Transcript of June 14, 2001 Meeting

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HEALTH CARE FINANCING ADMINISTRATION

Medicare Coverage Advisory Committee

Executive Committee Meeting

June 14, 2001

Baltimore Convention Center

One West Pratt Street

Baltimore, Maryland

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Panelists

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Executive Secretary

Constance Conrad, R.N.

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PANEL PROCEEDINGS

(The meeting was called to order at 8:33 a.m., Thursday, June 14, 2001.)

MS. CONRAD: Good morning. Welcome, committee chairperson, members and guests. I am Constance Conrad, the executive secretary of the Executive Committee of the Medicare Coverage Advisory Committee, MCAC.

The committee is here today to act on the recommendations of the Medical Devices and Prosthetics Panel of February 21st regarding ambulatory blood pressure monitoring, to discuss the recommendations for evaluating effectiveness, to discuss the future role of the committee in light of the provisions of the Benefits Improvement and Protection Act that removes the requirement that the

Executive Committee ratify all medical specialty panel recommendation, and to discuss the contents of and framing the questions for a future presentation of neuroimaging for dementia, to be presented to the Diagnostic Imaging panel later this year.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of improprieties. The conflict

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of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. To determine if any conflict existed, the Agency reviewed all financial interests reported by committee participants. The Agency has determined that all members may participate in the matters before the committee here today.

With respect to all other participants, we ask in the interest of fairness that all persons making statement or presentations disclose any

current or previous financial involvement with any firm whose products or services they may wish to comment on. This includes direct financial investments, consulting fees and significant institutional support.

At this time I will turn the meeting over to Dr. Harold Sox.

DR. SOX: Thank you. Sean, do you want to make a few remarks before we begin?

DR. TUNIS: Only one brief remark, which is, the scheduling of the section on neuroimaging for Alzheimer's was put in the morning session to accommodate the schedule of Dr. Zarin, from AHRQ. She is going to have to leave us at 11:00 this

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morning, so we may have to fiddle with the agenda a little bit and possible move the break a little bit later in order to have the maximum amount of time with Dr. Zarin. So with folks' indulgence, we may modify the morning schedule just a little bit.

Other than that, I think we're ready to go.

DR. SOX: Before we get into the substance of the meeting I would like each member of the Executive Committee to introduce themselves, starting with you Barbara. Could you say where you're from and the like?

DR. MCNEIL: Barbara McNeil, I'm chairman of the Department of Healthcare Policy at Harvard Medical School, and a radiologist at the Brigham and Women's Hospital in Boston.

DR. MURRAY: Robert Murray. I am the technical director for Laboratory Services Forensic Health Associates.

DR. JOHNSON: Joe Johnson, chiropractor, private practice in Florida.

DR. GARBER: Alan Garber. I am a staff physician at the VA Palo Alto Healthcare System, and professor and director of the Center for Health Policy at Stanford.

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DR. HOLOHAN: Tom Holohan. I am chief of patient care services for the Veterans Health

Administration.

DR. PAPATHEOFANIS: Frank Papatheofanis. I am in the department of radiology at the University of California, San Diego.

MS. RICHNER: Randel Richner, vice president, reimbursement, Boston Scientific Corporation.

DR. DAVIS: Ron Davis. I work at the Henry Ford Health System in Detroit, where I am director of the Center for Health Promotion and Disease Prevention.

DR. FRANCIS: I'm Leslie Francis. I am professor of law and philosophy at the University of Utah.

DR. SOX: I am Hal Sox. I am currently unemployed, but I will be starting as the editor of the Annals of Internal Medicine in July.

Well, this is going to be, I think, a really nice meeting. We have a configuration that brings us all closer together physically, and I think, and we have a number of topics that are going to have some real meat to them.

Briefly, we are going to start by carrying

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out one of the what I think is a very important, I guess really statutory function, which is to give advice up front to HCFA and to the evidence based practice center that does the evidence report for a future topic for us. And it's an example, I hope, of the Executive Committee being able to get the process of evaluation off on the right track by providing advice at the beginning rather than trying to make do with the situation that might have been better if we had a chance to talk about it up front. We will spend the morning doing that.

After the lunch break, we are going to hear a report from the Medical Devices and Prosthetics panel about ambulatory blood pressure monitoring. It will be an opportunity to hear that panel's analysis of the problem, to discuss the process, and then it's one of our last acts in terms of voting approval to do so.

Finally, after the afternoon break, we

will briefly go over the major changes in the interim guidelines for evaluating effectiveness. This is a topic that we discussed at, in some length at our last meeting, and actually approved, but this is an opportunity to revisit that and in particular to give an opportunity for members of the public to comment,

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and for us to react to those comments. And then we will adjourn.

So, we start with a presentation from HCFA on PET scanning and Alzheimer's disease. And, could you introduce yourself, and go ahead.

DR. CANO: Good morning. My name is Carlos Cano. I am a medical officer with the Coverage and Analysis Group in HCFA. I am a member of the team working on the issue of PET for diagnosis and management of dementia. The purpose of my brief introduction is threefold.

First, to provide some context, to situate the request HCFA is making today to the Executive Committee to provide commentary and suggestions as to what the analytic framework, and questions that will

be pertinent for the technology assessment.

Secondly, I would briefly inform the audience and the public about the material that was submitted to the Executive Committee prior to this meeting to get the conversation started, so to speak.

And finally, I would like to preface the presentation of our next speaker, Dr. Zarin. Dr. Deborah Zarin, as many of you know, is director of the Technology Assessment Group at AHRQ, the Agency for Healthcare Research and Quality, and HCFA

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and AHRQ have been having collaborating closely in preparation for the technology assessment.

So, first, a bit of recent historic context for the request. In July of last year, a number of sponsors, primarily associated with the University of California in LA submitted a report in support of a broad request for a number of indications for PET. Among them was the use of PET in the work-up for dementia.

In November of last year, the EC after

some deliberation recommended that HCFA proceed with additional analysis on this issue before a recommendation could be made. In December of last year, we at HCFA issued a decision memorandum citing the EC recommendation, and deciding that a referral of this issue would be made to MCAC, and that was the same position memorandum when some indications for PET were covered and others that were requested were not covered.

Last month, we submitted a formal request to AHRQ for a technology assessment. Today we are consulting with you and we expect to have a systematic review prepared, including the technology assessment, for review of the Diagnostic Imaging panel in the fall.

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Just briefly to mention what material was submitted to the Executive Committee, there was the agenda for today; the HCFA tracking sheet, which as many of you know, is the document that we post on the web site and regularly update to keep the public informed of the progress of individual coverage

requests. We extracted from the reports submitted by UCLA the portion that was pertinent to the work-up of dementia and included that in the package. We provided a copy of the formal request we submitted to AHRQ, including some very preliminary questions that I will also mention in a few moments.

And finally, we added a few articles, abstracts and reviews as background on the issue. Included among them were three systematic reviews that the American Academy of Neurology recently published on the early detection, diagnosis and management of dementia. A chapter from a volume of Neurology Clinics on neuroimaging and dementia; the volume was published in November of last year. A few abstracts of ongoing clinical trials of various therapeutic agents applied to patient populations that are either at high risk of dementia, or already have mild to moderate dementia. And finally, we thought it proper to include an article cited by the

requestor on FDG-PET in dementia that shows the

relative accuracy of PET and the metabolic pattern, compared to conventional diagnostic and other neuroimaging techniques.

When we were trying to put together a formal request to AHRQ, we thought about some questions that an informed layperson or a concerned clinician might initially pose. Is PET better as a diagnostic tool than the currently utilized clinical and neuroimaging techniques? If so, if PET is able to detect Alzheimer's disease earlier, what impact would that have on clinical management? And we included in those considerations the possibility that early false positive might create a potential harm and we would like to look into that. And finally, is there any direct evidence or indirect evidence through these various linkages that use of PET in fact results in lesser morbidity or mortality, or affects other appropriate outcome measures.

So, based on these very preliminary questions, we passed the ball to AHRQ so to speak, and Dr. Zarin developed and will be presenting an analytic framework that also includes the guidelines

for evaluating diagnostic services that the EC has been working on, and because there are a number of

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gaps in the data on this matter, she will also be including some concepts regarding decision modeling.

So, I am looking forward to Dr. Zarin's presentation, and this completes my brief introduction, and I will be glad to answer questions, if there are any.

DR. SOX: Any questions for Dr. Cano?

DR. TUNIS: I just wanted to sort of highlight for the Executive Committee that what we're really interested here in is, we're sort of proposing almost as a strawman, if you will, set of questions and framework and an approach for dealing with this question of PET for Alzheimer's disease, and what we're really looking for is direction from you not just on the sort of content of the analytical framework that Deborah is going to present, but really more strategically in your role as giving HCFA advice on coverage, that this, there's some sort of

new avenues that are being explored here and haven't really been done to a great degree before.

One is, one key question is to what extent you would be advising us to focus more on the technical performance characteristics in relation to the potentially early diagnosis of Alzheimer's, but how much emphasis in addition to that, obviously, to

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give to the issues of effectiveness of therapy and impact on outcomes, and how strong the evidence needs to be in those areas. So that's, you know, one question that we will need to spend some time talking about, and obviously you have addressed it to some extent in your framework, but I think in the area of Alzheimer's it kind of raises to an extremely important level in terms of ultimately a coverage policy related to this, and I will come right back to you.

And then the second thing is, we have decided here to propose not just looking at the question, the narrow question of the use of PET for Alzheimer's disease, but potentially broadening the

question to neuroimaging for dementia, and looking at the competing technologies as well as PET, and that will be functional MRI, potentially CT, and will probably, and Deborah will get into this in detail, be including in the systematic reviews a formal look at the technical performance and clinical utility of those competing technologies in the context of PET.

And I really just needed to highlight that neither of those decisions has been -- we are sort of looking for direction from you all on both of these key issues, if not others that you identify. I'm

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sorry, Randel, go ahead.

MS. RICHNER: I know that this is all a new process and we are all learning along the way, but I'm very curious as to why you sent this to the Executive Committee and not to the Diagnostics, or that panel. If we're going to follow our operations guidelines, this doesn't flow with what we've written here, so I want to know why this was done this way. And what, why did you choose AHRQ for the technology

assessment, versus other assessment groups, that's another question.

Another question is why, I mean, one of the things that we have written in that operations, was that questions would be formed, which is what we're doing here, but I thought that the Diagnostics panel was supposed to do that, number one. And number two, those questions then would be posted on the web for input.

I mean, there is a lot of things we have written in here that don't flow with what we're doing here, so I just want to know why we're doing it differently.

