SVTs respond.

Craig Blackmore: Okay.

Kevin Walsh: So I'm separating them for that reason.

Ramakota Reddy: Can I comment?

Craig Blackmore: Yes.

Ramakota Reddy: One of the things to know is that WPW, I don't think this has been brought out historically, but WPW is an EKG finding that you can see where there's a short circuit in the heart on it. EKG even from 1950 the diagnosis was easy to make on an EKG. What's going on inside the heart is that there's a short circuit and it just so happens that if you have a short circuit that you can see on the EKG then you call it WPW. What's been learned since then, afterwards, is that AVNRT and AVRT are also due to short circuits just like WPW is, but you can't really see it on an EKG. So there's more data on WPW primarily because it was the easiest one to pick up first, you know, these people coming in for EKG that shows WPW and you can actually see it very easily, do an ablation and the EKG becomes completely normal. It's fixed. When we learned—we've learned inside the heart that there was things that we sometimes actually probably incorrectly called WPW that aren't properly speaking that because they are short circuits in the heart, but they don't see it on the EKG. It's fairly obvious it's the same thing going on. So the ablation technique is essentially the same. WPW just happened to be the first one that was the—it was like the layup. It was the easiest thing to apply catheter ablation to because you could tell even without the patient coming to you whether it's successful. You can look at the EKG before, look at the EKG afterwards, and there is a dramatic difference that you knew that short circuit was gone because you could see it from before. For the other ones you have to go to their EP study. You have to go into the heart again to see if the short circuit is gone and that was done early on in really small studies and then it was obvious that the same outcome was going on with WPW so no one bothered studying it after that. They said, well, this is the same.

Kevin Walsh: Can I—

Ramakota Reddy: I think you're still—you can treat it separately, but I think that they are, from my perspective, I think of them as in the same—

- Michael Souter: Can I propose that we classify it slightly different, Craig?
- Craig Blackmore: Please.
- Michael Souter: You have atrial fibrillation, atrial flutter and then re-entrant tachycardias, which essentially encompasses, you know, what we've been doing.
- Ramakota Reddy: Absolutely correct.
- Michael Souter: And then everything else.
- Craig Blackmore: But I'm still hearing that there may be different levels of evidence for WPW specifically compared to some of the others, whatever terminology we use. Can I get you to expand on where you're going with that? You're a little more comfortable with the WPW or—
- Kevin Walsh: I thought that the evidence was more clear.
- Craig Blackmore: Okay.
- Kevin Walsh: I think the AVRT, AVNRT there's probably evidence to show benefit for those too, but it wasn't—for some reason they didn't seem exactly as impressive to me.
- Craig Blackmore: Okay. So we can accept the—we know it works so we don't study it approach or not. But at least you're suggesting that the data is a little more convincing on the WPW. So why don't we just for the present confine ourselves to those one or two groups, however we say it. I'd like to get other people's perspectives on the evidence in those areas.
- Richard Phillips: On what?
- Craig Blackmore: So this would be the WPW and the other re-entrant tachycardias, the AVNRT, etc. as a group. So we're going to address flutter and fib later. But starting with this other group.
- Michael Souter: I think you've got evidence in the basis of some, you know, of the trials that we've seen, the RCTs that there is certainly more attention being focused on WPW. I'd have a great deal of problem believing that physiologically that there would be a difference in effect between the other re-entrant tachycardias in WPW. And I think that underscores what I was saying before and I think that

there is registry data there that has not been considered in this report that I think does warrant some scrutiny. It's been shelved to the side. I would just include all re-entrant tachycardias together. There's another cohort of cardiovascular of the arrhythmias that we have—that the medical directors suggested not covering, which I'm entirely in agreement with and that's all the sinus tachys, the atrial tachys, basically anything that's a non re-entrant tachycardia. I see perfect sense in not covering that. There's no evidence to cover that particular classification. But re-entrant tachycardias it makes eminent sense to me that an ablation therapy should actually work.

Craig Blackmore: And you're saying then that—you believe the evidence for that group, the re-entrants including the WPW?

Michael Souter: I think there is evidence for that. I don't think it amasses as much as there is for WPW, but I think there is evidence for it.

Craig Blackmore: Okay. Other thoughts on re-entrant?

Chris Standaert: I sort of agree. I think the terminology gets confusing because again a lot of these things are not diagnosed until you're in there and WPW you can see. Like he said, I mean I remember this from medical school. That's classic EKG sort of findings. And the other ones, a lot of them are diagnosed in the procedure and sort of treated there. And all of them I am troubled by this idea that, you know, you sort of state, you know, oh we cure it therefore it never comes back. Well, we only have one year of data and that's where—I know fingers don't grow back, but nerves grow back. You know? I hate to say I don't know that you've cured it, but I don't know that you've cured it. Nobody proved to me that you've cured it. You followed people for a year. That doesn't prove much. So we're missing this other data. But if it exists it would have really helped me personally in understanding the long-term consequence of these things. But as a fundamental classification I have difficulty separating these things out very well—AVNRT versus WPW, AVRT because they are electrophysiologically very similar. And they sort of received a very similar treatment just one is much easier to monitor the outcome simply by EKG because of its—the location of the abnormality.

Robin Hashimoto: Can I say something just to clarify the evidence?

Chris Standaert: Yes.

Robin Hashimoto: For WPW, so we did have one RCT and it did provide 48 months follow-up and ablation was significantly better than drugs alone.

- Craig Blackmore: Which slide are you on, Robin?
- Robin Hashimoto: I am on slide 31.
- Chris Standaert: That's where the evidence for WPW as an entity is better because of that study it looks like because it can identify the patients before and actually study it more readily, I imagine.
- Robin Hashimoto: Right. So just looking at the middle column is what I'm referring to.
- Carson Odegard: But that was comparing it to no treatment.
- Robin Hashimoto: That's correct.
- Carson Odegard: See, that's the difference between the AVRT where you've got, you know, compared to the drug.
- Chris Standaert: And the other ones, unfortunately are, you know, patient reported free from symptoms over, you know, 8 to 58 months for the AVRT up there. Because they can't follow them electrophysiologically to know if it's gone short of going back into the EP lab or sticking a Holter on them forever to see if something happens, which are both relatively impractical. So you're left with patient-reported symptoms. In that one study at least ablation certainly worked well, but it's a small number and it's subjective.
- Craig Blackmore: Any other thoughts from the committee members around this group?
- Richard Phillips: I think some of the focal tachyarrhythmias congenital related – I don't think there's a lot of data provided, but the lack of data to me doesn't necessarily mean they're not—that that's an accurate depiction of what's going on. In other words we don't have data that favors them. I think it would be an error to say that there's no evidence for coverage, because it's probably curative in some of them. I think Dr. Poole mentioned that in her comments. I don't know to what degree that's the fact, but I feel very uncomfortable voting based on the lack of evidence.
- Chris Standaert: Some of our problem in this case is the alternative treatments for some of these things. I mean amiodarone is not a benign drug to stay on for twenty years. I mean these alternative treatments are not benign.

- Richard Phillips: That's another point I'd bring up. I mean I've had a lot of experience with those drugs myself in my lifetime and I have a real aversion to most of those drugs. I've had people die with them. So I don't know what the electrophysiologists think about it. I'm sure it's all they have—it's what they deal with. And I'm not sure to what degree we can apply that kind of information to making our decisions here, but it is certainly a bias I carry into making any decision. I'll say that.
- Seth Schwartz: I would also comment I think what we're hearing is that this disease is a very different disease than AFib and atrial flutter, which is a very different patient population. And when we start thinking about what are the implications for cost of a single procedure, which may be, you know, \$17,000 or \$30,000 versus a lifetime of medication could be somewhere on the order of \$4,000 to \$5,000 a year and suddenly the cost difference looks pretty strongly in favor of this even if it's marginally beneficial and yet we're seeing it is, you know, the one randomized trial we have is at least 95% beneficial. I think that's the powerful difference based on the natural history of the disease in these patients. What's harder is with the AVNRT and the AVRT is understanding how they are similar, but I think we kind of have to defer to our expert and he's telling us that they are basically the same disease. I don't know anything other than that. So it doesn't make a tremendous amount of sense to me to try to pick those apart. I think the advantages are going to be the same in that group if the treatments work the same way. I would love to see it in harder data, but I think we have at least one cohort study and that's about as good as we're going to get because the clinicians are already convinced.
- Craig Blackmore: So if we lump AVNRT, AVRT and WPW we're still left with now a fourth group, which is not specified sinus tachycardia, atrial tachycardia, focal junctional ectopic tachycardia, and nonparoxysmal junctional tachycardia. Now I've gotten to four groups.
- Chris Standaert: But can you classify them by re-entrants or non-entrant tachycardias?
- Craig Blackmore: I think that's a great question for our clinical expert.
- Ramakota Reddy: That's how we think of them. That's actually—I wish more referring doctors sort of recognized that difference.
- Craig Blackmore: So for the non-cardiologists in the crowd—
- Ramakota Reddy: Re-entrant tachycardia has excellent outcomes.

Craig Blackmore: So that would include WPW?

Ramakota Reddy: WPW, AVRT, and AVNRT. The non re-entrant atrial tachycardias, the focal types of tachycardias, we do take them to the EP lab, we do ablate them. Sometimes we find that when we're looking for something else. We think it's AVNRT and it actually turns out to be a non re-entrant atrial tachycardia, a focal tachycardia. We try to ablate it. They are harder to ablate because there isn't a short circuit. You're trying to find a tachycardia that's coming from a certain location. The problem you run into in those cases is that the patient doesn't always go into the rhythm while you're there. So you have to actually induce the arrhythmia and find it, find the focus it is coming from. So they are more difficult to ablate. Now if it's a single focus and you ablate it then it's going to be gone. But the success rate on those—I'm not pleased when they go in expecting to have AVNRT and they have a non re-entrant tachycardia because I know it's going to be a longer case. I know I have to work harder to bring it out. It's not as successful, but the rest of your thinking is about the same. You know, the drug comparison is about the same.

Craig Blackmore: So for our purposes these are physiologically different groups.

Ramakota Reddy: Right.

Craig Blackmore: So when we're looking at this, which is our job, we're asking for data on these non re-entrant arrhythmias and we're getting our evidence from our evidence vendor, that there isn't any good evidence on those categories. Is that where the committee—am I summarizing in a reasonable way for the committee?

Chris Standaert: All these studies were on AFib, aflutter or re-entrant tachycardias. So we have nothing.

Craig Blackmore: So Robin, did we attempt to look for—I mean it's one thing if it doesn't exist. That's great, as long as we looked. Thank you.