DR. TUNIS: Well, I can make some comments and maybe Hal would as well, but a couple things. One is, we're in this kind of post-BIPA but

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preimplementation of BIPA transitional phase, where the role of the Executive Committee is actually evolving from its ratification function to a broader function of giving more general policy direction around coverage to HCFA.

And remember, if you were at our blizzard shortened meeting where we talked a little bit about some of the potential future roles of the Executive Committee, but actually this topic specifically of neuroimaging and dementia came up there, and I thought we had, my recollection is that we had asked the question of whether the Executive Committee would feel it to be an appropriate role to give some general direction on how to approach this.

I think that there is, in my view, there is sort of a division between the general level conversation about what we will have as the strategy for approaching this issue at the Executive Committee level than will happen at the level of the Diagnostic Imaging panel, which will ultimately have to focus down on the specific questions to be asked and take the input of the Executive Committee into account when they decide exactly how they want to frame this issue to discuss it as a panel.

MS. RICHNER: So this is sort of a -- this

will be different than what we're normally going to be doing then is what you're saying, that this neuro process that we're going through here is maybe different than what you're going to ask normally for the Executive Committee to do?

I'm just trying to figure out -- I mean, if this is a better process, then maybe we should revise our operations. That's all I'm saying. I mean, this may be what we want to do, in which case we need to look again at what we've written. So -- I mean, I know that these weren't ratified and that they are draft and that we're all working on these and thinking about what's the best way, so I'm just suggesting that we need to think about if --

You know, I was surprised that we were going to be doing this today, and so I informed the PET people that we're going to have this discussion about forming the questions today, and so I had a discussion with them yesterday about this, I mean, so how are we going to make this work?

DR. TUNIS: Actually, this was on the agenda. They had been alerted, and we had actually

called them several weeks ago, so they knew about this. Did you want to say something Alan?

DR. GARBER: Well, whether or not HCFA

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intends it to be the routine way of operations, I just want to address one of your questions, Randel, about consistency with the interim guidelines, which actually this group has already ratified. It was only a redrafting that's being presented today.

It's my view, and I have looked at these fairly recently, there's no contradiction between the procedure that HCFA is following today and what's in those interim guidelines, and I think Sean was getting at this. Certainly the panel chair and members of the panels need to refine the question that's posed to them and provide input before the panel meeting. But there is nothing inconsistent with using the Executive Committee to help frame broad questions.

And in this particular instance, the issues are not just about PET, they are refining our

thinking about how to evaluate diagnostic tests, and some of these issues I think will come up on other panels beside the Diagnostic Imaging panel. So I at least personally feel that not only is this consistent with what's in the interim guidelines document, but this is one of the most useful activities of the Executive Committee, because this is a set of methodological issues that spans multiple

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panels.

MS. RICHNER: That's fine, but I don't see it being totally consistent, but that's okay. I mean, there is still a -- you know, I'm a very process oriented person, I work in business, and I look at how things are done in a timely fashion and that kind of thing, and if I looked at how we did this, and looked at how we wrote this, they don't match, but that's okay. So we just need to make sure that you know, we want to do, we're doing the right thing, and that we agree with what the process is, and I think this is fine.

We're, you know, posing these questions to

the Executive Committee, it's a good idea, but there needs to be a process so that the public has a chance to input along the way. And I also don't know how you chose AHRQ as the TEC assessment group.

DR. TUNIS: Actually, we are virtually a hundred percent of the time working with AHRQ as our sort of source of analytical expertise to identify a center to do the technology center. AHRQ will not be doing the technology assessment, they are going to be identifying one or more EPCs to work on the technology assessment. What we've asked AHRQ to do is to try to present a kind of a dummy, no offense to

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Deborah, I mean one version of an analytic framework that might be used for purposes of discussion and nothing else.

DR. SOX: I have a couple comments in response to your point, Randel. The first is that I believe we ought to change our interim guidelines so that we explicitly write the role of the EC into it, and possibly we could do that this afternoon, since

it's really a pretty minor procedural change.

The other point which we may want to argue if we get around to discussing the role of the EC this afternoon, our last agenda item, is the role of the Executive Committee in trying to keep this whole process at the same standard of rigor and depth across different panels. I think that one of the important functions of the EC is to set standards for the performance of the panels, to discuss how the panels perform as a way of learning from that experience in building a body of case law, and for us to have input at the beginning. The panels ought to take our input seriously and if they think we're off, they ought to be able to explain pretty clearly why they went in a different direction.

So I think it's part of, if you like, sort of the quality control function of the Executive

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Committee.

Any other comments before we move on? In that case, Deb.

DR. ZARIN: Thanks. Let me just start

here and clarify that AHRQ will be working with one of our EPCs on this topic, and our role essentially is to make sure that the EPC, that the report that you get at the end is the report that you will find useful in helping you to make your assessments, so that we essentially at AHRQ will function as the liaison to make sure that the EPC report meets your needs. And that's why we're eager to be here today to lay out and sort of use you as a sounding board. A dummy proposal isn't a bad way of saying it.

Let me just go over, and Sean alluded to this, that we were asked to provide an assessment of the use of PET and/or other neuroimaging tests, and that is one of the questions to ask today, in the management of patients with suspected AD, and I'll use that term for Alzheimer's disease, or other dementias of old age.

The time line is that it's supposed to be considered by the MCAC panel in November of 2001, which really gives us four months, and given that time line, I will ask you all to consider carefully

the sort of scope of the problem, because four months isn't that long. Okay.

I'm going to go over briefly some background on the diagnosis and treatment of dementia to make sure that we are all on roughly the same page there, the potential uses of PET, the MCAC criteria for evaluating diagnostic tests, a proposed model, and some issues for the MCAC to consider.

Again, let me just lay out some caveats that what I'm going to present in terms of background is not based on systematic review, it's based on the Academy of Neurology documents, and it's meant to just provide you with background so that you can listen to the proposed model. And all of this is in the sort of order of very broad stroke kind of proposal, because I would like to get your reaction to sort of a broad concept of the model as opposed to any details. Okay.

The Diagnostic and Statistical Manual definition of dementia is impairment in short and long-term memory, impairment in abstract thinking and

judgment, frequently other disturbances of higher cortical functioning and sometimes personality change. For differential diagnosis, and this is where it immediately gets complicated, because the

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proposed uses of PET cover many different patient populations.

One of the populations is what I call subsyndromal symptoms, or mild cognitive impairment which is abbreviated MCI frequently, and the differential for those people, people really with complaint of memory loss, most of their cognitive functions are intact, and the question is whether this is sort of memory loss associated with normal aging that is likely to have a benign course, versus a very early manifestation of a dementia. And so, the differential for those populations is really sort of normal versus dementia.

Whereas, another proposed use of PET is in people who obviously have dementia based on clinical diagnosis, and then there's a differential that has

to do with the cause of dementia. There's Alzheimer's disease, which especially in the older population, 65, 70, over 65, 75, et cetera, is the most common, vascular or multi-infarct dementia, Lewy body dementia, frontal dementia, and chiron disease like Creutzfeldt-Jakob disease, or some other much more rare causes of dementia.

So the diagnosis currently of specific causes of dementia, if you have an elderly person

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with clinically diagnosed dementia, the differential diagnosis is based on clinical presentation, including neurologic exam, neuropsych testing. Laboratory tests are generally used to rule out other treatable conditions, for example a thyroid condition, as opposed to ruling in one of those causes.

And similarly, structural neuroimaging is generally used to rule out something like a cerebral neoplasm. That's something else that might be causing it, as opposed to ruling in one of the disorders that we just listed, with the exception of

multi-infarct dementia where there are indices based on structural neuroimaging.

So the diagnosis of Alzheimer's disease again, during life, is based on characteristic symptoms and exclusion of other causes of dementia, early and prominent short-term memory loss, early deficits in executive function, personality and language is relatively preserved. Definitive diagnosis is based on autopsy, based on pathological findings at autopsy.

However, there are a variety of criteria of reliable and valid criteria that when used clinically have a reasonable sensitivity and

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specificity. Those are actually, studies are a little bit complicated, but the Academy of Neurology document has some of the data in there. The predictive value positive is about 80 to 90 percent for clinical diagnosis in a academic center at this point.

This is, you can't read it (indicating

chart), but you can see the general shape, which is to show you the rise in incidents of Alzheimer's disease by age, and it starts on the left at age 65 and ends at, the last number on the right if you can't see it, is 90, and you can see that the incidents go sharply up. It may or may not plateau but if it does, it doesn't plateau until somewhere in the 90s, so that both the differential diagnosis and the prior probability for anyone is very different with age.

Course of AD is, death generally occurs between 10 and 15 years after diagnosis, but especially given the age ranges we're talking about, it depends heavily on the age at onset and competing risks.

The reference standards, as I mentioned, when the differential diagnosis is whether you're normal versus very early dementia, the reference

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standard would generally would be course; in other words, follow the person for five years or so and see what the course is. For multi-infarct dementia there

is, as I mentioned, some indices based on structural neuroimaging. And for the other cause of dementia, the reference standard is generally based at autopsy on pathological findings.

Just a very broad overview of treatment issues. You can divide the world into cognitive symptoms and noncognitive symptoms for patients with dementia. For cognitive symptoms, the pharmacologic treatments in general have been shown, the ones that have generally been shown to be effective are generally tested in people with Alzheimer's disease. They are cholinesterase inhibitors, perhaps Selegiline, Vitamin E, and the effect size is summarized by saying it's about six months, so that there is some studies that seem to show an improvement that seems to be equivalent of about six months worth of sort of putting you back in the course about six months, and other studies that show a slowing of progression. The sense is about six months, some people say 12 or more months.

Again, the caveat is that this slide, none

of these slides are based on a review of the data.

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I'm trying to give you an overview so you understand the issues. Obviously for the assessment, this would be heavily data driven.

For noncognitive symptoms, the treatments tend noto to be diagnosis specific. Besides behavioral treatments, there are pharmacologic treatments, generally antipsychotic drugs and again, not diagnosis specific.

There are some studies going on on the prevention of AD. Just looking at the National Library of Medicine database at clinicaltrials.gov, I found several studies that were looking at people who were either asymptomatic individuals, asymptomatic elderly individuals generally. Some of the studies had people with a family history of AD, some had a family history of other dementia, and some had just a family history of memory problems. So you are talking about normal elderly people who are considered at risk based on family history.

The agents being evaluated are

nonsteroidal anti-inflammatory drugs, estrogen, and Gingko Ballivo. I presume there's other studies that are not in that database, but this is just to give you an overview that people are studying these sorts of agents in the prevention of AD for people at high

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risk.