Robin Hashimoto: We looked, yes.

Craig Blackmore: Thank you, okay. So now we have four groups and we talked about lack of evidence in the non re-entrants. We've talked a bit about not necessarily all on the same page, but we've at least talked around the re-entrant tachycardias and what evidence there is. That leaves us with the AFib and aflutter, which is first? How about AFib? That's where the data is. We just have to decide if it's good data or not. Anybody want to start us off in the AFib land? Richard, you look like you're ready.

Richard Phillips: I think the data is supportive to atrial fibrillation mostly because I think the alternative is not very good. It's not a curative procedure. I mean that's the thing we've pretty much decided. It's palliative, but it's pretty damn palliative and it helps improve quality of life. I think the data's there that shows that. I think it's supportable. I think it improves the quality of life and the efficacy is there.

Craig Blackmore: Anybody want to expand?

Chris Standaert: We have eight RCTs they gave us on this and all of them have positive effects. None of them cross 0 on their little graph. They all have positive effects and you have an NNT of 2, which is about as low as I've ever seen on these things, personally.

Michael Souter: I think this is one of those rare self-evident truths. I wish we actually had that for all of our cases.

Craig Blackmore: Does anybody differ? Does the group believe that that applies to everybody or does the group believe that applies only if you've failed first line medical therapy? 7 of the 8 or 8 of the 9 clinical trials were on people who failed drug therapy and one of them wasn't. One of them was as an initial, although they were still symptomatic for up to six months.

Carson Odegard: I think that's a very complex question because you're, you know, I think the answer to your question is yes. But then I think there's also the thing that the risk profiles of the patients are very complex too. You know, you've got atrial fibrillation in a patient with decompensated congestive heart failure. It seemed like maybe it works there too. But are you going to do it on a 90-year-old with paroxysmal atrial fibrillation? I don't know. It almost has to be individualized to some degree. But in general I think that we should say—put some kind of disclaimer on it that it's only going to be done if you have failed medical therapy or failed the medications.

Chris Standaert: You either fail it or it's not appropriate to put people on them and [inaudible] look and say that the drugs are worse than—we can't do this. Those fails are inappropriate for medical therapy.

Carson Odegard: Yeah, exactly.

- Richard Phillips: That's what most of the Class 1 recommendations are anyway, aren't they in these guidelines? I don't know how they derive those recommendations anyway.
- Craig Blackmore: We don't have to follow non evidence-based guidelines.
- Group: Right.
- Craig Blackmore: Although we should discuss them and we should understand them. And there's no national coverage decision so we don't have to worry about that. Does anybody else want to expand on that? Agree or disagree?
- Joann Elmore: What wording do we want on the cover with conditions for atrial fibrillation? Symptomatic and drug-resistant is what Steve Hammond had proposed. But it seems like they are both refractory and they are intolerant or they failed. So what wording would the group like?
- Craig Blackmore: Joann wants to jump to wording.
- Joann Elmore: I want to start seeing it in front of us.
- Chris Standaert: I think symptomatic is a tricky word for AFib.
- Joann Elmore: I do too. He wrote symptomatic and drug-resistant. I'm not certain that I like either of those words.
- Chris Standaert: Drug-resistant implies you try every—it's like a drug-resistant and a bacteria or something that no drug can kill. Not just that one drug can't kill. I don't care for that word either. And I think the symptomatic is tricky because that's very vague in this population and if you see them going in and out of fib all the time this is bad whether or not they're overtly—you can clearly correlate their symptoms.
- Craig Blackmore: Have a stroke if you're not symptomatic.
- Marie Brown: It would be hard to diagnose if you didn't have symptoms.
- Seth Schwartz: Can you say something like clinically significant symptoms or something like that?
- Richard Phillips: Or it could be refractory to alternative medical therapy, too. I mean, you know, it's sort of generic.

Craig Blackmore: So since we started we'll continue. Turn to the tool, to the evidence—to the tool. Coverage and reimbursement determination analytic tool. That contains a list of clinical guidelines that exist. We also have the suggestions from the associated—from the medical directors and—which we've got some pre-populated verbiage here. And so focusing specifically on the atrial fibrillation population if we elect to go with a covered with conditions decision what might that look like? And we've got sort of sample language throughout our tool and like I said we have sample language from the medical directors. I think we've already heard that we believe there should be a trial of medical therapy, antiarrhythmic therapy, although there might be some patients in which that's not appropriate, and we also, I think, are hearing that there might be—that we want to make sure it's clinically important to atrial fibrillation, I guess, is what I'm hearing. However we definite that, whether it's symptomatic or—I don't know what.

Chris Standaert: We're not saying failed medical therapy either.

Joann Elmore: Either not tolerated or ineffective.

Craig Blackmore: Give us words here.

Joann Elmore: Drug therapy is either not tolerated or ineffective.

Chris Standaert: What did we say a second ago? We had—

Craig Blackmore: So one would be to say, well, one group says symptomatic AF refractory are intolerant to a Class 1 or Class 3 antiarrhythmic medication, except they recommend it—so that's one way of saying it. Symptomatic AF refractory or intolerant to antiarrhythmic medication. That's one choice of language. Another group said – NICE says ablation procedures may be used for atrial fibrillation when drug therapy is either not tolerated or ineffective. So that's kind of the same message. Pharmacologic therapy is insufficient or associated with side effects. That's another way of putting it. I think we are consistent with what these groups are trying to say. I like the NICE—personally, their wording ablation procedures may be used when drug therapy is either not tolerated or is ineffective. I don't know that we need to specify class of drugs because that's just beyond our charge. Did you guys get that? Drug therapy is either not tolerated or is ineffective. The Canadians on the other hand say recommended in patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm control strategy remains desired. I like that.

- Michael Souter: That does cover the [inaudible]. I like that, yeah.
- Craig Blackmore: Okay. So that's one sort of—
- Chris Standaert: Can you run the Canadian one by me again?
- Craig Blackmore: Canadian's say patients who remain symptomatic following adequate trials of antiarrhythmic drug therapy and in whom a rhythm control strategy remains desired. I don't know if we need all that. It encompasses more. So drug therapy is either not tolerated or ineffective. Are there other—
- Joann Elmore: But doesn't everyone have symptoms?
- Craig Blackmore: No.
- Chris Standaert: I don't treat a lot of this, but symptoms from atrial fibrillation. So they could have a little bit reduced exercise tolerance, they could get short of breath, they could get overtly fatigued, they could get all this sort of stuff. These are very non-specific symptoms in a—I see them all the time and I don't see atrial fibrillation ever, really. I make the diagnosis anyway. But half my patients complain of that. So they are very non-specific symptoms and so defining someone's fatigue. That's where—I assume you can do it physiologically and you can see their fatigue is better when you fix the AFib, but I assume it's tricky.
- Kevin Walsh: Isn't this a circumstance where someone will just defer to the clinician and say, symptoms related to untreated atrial fibrillation or something like that, and leave it up to the discretion of the clinician to say either their symptoms are likely from AFib or not.
- Craig Blackmore: What about paroxysmal AFib and the risk of emboli clot.
- Chris Standaert: They're not even symptomatic and you're trying to reduce the risk of the recurrence rate so that you lower the risk of embolization, again, which they don't go in often enough so they need to be on coumadin. So that's where I don't know—the symptom thing.
- Ramakota Reddy: Can I say something?
- Michael Souter: That's where the Canadian definition had some strength and that you're seeking medical control of the arrhythmia.

- Chris Standaert: But they mandate they are symptomatic. They are symptomatic and—
- Michael Souter: Yeah, but if they are symptomatic then you're usually seeking medical control.
- Craig Blackmore: But it's also implied. I mean this is a reimbursement decision. Right? So somebody's not going to say, pay me for this procedure that I didn't need to do because I didn't really want to control their rhythm. I mean it's just not—
- Ramakota Reddy: I think our guidelines will say symptomatic atrial fibrillation because it is—it's sort of recognized that one of the primary benefits of doing an atrial fibrillation ablation is that you can improve people's symptoms even if you don't completely cure the arrhythmia. And there's really precious little data that shows that in asymptomatic people anything you do to atrial fibrillation is actually hugely important in the long run. So I think that the reason the medical guidelines say that is because that is not to imply that treating asymptomatic people with atrial fibrillation is strongly indicated, you know, we don't know that. If they are symptomatic and you feel better that is worth it all by itself. So that's why the guidelines specify symptomatic atrial fibrillation because even if we do nothing else we at least make people feel better.
- Chris Standaert: How do our studies define it for the inclusion criteria? Do they define symptomatic AFib in some way? Do they just sort of say symptomatic?
- Ramakota Reddy: It's very hard to enter it into the trials.
- Craig Blackmore: Let's hear from—
- Robin Hashimoto: Most of them did specify. Most of them were for symptomatic patients.
- Chris Standaert: Is that where they just say symptomatic patients? They don't define it any other way? Because we can just leave it there and then it becomes whatever people interpret it to be.
- Robin Hashimoto: I'll need to look in the appendices to see what their specific criteria were.
- Craig Blackmore: Okay. Anything else on here for verbiage? Okay. So just in terms of procedure this document will be all inclusive. So we should have—can you guys, Margaret or Christine or somebody, who's running this?
- Christine Masters: Margaret is.

Craig Blackmore: Okay. Margaret, can I get you to have four subheadings, which you've already got in parts. So you've got them up there. So those two lines we just gave you, symptomatic and drug therapy, are going to go under atrial fibrillation. That's fine where they are. Get rid of everything else. That's fine. And then scroll up and we're going to say non re-entrant tachycardias would be non-covered, which I think is what I'm hearing from the group. So then those are the conditions under atrial fib. Do we want other conditions under the re-entrant or are we just kind of happy with having them.

Group: We're happy.

Craig Blackmore: Okay, and so that leaves atrial flutter. Are finished with atrial fib? Are we happy with where we are?

Richard Phillips: Yeah.

Robin Hashimoto: To answer the question about how the RCTs defined symptomatic was with the word symptomatic; if that's helpful.

Craig Blackmore: We can match that. That's the language that's used in the guidelines that are published. Okay. So atrial flutter. Let's get some input on atrial flutter from the committee here. What do we think? Somebody want to take a start? I'm on the wrong page. Here's the right page. So I think the most relevant information is slide 28. Right?

Richard Phillips: Uh huh.

Craig Blackmore: One RCT 104 patients. Number needed to treat of 4. Moderate quality. Follow-up of 13 months. Freedom from recurrence as an outcome.

Marie Brown: And on slide 51, they have – it's a summarizing—they summarized it as moderate overall strength of evidence.

Craig Blackmore: So what do you think of that, Marie-Annette? What do you think we should do?