The kinds of outcome measures that would generally be used come in three categories, cognitive tests, functional measures and time to specific concrete events. For cognitive tests, there are brief measures like the midi mental state exam and they are more elaborate, basically neuropsych testing. Functional measures are things like, can you perform your activities of daily living or instrumental activities of daily living. Time to specific concrete events are things like time to institutionalization, time to death. You can imagine that certainly some of these measures would be very dependent on the time of the diagnosis.

Populations of potential interest. There

has been mention of using PET to diagnosis AD in people who are considered at high risk but currently have no symptoms, in other words, the types of indidivudals who are in those prevention studies. It has also been mentioned being used in people who you can consider to have mild cognitive impairment or some other subclinical dementia symptoms. It's also been mentioned as using to help in the differential diagnosis of people with dementia.

It's important to mention that those three

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populations pos different issues in terms of the sensitivity and specificity of the test or the kind of data you would look for, the clinical management issues and the treatment issues. One way of showing this is, the biggest box is the universe of patients over 65. Some proportion of those patients are going to be concerned about the possibility of dementia due to a decrease in memory or for some other reason, say a family history. A proportion of those will mention a concern to their physician or another caregiver. A proportion of those will be referred for work-up

because of signs or symptoms or family history. A proportion of those will get the clinical diagnosis of dementia. A proportion of those will be thought to have AD and a proportion of those will actually have AD.

The arrows don't show up, but you can see that PET has been mentioned in many of those boxes and again, I need to emphasize since this is an important point, that the issues in using PET at those different stages can vary quite widely.

So how would you evaluate PET? Well, the basic point, the argument is that earlier diagnosis of AD or another specific cause of dementia could lead to earlier treatment of dementia, which can lead

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to better health outcomes.

The arrow A would correspond to what this panel has called direct effects, so if there were studies that showed that the earlier diagnosis directly led to health outcomes. The arrows B and C would be equivalent to indirect effects.

So here's the MCAC criteria, the first criteria as applied to this. Are there high quality studies that provide direct evidence that use of PET improves health outcomes? That would have been arrow A on the previous slide. If not, are there studies that would allow us to determine the test accuracy, especially in comparison for alternatives, determine the impact of improved accuracy on patient management and determine the impact of change in patient management on health outcomes. So those are probably where we are heading in terms of looking at these three questions.

So here is, and I'm sorry it's not quite bold enough, but here's the beginning of a decision tree which I'm presenting, again, it's very broad strokes, it would be a lot more detailed if we were actually going to go down this path, but to show how you can think about this. So at the beginning on the left you have patients, and I left it very generic

because again, it will be important to specify which patient group we're talking about, whether it's

people with MCI, people with dementia, people with a family history, but neither of those two symptom sets.

Suppose you have a choice of using PET scanning or not. Obviously, by the way, if you were to consider other diagnostic tests, there would be other branches coming off that first decision node. Okay.

You can either have the disease in question, in this case AD, or not. And in the PET arm, the PET could have been positive or negative for either people with or without the disease. So you can see on the upper left, the first branch would lead to true positives, those people who actually had AD and had a positive PET scan. The next branch is false negatives, people with AD who had a negative PET scan. I'm just going to talk you through it. The next branch are people who are false positives, people who had a positive PET scan but don't actually have AD. And the next branch on true negatives, people with no disease and a negative PET scan.

So all of these people would go to the treatment algorithm, which again, the choice is to

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treat or not, obviously oversimplified. Now you can think about, if the test is positive, presumable people would get the treatment that you're thinking about. If the test is negative, they wouldn't get the treatment. If there is no test, I think we would have to consider two options, whether to treat everyone or not to treat anybody, especially in light of the relatively safe profile of the medications that are being evaluated right now.

Then you would go to the outcomes module, and there are three or four categories of outcomes. The bottom one just says other, so don't worry about the fact that you can't read it, I'm sorry. The top one is rate of progression. There could be the no change in cognitive status, slowed progression compared to what it would have been without the treatment, or typical progression. Then another type of outcome is treatment side effects.

The third bullet there says worry could

increase or decrease. There are obviously huge consequences to telling someone, especially somebody who is currently asymptomatic that they do or do not have Alzheimer's disease based on a test.

So let's think about it. The true positives, you can imagine that early treatment may

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be more beneficial than later treatment and they would get a health benefit from that. The true negatives might get reassurance. The false positives might get unnecessary worry and unnecessary treatment with the consequence of that. And the false negatives might get inappropriate reassurance and not get a treatment that might have been helpful to them. So that's one very broad way of thinking about it.

So points to consider, again, I keep emphasizing, the phase of illness is important, and I think it will be important based partly on this discussion to think about which sort of groups of patients we want to consider in the analysis.

The appropriate reference test or tests is

uncertain. Impact of negative tests and false positive tests are important to evaluate, what I was just talking about, the impact of the psychosocial, legal and other kinds of consequences to people with test results.

Patient management is a moving target, as I mentioned, both in terms of treatment of sort of full-blown dementia as well as prevention of dementia in people considered at high risk. There are many many clinical trials going on now and my guess is we will have a lot more data in five years that we have

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now, and clinical practice is evolving daily, so there is an issue of how to model that. The choice of appropriate measures of health outcomes is very important.

The evaluation will ultimately depend on the operating characteristics of the test at different phases of illness, and again, we are unlikely to have data at all those phases of illness, so that will be an issue.

Modeling of patient management decisions,

data regarding treatment effectiveness at different phases of illness, and the question, one question is whether we should consider and how to consider data about the impact of true and false positive results at different phases of illness.

So the issues that I would ask the MCAC to consider are, does the MCAC agree with this basic broad approach? How much consideration should be given to the role of other diagnostic imaging procedures? What are acceptable reference standards when evaluating the operating characteristics of any of these tests? And how should the psychosocial, legal or other consequences of different PET outcomes be considered?

I think I will end it there.

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DR. SOX: I think the next part of the agenda is to have scheduled or unscheduled public comment, but before that, and also before we get into discussion of the AHRQ model, are there any sort of specific questions that you would like to address

today?

DR. FRANCIS: Did you think about, because when you talked about how a false positive might have the risk of too much treatment or inappropriate therapy for Alzheimer's, what you didn't raise in that bullet in the slide, might it also result in people not getting other sorts of treatment that would be beneficial.

DR. ZARIN: You mean if it led people to not acknowledge that there was some other disorder?

DR. FRANCIS: Well, not necessarily that, but sometimes when a patient has a diagnosis of Alzheimer's, other things don't happen. For example, there are recommendations that you don't have breast cancer screening or whatever else it might be, totally unrelated to Alzheimer's, so that that bullet needs to be, I think, not only is there a risk of getting inappropriate care but also, is there a risk of not getting appropriate care.

DR. ZARIN: I think that first of all, the

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answer to that would depend also in large part on

which population you are dealing with, so that if you are someone already demented and you are dealing with just the differential diagnosis, the impact would probably be less in that regard than somebody who might actually be normal.

But, I agree with you. I think that for each of those endpoints, there is a whole slew of what I lumped under psychosocial, legal, other consequences, and then the question is how much do we need to flush that out again, considering that we have a relatively short time frame, the data are likely to be limited, but these are incredibly important issues, and so I think we need people's reaction to that.

DR. SOX: Alan.

DR. GARBER: This is about that relatively short time line. Can you just give us a brief description of how this would proceed after today, how much time to identify a contractor or set of contractors, send off for review and so on, and get it distributed to the panel and send it for public

comment?

DR. ZARIN: Well, we have an EPC lined up. It's not actually public yet so I won't announce

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which EPC, but that will be signed, sealed and delivered in a day or two. And then Sean can address the rest. I know for a November MCAC meeting, the report needs to be pretty much finalized about a month before the meeting, so you can do the math.

DR. TUNIS: And just to be clear, the November MCAC meeting is sort of a self-imposed deadline, if you will. It's trying to take into account, you know, the magnitude of the analytic work that would be required, depending to some degree on what this group sort of suggests in terms of the scope of what is actually looked at.

But there, you know, if this group actually recommends an extremely broad evidence based look, then the November deadline might have to be pushed back, but obviously, there is a lot of interest in making sure that this decision gets made as quickly as possible.

DR. SOX: I have a factual question. You presented a decision model. Do you plan to actually calculate expected quality adjusted life years or whatever for the test, no test decision, or are you using the model principally to lay out the structure for a more semiquantitative approach to the problem?

DR. ZARIN: I'm here to serve you guys, so

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whatever approach makes the most sense. I would, if it were me operating in a vacuum, I would probably look more at the probabilities of different types of outcomes, as opposed to moving all the way to getting qualities, but I think it's important for the MCAC to think about what kind of data they think are important, and again, my answer would also perhaps depend on the quality of data we find when we go searching.

I mean, I think that population of interest is a critical issue and from my very cursory look, we are going to be very limited in data, especially for some of those populations, but those

are also the populations where it's likely, where it's being advocated for use a lot.

DR. SOX: Okay. My question probably stepped over the line between sort of factual question and strategic question that we probably ought to defer to the discussion period.

DR. MCNEIL: I think I would have stepped over the line too, but it was a question that followed up on your question, so shall be wait?

DR. SOX: I have written this down, so we can reask the question when we get to the discussion period. Tom?

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DR. HOLOHAN: Are we to take the comments that you made that the definitions of true positive would be autopsy based? I mean, we talk about how one makes the diagnosis of Alzheimer's clinically, the correlation between autopsy results and the premorbid or preterminal diagnosis, and then you went on to talk about true positives, false positives. I presume positive in that case is a gold standard that would be based on autopsy study data?

DR. ZARIN: Well, I think that when you model it, you can either, it depends on how the data comes. We are unlikely to have -- the data that are using PET scanning, some of the data have autopsy results, and some of the data don't, and I think you have to model the best you can about the sensitivity and specificity based on those data. There is no hard answer. I think if there were a series of excellent studies, all of which did PET scans on a lot of people, some of whom proved to have Alzheimer's and some of whom didn't, and there were autopsy results on all those people, that would be the best data to use.

My guess is we are not going to find a lot of data like that, but again, we haven't look in depth yet.

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DR. HOLOHAN: So we would have gold standards, we might have silver plated standards, which is clinical diagnosis because the clinical diagnosis and the autopsy data, probably you will

find more studies that relate, so we will have absolute measures and surrogate measures?

DR. ZARIN: Well, if you're looking at PET scanning for people let's say presymptomatic, then one possible reference standard could be clinical diagnosis sometime later. In other words, did this PET scan on day one predict a clinical diagnosis of dementia five years later? That might be a logical study design and reasonable data to use.

If you're looking cross-sectionally, PET scan now versus clinical diagnosis now, that's not that logical because you have the clinical diagnosis, you know, if you're using that as the reference standard, the PET scan didn't add anything to the situation.

DR. MCNEIL: I think this is a clarification question, Deb. You talked about the changing time course relative to different management strategies and what data would be available when. And when I was looking at the stuff you pulled off in terms of ongoing clinical trials, one of the

questions I had, is it possible that some of those data or those results that might be very meaningful to this discussion are going to happen on December 1st? Are we titrating our time course to the availability of some of those pivotal clinical trials, or should we be, I guess is the other question.

DR. TUNIS: We haven't thought to do that but we can certainly, you know, look into the time course, and you know, consider whether we need to hold off until we have some of that data if it looks like it's going to be pivotal data. So I think that's a good point and we'll just make sure we're sensitive to that.

DR. SOX: Frank.

DR. PAPATHEOFANIS: Deb, can you give us a sense of the other neuroimaging modalities and sort of your preliminary read of the quality of that data, because if the PET data at least in issue don't appear very strong, we also are going to have comparator data that won't be strong in the other

modalities.

DR. ZARIN: From my understanding, based again on the AAN, the Academy of Neurology document, and some other reviews like that, are that the PET

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data in terms of functional neuroimaging, they are probably among the strongest. Well, I'm talking to a radiologist, so you might have a better sense of that, and that there is a limit to what structural neuroimaging can tell you.

DR. PAPATHEOFANIS: Right.

DR. ZARIN: However, again, it depends on which phase of illness you're talking about.

DR. PAPATHEOFANIS: It's a bit of a concern, and maybe Barbara, you can comment a little bit more too, that the functional MR data, the other data in the other competing modalities, if you will, is still very immature, it's a new set of criteria, new technology and so forth.

DR. ZARIN: Let me just add, one of the arguments I've heard is that even though, say the Academy of Neurology practice guideline recommends

structural neuroimaging at initial workup, it doesn't recommend repetitive structural neuroimaging.

DR. PAPATHEOFANIS: Right.

DR. ZARIN: One of the arguments we hear is that that happens in real life and that having a definitive diagnosis might put an end to that. I don't know, you know. I'm just telling you that, and so, that's the sort of thing that you could model or

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say no, we're going to stick with basics.

DR. MCNEIL: Just a follow-up to Frank's comment. One of the tests, the other tests that's mentioned in the AAN document and is used frequently is SPECT, and the issue there, I think there are really two things we want to consider, and I don't know how they get folded into the analysis, Deborah. One is that PET at least on the basis of these articles appears to be better. The counterpoint to that, though, is the fact that it's much less available. And then I don't know how we want to consider the availability of the technology relative

to its other possible uses and the availability of SPECT, which is relatively underused from a neurological perspective relative to PET in the total body perspective. Is that your sense, Frank?

DR. PAPATHEOFANIS: Right.

DR. MCNEIL: And whether or not that differential ability factors at all into our decision. For example, of at the end of the day it should come out that somehow, on a quality adjusted year or whatever the measure is, PET was 2 percent better than clinical scenarios, but it was essentially unavailable, 2 percent better than SPECT but it was essentially unavailable. Is that anything

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that we consider in these deliberations? That strikes me as an issue for the Executive Committee rather than for the diagnostic imaging panel.

DR. SOX: And for HCFA.

DR. MCNEIL: And for HCFA.

DR. TUNIS: Well, those sorts of issues certainly get raised and you know, it's raised also in the context now of, thinking to the issue of the

gamma coincidence camera PET versus full ring PET, and the availability of gamma cameras in rural where there aren't full ring PETs, so those issues do get raised to us as part of the consideration of the coverage process.

And I think other than sort of raising those points in this context, I'm not sure there is much further to go with that, but the points do get raised and certainly the committee raising those points for us gets noted and becomes part of the discussion.

DR. SOX: Alan?

DR. GARBER: This is really just a question about the agenda. It seems that we're starting to really get into our suggestions about how the model should be structured. Did you want to have the public comments before we carry out that

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discussion fully, or are you open to discussion of the model and suggestion for AHRQ?

DR. SOX: Well, I had hoped to keep the

discussion mostly to factual questions for Debbie about what she said, as opposed to comment and advice, and thanks for reminding us that maybe we're slipping, going over that line.

So, I guess at this point, we will ask you to stand down and be ready to participate in the discussion later on.

And we have one scheduled person to comment, Dr. Marilyn Albert. Is Dr. Albert here? Good.

Would you introduce yourself please?

DR. ALBERT: I'm Dr. Marilyn Albert. I'm professor of psychiatry and neurology at the Harvard Medical School, and I'm also director of the gerontology research unit at Massachusetts General Hospital. I was asked to speak today because I am also the chair of the medical and scientific advisory committee of the National Alzheimer's Association. And I have no financial interest in the outcome of these deliberations in any organization or business that is evaluating or using PET.

DR. SOX: Before you start, could I ask,

does anybody else plan to make a comment? Could you raise your hand if you plan to comment? I didn't see any hands. Did I miss anybody? So, in principle, you have lots of time.

DR. ALBERT: That's probably not a good thing. Well, I haven't brought prepared comments because I was only asked to do this very very recently, but we will prepare a summary of my comments when I'm done.

I should just mention a little bit about my relevant background with respect to imaging and diagnosis of Alzheimer's disease. I am the co-director of a clinic at Massachusetts General Hospital, where we regularly see patients who come with clinical complaints, older individuals with complaints of memory problems and so on, on a regular basis. I work with a team of clinicians evaluating, diagnosing people with Alzheimer's, so I'm very accustomed to using imaging in a standard way for making a diagnosis.

I also am the director, the principal investigator, of their very large program project that has used imaging in connection with other modalities to try and identify patients with Alzheimer's disease, and in the past we have focused

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on trying to compare individuals who were normal with people who had mild Alzheimer's disease, and right at the moment we're looking at the preclinical prediction of Alzheimer's disease.

So some of the issues that you just heard addressed with respect to looking at people who come with cognitive complaints and then seeing what happens to them down the line are the sorts of things that we're evaluating in a research setting, so I have seen imaging applied in both domains.

As you have already heard, in standard practice right now, imaging is used to rule out other diseases. When we see patients clinically, typically what's done is to do a structural MRI or a CAT scan to see if people have strokes or tumors, or a normal pressure hydrocephalus or other disorders that might

be causing their cognitive complaint. It's not used to rule in the disease in standard clinical practice because at least among most people in the field, there isn't enough uniformity and enough agreement among investigators as to how to do this, but that's in fact what the issue is here today, whether or not we can use PET to rule in the diagnosis.

Most of the data with respect to PET and other imaging modalities has therefore been conducted

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in patients who are very carefully screened, where other conditions have been ruled out by standard means, and then PET or MRI or what have you has been used to see if the imaging measurement is as good as the clinical diagnosis, or as good as the ultimate pathological diagnosis, or can predict progression of disease in people who are presymptomatic, as we have just heard.

And I think that in evaluating PET or other imaging techniques the really critical thing for you to keep in mind is what has already been

addressed, which is that Alzheimer's disease and other dementias are progressive illnesses and the critical thing you need to know in evaluating the data is how impaired the people were when they had this evaluation, what degree of severity they had when it was said that imaging could be equated with the diagnosis.

Needless to say, if you get people who are very advanced or even moderately advanced, you can be virtually certain that they have a dementia, you can't always be virtually certain what the dementia is, but you can be virtually certain clinically that they have the dementia, and imaging doesn't tend to add a lot of on top of that, so the real interest has

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been to see whether or not it adds something earlier in the disease, and that's why a lot of attention has been paid to looking at people with mild impairment or to looking at people in the preclinical phase of the disease. But, I think in looking at the literature that exists, it will be critical to see what stage of the illness people are at when the

disease was acquired.

The other thing that I think is important for you to evaluate is whether or not the data come from very carefully screened individuals or all comers. Most of the studies that are in the literature that I am familiar with have taken people who are exceedingly carefully screened because the goal is to see that they meet clinical research criteria for Alzheimer's disease, and those clinical research criteria, as we've heard, have an accuracy in major medical centers of up to 90 percent in comparison to diagnosis.

There are few studies that I am aware of that have taken all comers who haven't been carefully screened, which is of course the clinical challenge that we have, because these dementias are most common in individuals who are elderly, they have many other illnesses that can impact on their cognition, heart

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disease, they take various medications that can impact on cognition, and people with substantial

illnesses along those lines tend to be excluded from research studies, but they still would require a diagnosis. So one of the major questions is whether or not the literature that you will have in front of you has only taken very carefully screened people or all consecutive patients.

The other issue that you've already talked about but is very obviously important to address is the question of the reference standard. It was already mentioned that autopsy in respect to most of these diseases is the reference standard, but there are also to my knowledge few studies where all the imaging data relates only to people who have come to autopsy. The vast majority of the studies have to do with comparing the clinical diagnosis that has greater than 90 percent accuracy with the imaging data.

And then now more recently, there are a whole spate of studies looking at prediction of course, is the person that you see who is very mild, do they progress to the point where they get diagnosed with Alzheimer's disease or if they are

very mild, do they continue to progress in a way

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that's characteristic of Alzheimer's disease in the absence of having an autopsy.

The other topic that was mentioned only briefly of course is the question of differential diagnosis among the dementias. There are a variety or other demented disorders that are much less common than Alzheimer's disease such a frontal temporal dementia, Lewy body disease, and multi-infarct dementia. And again, the number of studies that have compared these dementias with one another using imaging is fairly modest in my experience, but that will be a very important thing to look at if the claim is, can we make a differential diagnosis among patients who already have a dementive disorder.

The last point that I wanted to mention touches on the topic that was just talked about at the very end of the previous speaker's session, which is other imaging modalities. We have talked about PET and SPECT. There is also a lot of work that has

been done with structural MRI and I think in general it's fair to say that there is enormous enthusiasm for the capability of imaging in general for, if not diagnosing a disease, systematically evaluating its course. There are drug companies, for example, that are beginning to look at imaging measures as outcome

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measures in studies, and that's because they feel that these measures in general are getting more accurate.

I think the reason for that is that technology has greatly improved over the last ten years, and also we have a much better idea of the actual nature of the disease process, so for example in Alzheimer's disease, we have a much better idea of where in the brain the disease is beginning, and so if you can measure that with great accuracy, you can become much better at diagnosing illness and therefore, in seeing the change in the progression of disease over time.

All of the measures that have been talked about have data with that, in that regard. There are

very few of them that have been compared with one another, so for example in the area of structural MRI, there are region of interest measures where you outline specific regions in the brain that you think are where the disease is beginning, and you also have whole brain measures looking at whole brain shrinkage. Both of those methods have been shown to be very promising.

There are no studies that I know of, although they might have come out very recently,

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comparing them with one another and the same is true with PET, that PET has been used but very rarely compared to the same individual to SPECT, or SPECT to structural MRI, so I think that comparison if you want to evaluate the entire of imaging is also going to be something that's important.