Marie Brown: Match with the quality of study.

Joann Elmore: I would just have a subheading of symptomatic and leave it at that.

Craig Blackmore: So you're saying that would be in the covered group? There's enough evidence there for you as long as it is symptomatic? Does that resonate with people?

- Chris Standaert: And do you treat it medically as well? Do you just treat it like fib? That's not the same disease as fib.
- Carson Odegard: No, it's a little different.
- Joann Elmore: You go straight to ablation.
- Chris Standaert: You go straight to ablation.
- Carson Odegard: Right.
- Chris Standaert: So you just leave it with the re-entrant tachycardia as an atrial flutter you just treat when you find them.
- Carson Odegard: Right.
- Chris Standaert: Do you have non-symptomatic atrial flutter that you treat? Is there such a thing? I'm getting a nod.
- Ramakota Reddy: Occasionally.
- Craig Blackmore: I'm just looking at wording.
- Michael Souter: So the study with the 104 patients only looked at patients with one documented episode of symptomatic atrial flutter who had not received previous antiarrhythmic treatment.
- Craig Blackmore: Who had not?
- Michael Souter: Yeah.
- Craig Blackmore: So first line therapy, but they were symptomatic is what we're doing.
- Michael Souter: Right.
- Craig Blackmore: That makes sense to me. Canadian Cardiovascular Society says symptomatic. Europeans—it's hard to understand.
- Chris Standaert: Europeans are hard to understand. Is this a general statement you're making?

- Craig Blackmore: It says left atrial ablation of common atrial flutter is recommended as part of AV ablation procedure if documented prior to ablation procedure or occurring during AF ablation.
- Chris Standaert: That means they find it. Either you have it or you find it and you can treat it. It doesn't say.
- Craig Blackmore: Okay. Any other thoughts on flutter? Okay. Then I think this is looking good. What about the question of radiofrequency versus cryo?
- Chris Standaert: Can I ask one question? So aren't there re-entrant phenomenon other than those three or are they all categorized into those three? Do we put that in or take that out? Can it all be categorized?
- Joann Elmore: And I was also going to ask with WPW isn't it just first line whereas with the other two shouldn't they fail drug therapy first? So I was going to ask whether we should really be merging them together versus separate WPW out separately. Because the data looks like for WPW it's first line. You don't need to have any of these clauses of having failed AADs.
- Craig Blackmore: I was happy with those as first line. If they are really re-entrant tachycardia in younger people.
- Joann Elmore: But some of the studies they had drugs first on AVRT and AVNRT. And again we're, you know, there's no data.
- Craig Blackmore: Yes.
- Richard Phillips: I'm not sure we want to get into, maybe we do, but I'm not sure we really want to get into the cryo versus non-cryo because, you know, cryo is sort of diffuse thing. There's the balloon cryo and then there's the focal catheter cryo, you know, which have totally different applications. I realize cryo is far more expensive, you know, but if we get into—as an example if in WPW they would use cryo all the time and it might be very effective, but, you know, is it safer than, you know, ablation—radiofrequency ablation? I mean some people would say yes. In others it might make no difference and be more expensive. So it's a mish-mash, I think, of data there that we're not going to come to any conclusion. I personally just think we ought to leave it alone and let the docs decide.
- Carson Odegard: I agree.

- Craig Blackmore: We're obligated to consider it, but we're not obligated to say why.
- Richard Phillips: You said it better.
- Craig Blackmore: So we're considering it. So I guess one approach would be to say we don't think there is sufficient evidence to make a determination one way or the other and cover either one as the physician/provider thought it was appropriate.
- Carson Odegard: We do have evidence that it's quite comparable.
- Craig Blackmore: So another choice would be to say we think there is evidence.
- Chris Standaert: Our data suggests that they're comparable.
- Craig Blackmore: That's right. I misunderstood. Does anybody think we should try to parse this more or that there is a difference that we need to emphasize? Okay. All right. Let me look at the key questions and see how we're doing. Anybody have the key questions?
- Richard Phillips: Now did we agree with the non-coverage for non re-entrant tachycardias at the bottom there?
- Craig Blackmore: Well, we should talk about it. I think I would, but I'm only one person.
- Richard Phillips: I just wondered if we chatted about it. I don't know that I have any—I'm not sure I understand—when you're talking about the non re-entrant tachycardias we're not talking about anything ventricular. We're only talking about something that comes above the node. Right?
- Chris Standaert: I guess we can specify non re-entrant supraventricular tachycardia.
- Craig Blackmore: So a—
- Richard Phillips: Supraventricular.
- Chris Standaert: Yeah.
- Craig Blackmore: So our decision is limited to supraventricular tachycardias.
- Richard Phillips: That's what I want to make sure.

Craig Blackmore: We have been asked to address supraventricular so everything valve and below I guess is outside of the scope of our decision.

Richard Phillips: I agree.

Craig Blackmore: That's where our evidence summary was based on.

Richard Phillips: And that's part of what I wanted to clarify. And then the other part of that was what are the alternative treatments to non re-entrant supraventricular tachycardias are some of these same medications, are they not?

Craig Blackmore: I believe so.

Richard Phillips: Is there, you know, it seems to me that sometime you're going to fail those medications. And so what I'm saying is that there may be an indication for ablation. I don't know that. But I'm not sure that it's covered in what we have either.

Joann Elmore: I think there was no data on that.