So, why don't I stop there and take whatever questions you might have.

DR. SOX: Thank you very much. If that's what you can do on three days notice, we look forward

to hearing you when you have time to prepare. Barbara?

DR. MCNEIL: I agree, that was a lovely presentation, Marilyn.

DR. ALBERT: Thank you.

DR. MCNEIL: I have one question that, I want to make sure I heard you right. You indicated that with patients with late disease for whom the diagnosis of dementia was certain, that imaging doesn't add much. Is that what you said?

DR. ALBERT: What I said was that in late disease you can be virtually certain that someone is demented. What imaging might add and I don't actually know that anybody has looked at that, is which of the many diseases they might have. So for

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example, if you have a moderate to severely impaired patient, do they have frontal dementia or do they have Alzheimer's.

DR. MCNEIL: So that would actually be an important part if we were to be taking late stage presentations, one of the questions would be is

imaging refining the differential diagnosis so that we would then know whether to treat, so that's still okay with you.

DR. ALBERT: Yes.

DR. MCNEIL: Can I ask her one other -- I'm not sure if this is a question that is for us or for her, and it's something that was said in the documents and Deb said it and you said it, and it is, in good academic settings, the probability of Alzheimer's disease can be up to 80 or 90 percent, if you have a super workup.

DR. ALBERT: That's right.

DR. MCNEIL: Now if that's the case, do we have any reason to believe that any imaging test is going to have a likelihood ratio that's going to get us to anything that is high enough to make a difference? It's almost a modeling question in the absence of any data, but what do you think about that?

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DR. ALBERT: That's why I mentioned the

aspect of carefully worked up patients versus not, because originally when people started to using imaging in this area, which was about 20 years ago, the hope was that we wouldn't have to carefully work up patients, someone could come in the door, we could give them a PET scan or a structural MRI, and we would know what was wrong with them by looking at the imaging. If you could do that, if you had any test, a blood test, genetic test or whatever, that could do that, you would save a lot of money, because it's very time consuming to do all the tests that exist now, there are a lot of experts that have to evaluate the individual, and the experts have to be good. I mean, the data about 90 percent accuracy comes from major medical centers where people really know the disease, so if you had something that was pretty good that you could substitute for all of that, that would actually help. I don't know that that's what anybody is claiming, but I think in theory that would help.

DR. SOX: Alan, I think you were next, and then Bob.

DR. GARBER: Thank you for your excellent

comments, and I just wanted to follow up on something that you mentioned briefly. One of the major

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purposes for PET in diagnosing Alzheimer's disease, or using it for suspected Alzheimer's disease presumably would be for prognosis, and you have briefly mentioned prognosis. And of course, if this is something that the evidence based practice center pursues, they will be looking comprehensively at the literature. This may be an unfair question but I'm just wondering, is there a strong literature to your knowledge on the role of PET or for that matter other imaging modalities, in determining prognosis? And I am particularly interested in the marginal contribution of the imaging tests, whether it's functional or structural, over the other clinical parameters that you routinely follow.

DR. ALBERT: When you say prognosis, you mean preclinical disease, you mean very very early people before the development?

DR. GARBER: No. They're already

suspected of having dementia, or they may have early dementia in some form, and in predicting disease course subsequently.

DR. ALBERT: There is a substantial literature on that. Most of the data is in people who clinically are said to have probable Alzheimer's disease, which means they meet clinical research

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criteria for Alzheimer's disease, they usually are either mild or moderately impaired, and somebody has done imaging to see whether or not they meet that diagnosis. And in many instances, although not in all, those articles will also tell you which of the people went on and progressed even if they didn't get an autopsy.

DR. GARBER: And do you have a sense of how PET compared to the other imaging modalities?

DR. ALBERT: Basically I think the challenge that's going to be in front of you is that there are very few studies that have compared imaging modalities head to head. In our particular studies for example, at Mass General, we have compared

structural MRI to SPECT, and to neuropsychological testing, but in general, there is not a lot where imaging, the same imaging modality, the same individuals have been evaluated with different imaging modalities. There isn't even much data on comparing different types of, for example, structural MRI measures to one other in the same individual, so I think that comparison is going to be difficult for you to find data on.

DR. SOX: Bob.

DR. MURRAY: It's my impression that many

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of the studies involve a treatment aspect and their proposed pharmacologic interventions and so on. If we're looking at, or if AHRQ looks at health outcomes, how will the various, how can you sort out the various interventions in evaluating the diagnostic accuracy? Is it possible, are there enough studies that look only at that diagnostic accuracy using an intermediate measure? Obviously if there were autopsies, it would make it easier to

assess the initial diagnostic accuracy.

DR. ALBERT: I'm not sure I understand the question, if you could just rephrase it.

DR. MURRAY: Are there good diagnostic studies that are unaffected or that have outcome measures that are not affected by the treatment interventions?

DR. ALBERT: I see. Well, the treatments as you heard, are exceedingly modest. They only statistically slow up course by six months, so by and large, the studies will not be affected by treatment outcome at all.

There are a number of studies that have now been using structural MRI to look at additional outcome measures, but because the treatment effects are so modest, they have mostly been used just to

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measure progression of disease and not to look at the relationship between treatment and the measures themselves.

DR. SOX: I will just go around, I don't know who's next, so Tom and then Randel.

DR. HOLOHAN: Forgive me for a question that asks you to act as a visiting lecturer, but I can't pass up this opportunity. You talked, when you were talking about the diagnosis, and you began with autopsy and then talked about clinical evaluation and clinical diagnosis being accurate in the best places about 90 percent of the time, and then you talked about progression. And what I wrote down, this isn't what you said, but progression may be "proof". Can you elaborate a little bit more on the increasing likelihood of a correct diagnosis in seeing the patient over time and how progression could separate say Alzheimer's disease from Lewy body disease, frontal temporal?

DR. ALBERT: Theoretically, progression could help you differentiate Alzheimer's disease from multi-infarct dementia, because you would expect that in multi-infarct dementia there would be these plateaus with big declines when there were vascular events. Frontal temporal dementia, I have the

predisposition that you can best differentiate that from Alzheimer's disease very early in the course and that as people progress, they look more and more similar, so without autopsy it would be very difficult to differentiate them, and the same thing is true with Lewy body disease.

I think the real point where progression is helpful is in this preclinical arena and that's why we have been focusing on that more, because you commonly have people who have complaints and concerns about their memory problems, and with all the publicity about Alzheimer's disease, that's the thing they worry about the most, and so more and more they are going to clinicians for evaluation and those people are very difficult to evaluate. And if you could -- and if you have effective treatments, like even the treatments we have now do slow up the disease a little bit and it's pretty clear that the earlier you take them the more beneficial they are. In other words, it you take it later in the course, you don't get back to the level at which people who took it earlier had achieved.

So if you could identify people in the preclinical phase of disease and be pretty sure that they were going to go on to develop the disease, then

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treatment intervention would be beneficial and there would be a great worth in that. So progression in that area is of substantial informativeness. You evaluate people when they have memory difficulty and then you follow them to see whether or not within a few years they meet clinical criteria for Alzheimer's disease. So, I think that's the setting in which making a more definitive diagnosis would be exceedingly helpful and beneficial in terms of health outcomes.

DR. HOLOHAN: Do you routinely treat most AD patients pharmacologically at Mass General?

DR. ALBERT: We do routinely offer treatment, yes. I mean, with the treatments that are now available, with the three medications now on the market, we do. Moreover, in this study that we're conducting where we're looking at preclinical

Alzheimer's disease because these treatments are now available even before people meet clinical research criteria.

We talk about treatments with them, we talk about nonsteroidal anti-inflammatories, antioxidants and the cholinesterase agents.

DR. SOX: Randel.

MS. RICHNER: My questions were answered.

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DR. FRANCIS: One of the questions for these panels is, is there any data about the Medicare population more generally, not just the folks in academic medical centers, and you mentioned that -- is there any data that you know, do you have any comments at all about what the world is like out there beyond Mass General? And really the reason I'm asking that is whether you have any comments about the likely sensitivity and specificity, and issues like false negative and false positive rates outside of academic medical centers, when you're dealing with a population that may not have been very carefully screened.

DR. ALBERT: Well, first of all, I do do research in a population that's in a very good nursing home in the Boston area, and even though it's a very good nursing home, it's astonishing that people don't get a regular workup. So the absence of, for example imaging, when somebody is thought to have a progressive dementia is quite striking in the general population.

But when it comes to the issue of false positives and negatives, the challenge is the prior probabilities. If somebody is 80 and walks into our clinic with a history of cognitive decline, the

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likelihood that they have frontal temporal dementia statistically is almost zero, because it doesn't present in that age range. If somebody is 60 and they walk in with a history of cognitive decline then the chances that they might have Alzheimer's disease or frontal temporal dementia are about 50-50, but of course that's a very rare age range in which to see the diagnosis.

So if you have a data from a population whose average age is 75, and somebody uses imaging to make a diagnosis of Alzheimer's disease, just by chance they will be right a lot of the time. So you have to factor that in to the way in which you evaluate the data.

DR. SOX: My question relates to Leslie's question, I think. You made a point that we should be looking closely at how the study populations were defined as to whether they were off the street folks with cognitive decline versus people who had been carefully evaluated with neurocognitive measures and the like. It wasn't clear to me from your remarks what impact making that distinction was going to have, whether it was likely to affect the likelihood ratios of the tests or mostly have its impact in the prior probability of disease.

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DR. ALBERT: In my mind, it relates to the issue that Dr. McNeil raised, which is, does it add anything above and beyond a good clinical diagnosis? So if you have a very good clinical diagnosis and you

have carefully evaluated patients, can you improve beyond that with good imaging? If you don't have carefully evaluated patients, then it relates to the comment I made before about cost saving. If you could make a good diagnosis with imaging and not have to do anything else, the cost savings would be really quite substantial.

And more and more, the other part of it is this early diagnosis. If you have people just coming in with cognitive complaints, if you could predict what was going to happen to them, and you knew that they were going to develop Alzheimer's disease and you could intervene earlier, then that would also be very beneficial.

DR. SOX: Barb?

DR. MCNEIL: I wanted to follow up to your question, Hal. The prior probability of 80 to 90 percent, which was defined for us --

DR. SOX: That was accuracy.

DR. ZARIN: That was prior probability of people who had been worked up. We start there,

that's the prior probability.

DR. MCNEIL: Right, that's what I meant to say if I didn't. Does that apply to a certain age range? In other words, you can't get there without being 75?

DR. ALBERT: No, that applies to people of all ages. It applies to anybody who comes for an evaluation in a major center where people have expertise in the diagnosis.

DR. SOX: If the prior probability is really 90 percent, how sensitive would the tests have to be to drive the probability low enough so that you wouldn't give a relatively benign treatment.

DR. MCNEIL: Right, that's what I sort of wanted to ask.

DR. ALBERT: But you know, our assumption, and I'm sure you know that all around the world, drug companies are racing one another to find better treatments for Alzheimer's disease. And the ones that people are looking at right now are based on what everybody feels is a much better understanding

of the biology of the disease. My guess is that those treatments are not going to be as benign, and that's part of the reason that people are working so hard to be more accurate in preclinical diagnosis,

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because if all you were going to say is take Vitamin E and ibuprofen, and you will greatly reduce your risk, then there is no point in our spending all our time trying to figure out if people really are at risk, but the likelihood is that the treatments will not be benign.

DR. SOX: Deb?

DR. ZARIN: What's the treatment implications of making a better differential diagnosis in somebody who is demented? I mean, I mentioned that there are studies of the medication for people with Alzheimer's, but what would be the value? I guess there is value in prognostic information and perhaps in treatment information.

DR. ALBERT: I actually think with respect to certain diseases, the impact on the family

in making a better diagnosis is very very useful. The biggest place in which it's useful is in the comparison between frontal temporal dementia and Alzheimer's disease. Frontal temporal dementia progresses in a very different way, the patients are behaviorally as a group exceedingly disturbed, families have a great deal of difficulty dealing with those patients and understanding what's happening to them and are very often frightened by them. And if

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we can make an accurate diagnosis, we can enable them to see it more as a brain disease and to figure out how to intervene, and the interventions are considerably different than they are in Alzheimer's disease. So, I think there are a number -- that's the best example, but there are instances where accurate diagnosis really does make a difference.

DR. SOX: I have one last question for you. I'm impressed with the complexity of this problem and the short time line, and the requirement to set some priorities. Where would you put the emphasis in this study, on what sorts of applications

of imaging, on early diagnosis, on evaluation of patients with a clearcut decline, where do you think the most important area is likely to be if we had to set priorities and not try to cover everything?

DR. ALBERT: I think the most important thing is in early diagnosis because that's the place at which there's the greatest ambiguity and where imaging measures could add the most. So either in mild patients or in patients with preclinical disease, I think is where the benefit is the greatest.

DR. SOX: So screening?

DR. ALBERT: Yeah, or very mild disease.

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I mean, unless you have people who are really expert in evaluating patients, individuals who are mildly impaired tend not to get picked up, they go to their physician and they complain, and the physician says this is just normal aging and they should go home.

DR. SOX: Randel?

MS. RICHNER: You said earlier that there

is limited data so in that sense, if we're posing the question to just simply look at that population, would that essentially limit what the results could be from looking at the question? I mean, I'm very concerned, if we just look at the screening, the preclinical phase, is there enough literature to support covering PET in that particular diagnosis?

DR. ALBERT: I wouldn't look just at the preclinical phase. I would also include mild disease. In the early stages of imaging a lot of work was done in moderate and severe disease, but as time went on, more data was gathered in mild disease and I think there is a substantial amount of it.

MS. RICHNER: From your perspective, the most benefit, clinical utility is in that early population, but our question is how are we going to assess this for coverage in terms of looking at the overall population, and I don't know if we're biasing

how we're looking at this if we just look at that small population where there might not be enough data, so --

DR. ALBERT: I think there is likely to be --

DR. RICHNER: -- the question is, are we going to look at the accuracy of the test, or are we going to look at -- what is the best utility?

DR. ALBERT: In mild disease, I think there is likely to be a good deal of data, and I think the data will be more likely to be related to the best technology that's currently available, because when imaging studies first were done, the thrill was just, could you say anything, and so very simple measures were used in moderate and severely impaired patients. But as the measurements became more sophisticated, they were done in milder and milder disease.

So I think, first of all, you will have a substantial literature in mild disease and I think also those are the measures that are more likely to be related to the current ones that are used.

DR. SOX: Tom?

DR. HOLOHAN: Let me extend and make a

statement and you correct me. If on the other hand

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we follow the prior recommendation and extend the review to patients with advanced disease, to be facetious, how much juice is there for the squeeze? You've said previously in advanced disease, even the very modest benefits of the pharmacologic therapies available are minimized, they are most beneficial in patients with early disease, they never return a person to the prior step, I think is the phrase you used. So what benefit would there be in looking at literature in people with advanced dementias, advanced Alzheimer's disease, for any diagnostic technique?

DR. ALBERT: I think the only benefit would be if there were treatments in some of these other diseases that might be beneficial. So for example, in multi-infarct dementia, if you could prevent more strokes, or if we understood more about treatments of frontal temporal dementia. If there were better treatments in those disorders, then diagnosis of more advanced disease might be helpful.

At the moment, the biggest benefit would be in multi-infract dementia.

DR. SOX: Ron?

DR. DAVIS: I think you also mentioned that there are a lot of drugs that are in

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investigation for treatment, so if we improve the ability to diagnose the disease early then we will be ready to go when new treatments come on line.

MS. RICHNER: Exactly.

DR. ALBERT: Well, that's why some people are working so hard with these imaging techniques, not because we have anything wonderful for treatment now, but we're anticipating that within a decade, we will have really effective treatments.

DR. DAVIS: And is that because, if I heard you correctly earlier, that we have a much better understanding of the biology of the disease and some of these new drugs under investigation are tailored to that understanding?

DR. ALBERT: That's exactly right, yes.

DR. SOX: Frank?

DR. PAPATHEOFANIS: One quick comment. This is in sort of anticipation of what Deb has to deal with at AHRQ in commissioning the assessment, and I guess what I'm hearing is, I'm almost envisioning two groups or sets of ROC curves, the 90 percent groups and then everyone else for each of the possible modalities. Also, the notion of preselection and the appropriate identification of patient, I just want to get reassurance from Deb that

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when she has framed this RFP that all of these data will be part of that assessment and that we can anticipate that Dr. Albert's comments are really going to be a part of this.

DR. ZARIN: You're talking about checking the data on the diagnostic accuracy for the different patient groups, or the different preclinical sort of mild impairment?

DR. PAPATHEOFANIS: Right. And top flight academic centers versus, you know, community, secondary tertiary centers. Is your RFP framed so

that we will capture those sorts of data as well?

DR. ZARIN: I don't think the RFP is the problem, finding the data may be the problem, but absolutely, I think the diagnostic accuracy part is in a way the easier part.

The question I have for the MCAC panel is the linkage with treatment, and we are hearing a lot of things about the value of prognostic information, and I think there is going to be a big question mark on -- there is going to be data on current treatment, but not for all these groups but for one of them at least, and there will be guesses about future treatment, which you could either model through sensitivity and specificity. So, it would be helpful

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to me to get a better understanding of your perspective on that, of how much treatment data you want in there, how much you will be interested in modeling, and saying well, if these new treatments are this good, it will look like this, if they are only that good.

DR. PAPATHEOFANIS: Thank you.

DR. SOX: Sean, then Barbara, and then we're going to take a break.

DR. TUNIS: I don't know if we mentioned this already, but one comment that had been made is that in patients with suspected dementia, that some number of them undergo repeated structural imaging studies over the course of their illness, and I'm wondering, you had mentioned that in the nursing home that you worked at that you were actually impressed with the infrequency with which patients with symptoms had imaging studies. And I just wondered, do you have any sense of whether both of those things might go on or in fact it's pretty atypical to be using structural imaging in this patient population?

DR. ALBERT: My experience with repeated imaging is that it's very infrequent for anybody to get repeated imaging, unless they're part of a drug study. In drug studies they are now doing repeated

imaging, bit just because of cost containment, I don't know of anybody that does repeated imaging

routinely on individuals who they have made a clinical diagnosis on. And as I have observed, it's been my observation that outside of major medical centers, even simple imaging that really needs to be done, such as CAT scans, aren't done.

DR. SOX: Barb?

DR. MCNEIL: I want to make sure I understand what treatment is that's fitting in here, and it's following up a little bit on what Deborah said. So the first thing that a model would do is, assuming we had the clinical, the patient groups correct, and assuming that we had the test characteristics correct. For early disease, we want to know what the impact on whatever the current treatments are. For early disease we might also want to model what new treatments are. For late disease, there are no current treatments.

DR. ALBERT: Well, it should be said that the people that are marketing the current drugs that are on the market for Alzheimer's disease are trying to argue in some instances that there medications are

also good for late disease. And I didn't mean to say that they weren't, they wouldn't slow up the disease

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by six months, but the data suggests that the later in the disease you take the medication, the less likely it is to put you back at the -- that you lose something by delaying treatment. It has been argued, and there are data to suggest that even treatment in more advanced patients is beneficial.

DR. MCNEIL: So we have for the late disease patients an estimate of how good the current treatments are.

DR. ALBERT: That's right.

DR. MCNEIL: Versus current treatments for early disease. So then, the final question regarding treatment is the issue that somebody raised regarding advanced disease and imaging, and you said the most important, or one of the most important benefits there was the differential diagnosis of multi-infarct dementia from Alzheimer's disease. So that would get complicated, because -- I'm talking out loud and I shouldn't. Because it would, you would have to

assume that the current treatments we were just talking about, current available treatments worked for Alzheimer's disease in some sense, and didn't work for multi-infarct dementia, and that there are treatments for multi-infarct dementia that actually delay the progress of multi-infarct dementia. Is

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that true?

DR. ALBERT: When I say treatments for multi-infarct dementia, I mean doing things that reduce your risk for stroke, so whatever would reduce, you know, treating diabetes, treating hypertension.

DR. MCNEIL: So you would be using the same data for that.

DR. ALBERT: That's right.

DR. MCNEIL: Okay.

DR. SOX: Is there actually evidence that using these treatments alters the course of multi-infarct dementia, or just that it might?

DR. ALBERT: That's a good question.

DR. SOX: Nobody knows?

DR. ALBERT: There might be, I just don't know.

DR. SOX: Deb?

DR. ZARIN: I just wanted to note, I think we're looking at late disease in two different ways. When I presented it, I talked about asymptomatic people or presymptomatic, then mildly impaired, and then people who clearly had dementia. And I think sometimes when you hear the term late disease, you think of people who clearly have dementia, but within

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dementia, people tend to use mild, moderate and severe, so I think basically, we are not all talking about severe dementia, we're talking about dementia, it must be clear that they have dementia, and then look at what stage of dementia they are in.

DR. JOHNSON: You commented on the preclinical detection diagnosis being exceedingly important in the management of the disease and also the usefulness in the accuracy of the differential diagnosis, being able to enable the interventions,

the early detections and those that had the ambiguity, using it as a screening in the early symptoms, mildly impaired. Given the availability of PET scanning, with coverage of the Medicare population in this disease management, how important -- and the expansion with coverage to be towards expansion of PET scanning availability, in that early disease detection, helping in that ambiguity, the differential, how do you see that in projecting the transformation in disease management towards the people with these various diseases, given your expertise?