Richard Phillips: I guess that's the thing I wanted to ask the clinical expert.

Ramakota Reddy: For ectopic atrial tachycardia is sort of a nice easy term for non re-entrant tachycardia. It's the focal area of the atria that tachycardias come from. The success rate is lower, and they are more difficult ablations and in general, I, and most electrophysiologists, sort of favor trying a drug to see if it works, but if drugs fail for that, an ablation is a fairly effective way to take care of it. If you can ablate the location it's coming from and it doesn't work, that's point number one. So, it is something that we reach for, generally second line if we know what the diagnosis is up front. The second point is that sometimes you find a non re-entrant atrial tachycardia when you're doing a study, or an SVT that is not otherwise specified. You go in and you think it's AVNRT and you find that it's an atrial tachycardia and you'll go after it, because there's a decent chance that you'll fix that and then the patient will still be better from – basically, the patient doesn't know any different. They went in for an SVT, they got treated, they don't have it again, and they are fine. So, you wouldn't want to not ablate when you're in there and find the location. If you find out that this tachycardia is not re-entrant but it is ablatable, then I will always ablate an ablatable tachycardia on somebody who is going into the EP lab for an ablation.

Craig Blackmore: So, the charge of the committee is to look at the available evidence, and we have done that, and we now have to make a decision as to whether we think

there's sufficient evidence to show that something is effective, safe, and cost effective, and therefore provide coverage for it. So I think not all of the committee members might be in the same place on that decision. I think we've had some discussion around this, and I think many of us are comfortable with stating that there isn't evidence to support this procedure in this non re-entrant arrhythmia group. I think since we're not all in the same place, it probably makes sense to have a show of hands as to whether that should be included as one of our conditions, as you will, and I think probably what we should do is go through all of these, and why don't we do that now. We'll go through all of these and make sure we have a majority for each one and then talk about whether there's others we need to add on.

Seth Schwartz: Can I just ask one question before we do that? I'm just curious why those were excluded or why there's no studies on those, and I'm wondering if there's any – I mean, do people tease them out and exclude those patients from the existing studies, or were they just lumped in all together. I mean, I'm just not sure why there's no data on this group if your perception as a clinician is that it's effective for that group, as well?

Ramakota Reddy: I can speculate in that it is a tough population to get a lot of people together on. Usually, these patients are found sort of incidentally. You do an EP study and you say, well this guy surprisingly has a crista terminalis tachycardia, and we ablated it by doing it this way, and you do it sort of a single case study thing. Sort of one of the things you find and take care of but don't gather up a lot of patients to try to do a prospective trial on. The second reason, non re-entrant SVTs kind of track more like atrial fibrillation. They're in that same category. In fact, a lot of atrial fibrillation starts from a non re-entrant atrial tachycardia. You see a burst of tachycardia and then that's what starts up atrial fibrillation.

Seth Schwartz: I guess what I'm thinking – where my mind is going with this is, if we say no coverage for that category, what does that mean? In other words, do you have a patient where you say, okay, I see this patient, you have a non re-entrant ectopic arrhythmia, we're not going to offer this to you. Or is it, you're working them up the same as an AFib patient, or whatever, and they failed their therapy so you're in the EP lab and it turns out they have an ectopic thing, we're saying – would this mean you have them in the lab and now you can't ablate that person who would have fallen under some other category?

Ramakota Reddy: As a clinician, I would want to know that myself. That would be kind of a bizarre way to practice to say that if I find something I can fix, but it's not in this category of re-entrant tachycardias, to not do the ablation. That would be...

- Chris Standaert: The trouble is in the phrase though, I can fix. On what data? I have no idea how you know you can fix it, and you use the word. I mean, I'm not going to argue with you, but from the data we have, how do you define an ablatable lesion or a lesion that can be fixed, because we don't have that.
- Joann Elmore: Any tissue that is there is ablatable, but whether there is data showing that if you ablate it, it will help the patient. We have not been shown that data from our vendor. We have not been shown any data on non – as you're lumping them as non re-entrant SVTs, or I would just say or any other and I might list a few, but we have not been shown any data that it is beneficial, and I have to say that when you look at the PEBB data for the four-year period that they showed to us at the beginning, one-third of all of the procedures are done for things like atrial tachycardia, which there was no data on.
- Craig Blackmore: I don't have a problem with somebody stopping a procedure and not doing an intervention because there's no data to support that intervention, but we might not all be on the same page.
- Marie Brown: Insurance coverage is different than whether or not they continue to do the procedure.
- Richard Phillips: I think you're right. Our charge is exactly as you say it, but there's a point at which I think the electrophysiologist in charge has a clinical judgment to make, and I hate to see us create a dictum that he has – the patient is not going to be paid for the procedure. The hospital isn't going to be paid for it, because of what we say, and it may not be good medicine.
- Carson Odegard: I think there's some value in...
- Chris Standaert: They're there to get an EP. They're in there for an EP basically. They're in there for the study in the first place and they find it in the course of the study, and then the question is, do you treat it? It's a diagnostic study they're in for to sort of see what they have. That's part of the multi-stage thing. Then there's this question do you ablate it not knowing whether you have any idea whether it's going to help somebody to ablate it or not when we don't have the data?
- Michael Souter: When we do that it turns into belief versus knowledge, and I think that we have to error on the side of where's there's knowledge. People will believe that they can do many things, but unless – our charge is to actually make sure that the money is spent doing stuff that we know will work.