DR. ALBERT: You're talking about with respect to the limited availability of PET scanning?

DR. JOHNSON: Yes. To have more

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availability of the scanners out there for a greater population to be scanned, and helping with the overall disease management.

DR. ALBERT: Well, I think first of all, you would need to be sure that PET scanning was

significantly better than the other available imaging modalities, and I think that's the question you have before you. Dr. McNeil mentioned that SPECT is much more widely available, and if you were going to make a comparison, at least I think you would want to compare those two, but also to structural MRI because in point of fact, a lot of measures that are now available that are very sophisticated for structural MRI are also very sensitive. And so, I think before you talk about trying to make PET scanning more available, you need to be sure that it really is substantially better than these other modalities.

DR. SOX: We're going to need to move on at this point. Alan, can your question be brief?

DR. GARBER: Well, if Marilyn's going to be here, I really had a very simple question though, and it gets back to something that you had mentioned about screening. You said that preclinical disease would be the most promising time. Can you give us some language so that we can in turn give direction

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to AHRQ about how to define a population of patients

that you have in mind, in real concrete terms like people suspected to have early dementia, or asymptomatic with a strong family history. What do you view as this optimal target population?

DR. ALBERT: There are several. One is this population that's been said to have MCI, which stands for, it's a poor choice of a name, it stands for mild cognitive impairment. In fact, most of these individuals have a substantial degree of memory difficulty but they don't yet meet clinical criteria for Alzheimer's disease, so that would be one group.

A lot of people haven't used subjects defined precisely in the way in which MCI is defined, so they have talked about progressive memory complaints as another way in which the groups have been defined. And then there are some studies that have looked at people only based on their family history or their geno type, so they don't have going cognitive complaints, but they just have this risk because of their genetic background. So it's all three of those categories that have been looked at

preclinically.

DR. SOX: Well, thank you very much. I hope you enjoyed standing up.

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Now, Deb has to leave at 11. And what I would like to do now is really try to aim for several goals. The first is, I think we need to have some discussion about whether the model that Deb has put forth squares with the model that we have adopted for our own use, and so I'm going to go over that fairly quickly and then try to get a response from members of the panel about whether what she is proposing to provide as the framework for the EPC in fact is going to fulfill or perhaps even exceed the model that we have adopted.

Then I think we need to address, try to answer for her the questions that she's raised, and that's probably the next step. An then finally, we need to try to think of questions that she hasn't thought of, and we can pass those on to her.

I would like members of the panel to be writing down pieces of advice that we can put into

some sort of list of suggestions for Dr. Zarin and for the EPC, because ultimately the product of this high level discussion has got to be some practical advice about pitfalls and the like.

So, I'm going to use the transparency projector and just briefly go over our model, and I would like some comment about whether what Deb has

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presented covers the essential points on our model, and I will try to be quick about this.

So again, we first asked, is there direct evidence for the effect of the test on clinical outcomes because of a randomized study comparing patients who got the test and patients who don't, this being probably the best example of that, or are we going to be stuck with indirect evidence in which we measure test performance and then try to infer differences in test performance between the procedure under consideration and the standard test on clinical outcomes. And clearly in this example, we're going to be doing the latter.

So then the first question is, is the evidence adequate to determine that the use of the test provides more accurate diagnostic information, so we have to evaluate studies of test performance according to standard criteria and decide whether we have enough, whether we are confident that differences or similarities in performance between the standard tests and the tests under consideration are real or not.

And just to remind you that there is some, the key characteristics are the definition of the study population, the frequency with which patients

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who get the index test, for example PET scanning, also get the gold standard or reference test. Issues of whether the person interpreting the test is blinded to all other information. And finally, whether the reference test is a valid measure of the disease state, which is clearly a key issue here.

Now remember, the reason we're doing this is to see whether what you're proposing fits with what we have adopted as our approach. So, then, the

next really important questions is to evaluate the extent to which the test under consideration correctly identifies patients that the current standard test fails to identify as disease. So does PET scanning in fact identify a population of patients that MRI for example, does not detect? Are the two tests complementary?

And the best way to do that of course is to do both studies in a population of patients who get the gold standard test and then see how frequently patients who are negative on the first test are positive on the second test, and under those circumstances, the second test would provide complementary information and we would argue that both tests ought to be performed and not simply one or the other.

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So, assuming that we have good studies of the diagnostic test performance, we then have to ask, is the evidence adequate to conclude that the improved accuracy will actually lead to better health

outcomes? And the approach that we took is really a modeling approach as well, that's less explicit than the decision tree that Deb laid out, but I think probably in fact leads to the same outcomes, but less quantitatively.

So first, the first step then in finding out whether difference in test accuracy would lead to important improvements in health outcomes, the first step would be to simply calculate the post-test probability of disease. If you know the prior probability and you know the sensitivity and specificity, you can calculate the post-test probability for the test under consideration but also for the sort of standard, the test in standard clinical use, and then evaluate in step two the potential impact of the difference in post-test probability and disease management.

Tests after all are just a device for moving probabilities around, and the question is, did two tests move the probabilities to a degree that is enough different to make a difference in the choice

of treatment and if not, you could argue that you don't need both tests.

And here is an example of a plot of pretest probability on horizontal against post-test probability for one of the PET scan applications that we considered in our November meeting. And here we have for example, CT scan in the solid line and negative CT scan, post-test probability with a negative CT stand versus post-test probability with a negative PET scan, and the difference in probabilities between here and here, the importance of those for choosing treatment is really the question at issue. And if the differences are small, for example down here, you might consider these differences to be so trivial that choosing between one test or the another really wouldn't be important, or alternatively, that PET scanning doesn't add something.

So, once we have determined the post-test probability for the test under consideration and the clinical standard test, then we ask, what is the

potential impact of the difference in post-test probability on management and health outcomes? And we make the point that distinguishing between -- the two tests are most -- a test is most likely to

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improve health care outcomes when the treatments themselves have an impact, either a big, there is a big opportunity to improve health outcomes or there are major harms associated with the treatment, in other words, where the stakes for treatment are substantial.

And if the stakes are minor for treatment, as in the use of vitamin E, for example, then being precise about the diagnosis isn't terribly important.

So, that's the model we have adopted, and I guess I'd like to ask the panel to briefly advise us as to whether what Deb is proposing is going to effectively follow the approach that we have deliberated on and decided to adopt. So I would like to open that discussion. Leslie?

DR. FRANCIS: Maybe a way to framework it is to go through things step by step, and I guess the

first step in what you had up there is the question of accuracy, right? And one of the things I wanted to be sure that you're going to get at is the question of accuracy for different populations and how much the data that currently exists is data that generalizes to folks out there who aren't in the fancy academic medical centers.

DR. ZARIN: I would assume that would be a

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high priority of the panel, and we would do that.

DR. SOX: So, let's try, since we don't have much time because Deb has to leave, so let's focus on the question of whether what Deb is proposing as a model for thinking this through sufficiently consistent with the model that we've adopted for evaluation of diagnostic tests. Alan, do you want to begin the discussion?

DR. GARBER: I think it's a very faithful way to follow the guidelines that we've used. I have a lot of questions about the details which I hope we'll get into, but this is exactly the kind of model

I think we will need.

DR. SOX: Barb?

DR. MCNEIL: I agree. I thought it was a wonderful model and it was reinforced by a lot of what Dr. Albert said. One question I had relates to what Sean raised earlier and I don't know whether it comes into the discussion now, and the issue was, where does technical performance fit in? Is that something that we want to address at this point, vis-a-vis the model, or whether we want to hold it until later?

DR. SOX: Okay. Does anybody want to take issue with these two about whether what she's doing

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is kind of on track with what we're doing? I agree with you, I think it is and we should move on.

DR. ZARIN: There is one place where I can say that what I proposed is somewhat different from your model, I think it's different from your model. Your model sticks basically with treatment effects on health outcomes and your model doesn't seem to include the value of prognostic information or other

kinds of psychosocial benefits of getting a test result. That was something I skimmed over, and obviously it's something that people would care a lot about in this disorder. The question is, does this panel want us to consider that, or do you want us to stick very closely to what we can find in terms of treatment effects and health outcomes?

DR. SOX: Alan?

DR. GARBER: Well, actually, our language on the diagnostic tests states that if it contributes to patient well being, then it should be considered, so I think that's completely consistent.

DR. SOX: What I would like to do because we don't have a lot of time with Deb is go over the questions that you want us to try to answer right now, and the first one as I read it was the importance of the technical performance of the test,

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on the one hand should the focus be there, or should it be on the effect of treatment on outcomes.

DR. ZARIN: I don't think I asked that,

because I was assuming that both were important. But when you say technical performance, do you mean which particular machine, which --

DR. MCNEIL: Yeah, I meant for instance, full ring versus coincidence counting, because I think the data are going to come up different and they may come up more different depending on the age of the system, so I think somewhere we're going to have to incorporate those differences.

DR. ZARIN: I agree. I think it will be important to try to extract from any studies details about the kind of equipment that is used because obviously the operating characteristics could be different, and presumably results different from different pieces of equipment.

DR. SOX: Yes, Frank.

DR. PAPATHEOFANIS: Also on that issue, are you going to also define other modalities according to those criteria as well, in other words, different MR scanners, different CT scanners? That could be disastrous if you do, so you have to be careful with that question. It's not full ring

versus --

DR. MCNEIL: Are they that different?

DR. PAPATHEOFANIS: Well, you know, as technology has improved for those MR scanners, sure.

DR. MCNEIL: But if we took a cutoff point, if the document said no articles before date X.

DR. PAPATHEOFANIS: Okay, if we do it that way.

DR. MCNEIL: I think if we took a date X, whatever it is, the difference between full ring and coincidence counting is likely to be greater than an MR from 1999 versus an MR from 2000, don't you think?

MS. RICHNER: Would the literature support different types of equipment? Do they divide it like that?

DR. ZARIN: I don't really know the answer to that.

DR. MCNEIL: You don't think we have a difference between coincidence and full ring?

DR. GARBER: This is bread and butter for AHRQ actually. I'm afraid this discussion may be getting a little more technical than is necessary. They have dealt with this kind of issue before and presumably the contractor will say what he examined

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and no more.

DR. TUNIS: I think it is worth pointing out at least as far as our having looked at the literature previously with PET in various oncologic applications that the vast majority of data is usually derived using full ring scanners, and so my best guess is we will be in the same situation here and will, you know, be kind of in somewhat the same difficult situation of then trying to make interpolations from inadequate data from different systems.