- Richard Phillips: I'm not disagreeing with you there. I'm really talking about the group of people where basically medical therapy has failed where you really don't have much alternative. I think that's where I'm looking at it within this group.
- Michael Souter: There's always the possibility, I think, of fielding this back to the medical directors as a singular exception, or doing the studies.
- Craig Blackmore: And there's no point in having this committee if we say, well we'll leave it up to clinical judgment. Clinical judgment, you know, we've been doing that for 70 years. Our costs are up here, and our outcomes are down here, and I would like to believe that we're all perfect in our clinical judgment, but we're not. So, our job is to look at the evidence.
- Richard Phillips: Well, I think the other thing is, the absence of evidence does not necessarily equate to proof that we shouldn't do things. Sometimes, that's exactly the extrapolation we make when we do that. So, I think there is room for clinical evidence in some situations, and I'm not saying that I don't agree with what you're saying up there. I really do. I really do believe we should go by our charge, which is the evidence-based thing, but I think there is some – my problem is I don't feel comfortable by just marking out something where I know that we're going to be hurting some patients.
- Craig Blackmore: I don't know that we're going to be hurting them.
- Joann Elmore: We don't know that.
- Craig Blackmore: Maybe it – it may be hurting patients by pulling parts of their heart when it doesn't do them any good.
- Richard Phillips: Well, I think we've made that decision in the past where I think we've hurt some patients. Maybe you don't agree with that, but I do.
- Craig Blackmore: Well, I hope not.
- Richard Phillips: I don't make that categorically at all.
- Seth Schwartz: I'm having trouble in the same way that Richard is. I mean, I think – it seems clear to me that there is no data on this, and I have a hard time supporting something there is no data on, and I agree with all of the things you're saying. What I'm trying to get at is, a lot of times we've excluded things, it's because we feel like it wasn't studied, and it wasn't studied because for whatever reasons. Often it was just because it was sexy and new and nobody got around to it yet,

or they just thought that the one or two case series were enough data to support the intervention, so they just went off and did it. What I'm trying to figure out here is, is there actually a way to study this group? In other words, and what would that look like, because if it's something that hasn't been studied yet, and we say you can't cover it unless – and then people might be inclined to say, okay, well then we're going to try and study it and prove that it works in that population. That makes a lot of sense to me. But, if this is like an X-type of situation where there's just – there is no way to know – or there is no way to design a study for these patients, then it troubles me a little bit to exclude them. I'm not sure that's the case at all. That's what I'm trying to piece out clinically what goes on, and I think you made a valid point that if you're doing an EP study and you identify one of these tachycardias, then you could design a study that says, okay, well we found one of these separate types of tachycardias. We're going to either treat it or not treat it, and then we're going to follow up. I mean, I think if it's reasonable to design a study along that, then I think it's totally reasonable to say, yeah, we're not going to cover this now unless it's with evidence determine. I mean, not that we need to specify that, but there is an avenue to study it, whereas if there is not, I don't feel as comfortable excluding it.

Craig Blackmore: I mean, one of the things that we are constantly called on to do, which is incredibly difficult, is to decide where to draw the line. There's a therapy and it's good for something, so should we allow it to be done for everything or do we draw a line, and how do you draw the line? What level of evidence do you need to shift the line, different groups of population, etc., and I think this is one of those examples. I think we have already said, alright, we've got some data on WPW. These other things seem physiologically very similar. We can extrapolate, but now we're into another group, and again I'm just one of the committee members, but I would say that this feels very different to me. I'm not willing to make that extrapolation without some data to support it. I think it's always going to be hard to say this is where the line goes.

Craig Blackmore: Other thoughts?

Joann Elmore: And I think there are some positive implications to saying there is no evidence and to change thinking about, well, we see that it works to we have to study this to know that it works.

Craig Blackmore: We don't know.

Joann Elmore: We believe that it works.

Craig Blackmore: Other comments from the committee members? Alright, go ahead Dr. Reddy.

Ramakota Reddy: I actually echo Seth's question as to what the study would look like for a patient population like this, mostly because that's a potpourri of arrhythmias that you discover when you're doing an EP study that – the reason we, as electrophysiologists, think its effective is that you have somebody who's having a fast heart rate, highly symptomatic. You ablate where you find the arrhythmia, and their heart rate is normal again. It's normal for quite a long time afterwards and medicine doesn't work. So, I have to admit that the way that, you know, it's one of those things that seems kind of obvious but is rarely studied for a number of reasons, one of which being it's hard to gather patients.

Craig Blackmore: One of the reasons we have evidence-based medicine is because lots of things seem obvious and turn out not to be true.

Ramakota Reddy: So, what would the endpoint be of a study to treat – to look at a population like that?

Craig Blackmore: I think we're getting off the target. So, if we get back to our sheet here, and again I think to make sure we're all on the same page, we should go through each of these and have the committee members, through a show of hands, confirm or not if this is something that should stay on our list or not.

Carson Odegard: That last non re-entrant not covered for, can we say other non re-entrant supraventricular tachycardias or atrial flutter and fibrillation are non re-entrant.

Craig Blackmore: Yes. We can say other non re-entrant. That would make much more sense. So, I'm going to start at the top. Is everybody in agreement with including the re-entrant tachycardias, WPW, etc. under our coverage to cover? So, just a show of hands, do we want to cover these?

Joann Elmore: Yes.

Craig Blackmore: Okay, so I'm seeing a lot of hands, in fact, everybody. Are we in agreement with symptomatic atrial flutter without other limitations? Okay. Are we in agreement around the first limitation condition under atrial fibrillation, which is that they have to be symptomatic? Okay. Are we in agreement that we're only going to cover it if drug therapy is either not tolerated or ineffective? Okay. And are we in agreement that we will not cover the other non re-entrant supraventricular tachycardias? So, we've got nearly all or all. Okay, and then I guess the other thing we didn't say is, are we in agreement that we will include

both radiofrequency and cryo under this list and basically treat them equally?  
Okay.

Man: May I suggest the first line be an ablation procedure and then parenthetically RF or cryoablation?

Craig Blackmore: Sure. You got that, Margaret?

Margaret Dennis: No, I didn't hear it.

Craig Blackmore: Cardiac ablation procedures, open paren, radiofrequency and cryoablation, close paren. And then change the and to an or.

Now, I want to go to the key questions, which we talked about different types. We talked about efficacy and effectiveness. We talked about differential effectiveness in subpopulations. We included adults. We also included children. I guess that was another one. We limited this to adults in the key questions. Is this correct, Robin? The search was limited to adults?

Robin Hashimoto: Yes.

Craig Blackmore: Okay. So, then I would, therefore, suggest that we include adults as a condition.

Robin Hashimoto: Can I make a quick suggestion? Instead of just saying cardiac ablation, you might want to specify catheter ablation, because there are surgical ablation procedures?

Craig Blackmore: Okay.

Robin Hashimoto: Or not.

Chris Standaert: Can we say if there is supraventricular tachycardias as follows or something?

Craig Blackmore: Well, that's up at the top, supraventricular – SVTA is at the top. Okay, so we need to move the for adults. We didn't actually talk about children. So, is the SVTA adult HTCC coverage decision. It's not a condition, it's a scope. You got that Margaret?

Margaret Dennis: [Inaudible].

Craig Blackmore: Okay, that's fair. So, then for adults with SVTA. Okay, does that resonate with people? Alright, I want to turn back to the decision tool. So, we work our way

through the tool. The first thing we do is talk about the safety, effectiveness, and cost outcomes that we considered in our decision making and the staff has prepopulated this document with relevant outcomes. Under safety, we have mortality, thromboembolic events, etc. Are there other outcomes in any of these, including the special populations, that we need to add to this list? Or does this encompass the factors that we used in our decision making for any of them, safety, effectiveness, cost, radiation?

Okay, I'm going to move us to the first nonbinding vote. So, wording is always important. In this case, we will be voting with our tan cards, and the question is, is there sufficient evidence under some or all situations that the technology is effective, safe, or cost effective with comparison to basically standard medical therapy, antiarrhythmic therapy, and if you believe that it is more effective under any circumstance, you would vote more. If it were less effective under all circumstances, you would vote less. Then unproven and equivalent are self-evident. So, for effectiveness, if I could have the committee members.

Josh Morse: Nine more.

Craig Blackmore: Alright. For safety, and again to be clear, if you think that catheter ablation is safer under any circumstance you would vote more. If you believe it is less safe under all circumstances you would vote less, and then equivalent you would vote equivalent, and unproven you would vote unproven.

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

Craig Blackmore: Okay. Then cost-effectiveness, again, if you believe that under any circumstances it is more cost effective for the ablation, you would vote more. If you believe that it is always less cost effective to do the ablation, you would vote less. Then equivalent and unproven.

Josh Morse: Three more, six unproven.

Craig Blackmore: Alright, further discussion at this point from the committee? So, the next step in the process is the binding second vote or the coverage decision, and your choices are that you will vote for cover, which means it's covered under all circumstances, noncover, which means it will never be covered, and then cover with conditions, and the conditions are those that we have discussed and delineated on the board. Are we happy, or do we need? Are you okay, Joann?

Josh Morse: Nine cover with conditions.

- Craig Blackmore: So, we are, by statute supposed to determine if we are in agreement with Medicare coverage decisions, as well as expert clinical guidelines, and if not state why we might differ, and there is no national Medicare coverage decision. There are a number of society consensus possibly evidence-based guidelines, and what we have determined, based on the evidence, is similar to what is in many of these guidelines, although there are some areas where the presence or absence of evidence has caused us to differ from the wording. We also, I think, are a little more up-to-date than a number of these guidelines, some of which are five, eight, or ten years old. That concludes the meeting.
- Margaret Dennis: Wait, can I?
- Craig Blackmore: That doesn't conclude the meeting. Yes?
- Joann Elmore: For the last line, not covered for other non re-entrant supraventricular tachycardias, should we just say for other cardiac arrhythmias, because what about junctional tachycardias? I mean, does supra cover everything? I know supra covers the atrial and the sinus tachycardias, but?
- Craig Blackmore: So, our evidence vendor looked at supraventricular tachycardia. That was the...
- Joann Elmore: Oh, they didn't look at junctional or anything else?
- Chris Standaert: It's the supraventricular tachyarrhythmia. That's the scope of our study.
- Joann Elmore: Got it. Now, I understand why we worded it that way, even though there might be other – okay.
- Chris Standaert: We're not talking about arrhythmias that are not supraventricular.
- Craig Blackmore: We only look at – we only vote on – we only decide on what the evidence has provided. Okay, then we are adjourned. Thank you.