But you know, we -- and I agree, you know, AHRQ as well as the EPC, is sort of well armed to deal with that issue, although there remains a somewhat more policy issue around that of what to do about the relative paucity of data, for one. The

more prevalent type of PET system in fact will be where the paucity of data is.

MS. RICHNER: I have one more question on the treatment effects and health outcomes. Because it is so relatively benign, the types of treatments that are available, you have three drugs and you have the psychosocial implications for families, et cetera. I'm just concerned whether you know, we're being fair in looking at PET versus structural

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MRI, versus the others, and how that's going to affect treatment ultimately, because the treatment is not adequate for any diagnostic intervention. So I'm just curious as to how you are going to handle that in your assessment.

DR. SOX: Deb, I thought one of your questions was to what degree should we be looking at competing technologies.

DR. ZARIN: That's definitely a question and I was going to refer you back on to the previous discussion, which is, there is three approaches I can

think of. One is, we could look at the use of PET versus no technology other than, let's say the standard workup, which currently includes one structural imaging test, okay?

Another approach is to look at PET versus one of the best competing alternatives, but within that approach, we could either say we're going to do a primary review of all the PET data, but for the other approach we're going to depend on other systematic reviews, we're going to basically say, the literature seems to say that this is how good CAT scans are, this is how good MRIs are, but we're not going to personally, or the EPC won't personally review those data.

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And the third approach is that you want us to look at those data with the same level of rigor that we look at the PET data, and those have huge time and resource implications, so I would like your feedback on that.

DR. SOX: All right. Advice on this score?

DR. GARBER: I think you've answered your own question, number two. You can't avoid the other tests, so you can't do number one. And it would be difficult to accomplish number three.

DR. ZARIN: Not within the time frame, no.

DR. SOX: But you clearly have to specify the quality of the other systematic reviews and give us confidence that they're good. Alan.

DR. GARBER: Well, I don't know if this is the right point to inject this into the discussion, but it's such a critical issue for the analysis, I wanted to make sure we discuss this before you left, Deb, and that is, what the reference standard is here. I was getting a little concerned at the turn the discussions was taking earlier, at the idea that the reference standard might be something like autopsy, proven Alzheimer's. My objection isn't because that's infeasible, though it clearly is; it's

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because it's also largely irrelevant as far as I can tell. What we are interested in and what your model

really gets to are final health outcomes, and you can imagine an imaging modality that perfectly predicted the autopsy finding of Alzheimer's disease, 100 percent sensitivity and 100 percent specificity for biopsy or autopsy proven Alzheimer's disease, but wasn't a very good predictor of response to treatment. An alternative test was inaccurate at diagnosing Alzheimer's disease according to pathologic criteria but was highly sensitive and specific at predicting response to the available treatments.

So the question is, which is a better test, and I think your decision analytic framework makes it absolutely clear, if you care about the health outcomes, the latter test is the better one. So I think that your direction to your contractor, there may be reasons you want to look at the autopsy literature and whatever literature there is on biopsies, but the heart of your model truly is which imaging modality or which diagnostic modality, including the timing of that modality, is most likely to improve health outcomes. And so, the whole

accuracy modeling sub -- the whole accuracy component

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of the model really has to be oriented around response to treatment, and also prognosis to the extent you can model that.

DR. SOX: Well, Alan, so how do you under those circumstances, how do you advise them to actually measure conditional probabilities of positive tests given, how do you define disease? How do you find disease when it's really, a probability positive test given response to treatment, the probability of the test --

DR. GARBER: Well, the positive predictive value here is going to be the probability of a positive response to treatment, given a positive test rule, right? And so that's going to be dependent upon the population screening. Hence, my question earlier to Dr. Albert about how you define this promising population. And then the next element will be, given the test result, how do people do, or given treatment, how do people do and how does that vary

with the test result?

And one of the difficulties here undoubtedly is going to be finding out how imaging defined disease predicts response to treatment, will there be any literature on that. And I know that there is some, and there will probably be varying

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definitions of patient populations included in these studies. But ultimately we need to know, so it is going to be -- the conceptual issue I think is very straightforward. The practical issue, I have no idea about because you have to go into the literature to see if it really addresses this question.

DR. ZARIN: Can I suggest that since on some level we're talking about future treatment, we know those data won't be there in terms of --

DR. GARBER: Well, I had a separate comment about future treatment. Let's stick with current treatment right now.

DR. ZARIN: Okay. Let me just say that for some of the populations, the presymptomatic and the mildly symptomatic, perhaps a reference standard,

which I did list as course, so the ability to predict either that you're going to develop dementia, or that you're going to develop mild dementia, or within dementia that you're going to develop a clinical diagnosis of Alzheimer's disease.

DR. GARBER: Well, yeah, I can imaging that what you're trying to do is to estimate an absolute risk reduction if you want to call it that, in future development of severe disease, and you may have a relative risk reduction from a trial of Pacrin

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or one of the other treatments, and you want to apply it, and then you have some estimate of disease course from some other source of data, and then you apply that relative risk reduction to the disease course, so yeah, that is one approach that you can imagine taking to answer that question.

And then the imaging might be the key to predicting disease course.

MS. RICHNER: The problem is the treatments for this disease, like for instance Ivis

or something like that, if you use Ivis for intervascular, when you're doing a PTCA for instance, it may mean that you have reduction in restenosis or whatever, and that's a health outcome. But in this case, I can't see other than family intervention that there is going to be a difference in health outcome, so I'm very worried about this. I mean, unless we're looking at the early prognosis, looking just at that population, so that's what I'm concerned about, Alan. I mean, I think in theory this is all wonderful, but if the disease doesn't have good treatment --

DR. GARBER: We've heard that the treatment sets the disease back six months.

MS. RICHNER: Six months, I guess, is that going to be your health outcome measure then?

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DR. GARBER: Right, if that is true, I think that is highly significant and that would be reflected in the model.

MS. RICHNER: Okay. So the six-month improvement in health would be your measure then.

DR. MCNEIL: It's not improvement in

health, it's failure to deteriorate, and I can tell you from a personal experience with a relative with this disease, six months is a big deal.

MS. RICHNER: Oh yes, absolutely.

DR. MCNEIL: It is a big deal, so I would take a six-month stability course, I would take it any day.

MS. RICHNER: Compared to structural MRI.

DR. MCNEIL: No, no. You were asking about effects of treatment, the outcome, and I don't care how we get to the diagnosis. I was answering the question, would six months of stability in a patient with Alzheimer's disease be good, and I can tell you it is certainly good for the family and it is certainly good for the patient, because it reduces nursing home admissions in a fairly substantial way. So while it's not two years, six months is a nontrivial increment in this disease, I think.

DR. HOLOHAN: We routinely provide care in

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advanced cancer that doesn't give six months. That's

far more expensive and much more risk involved.

DR. ZARIN: I think the issue is (inaudible) in terms of the modeling and to see how it would play out, is that treating everyone. In other words, the current treatments have a very good safety record.

DR. GARBER: So that would be important to know. I think that you need to clarify those issues for us. That would be very important information. It's like if we ever find out that folic acid happens to prevent coronary disease, we probably aren't going to end up doing fancy tests to find out what people's folic levels are, or even a simple test, so that would be important to know.

DR. FRANCIS: I wanted to ask you about, I think it would be really neat if I were going to be on the panel, to have a little chart about all the possible benefits of treatment and the side effects, because at least as I as a nonphysician read the various materials that I was given, it seemed that there were, the drugs for which the six months was being associated, were drugs that are not as benign,

that there were at least some fairly significant dropout rates of patients using those drugs. And the

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ones for which we didn't have as much evidence yet, or was a trial period, like vitamin E, that's an open trial as I understand it right now, that's the benign stuff. So it would be nice to have a little chart.

And I also would encourage you all, though I know it makes the job harder, when you got to the legal social kinds of things, if there is any data about not just whether there is a drug somebody can take that would slow it down, but about whether there are other helpful quality of life features for people about having a diagnosis, or whether there are problems about having a diagnosis if the diagnosis is inaccurate, just a neat little chart to do all that, to just show where there is data and where there's not data, because one of the things the panel can also do is to try to encourage more data.

And I know that's a mess, because it's just a huge set of questions, but I guess the way I'd

try to limit that would be to look at a defined population, like say folks with mild cognitive disorders.

DR. PAPATHEOFANIS: Hal?

DR. SOX: Before you go on, Frank, I want to make sure, Deb, are there other questions, are we helping here and are we getting the things that were

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most important to you, or were there some others you want to raise?

DR. ZARIN: You are helping. Let me just ask, were you suggesting that perhaps we limit the whole analysis to one patient group?

DR. FRANCIS: Not necessarily, but if you have to choose, I would choose it that way and try to have a chart about more of the possibilities, rather than limiting the outcome that you're looking at to the question of, do we in all across the whole patient population, do we see outcome differences, because we probably aren't, there probably isn't going to be data that's going to be that helpful to look at.

DR. SOX: Are we getting what you want, or are there some issues that you raised on your last slide that we haven't discussed?

DR. ZARIN: No. I think the last issue that would be helpful to me is to hear, I think Alan, I don't know who said it, not to consider new drugs or not during that question, what people felt about either modeling or possible effects of beneficial and negative new treatments, or the role that you would like sensitivity analysis to play in the model, or strictly data curving.

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DR. GARBER: Well, I think you should do what you always do, which is to have an extensive sensitivity analysis. I have seen a number of studies that you had where they tried to speculate about new treatments and I have never found that to be useful unless there is some completely unexpected finding, and I'm sure that you will find that if you have a new treatment that's highly effective in Alzheimer's disease and highly risky at the same

time, then any test that improves accuracy of discrimination between people with the disease would be a good thing, but I don't think your contractor has taught anybody anything by going through that exercise.

If you have preliminary data that's reasonably solid on a new treatment versus writing this, then I think would be interesting to put in, but a speculative exercise about future treatments is likely to be completely uninformative, especially because you don't usually have any advance notion of how severe side effects will be.

DR. SOX: You raise an interesting point Alan, in the strategy of doing this study. Should you study the results of treatment and characterize side effect profile magnitude and impact, costs, and

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decide whether these treatments require a lot of diagnostic accuracy, because it's important to distinguish between whether or not to use them, or should you -- and therefore spend a lot of time working on the accuracy of the tests -- or should you

start with studying the accuracy of the tests very carefully and then work forward to the performance of the treatments.

If the treatments aren't any good or if they are very benign and not any good, then a lot of attention to characterizing precisely the performance of the tests in effect isn't very important, according to our model.

DR. ZARIN: Well, it might be important in terms of the prognosis and then the psychosocial effect. In other words, the potential harm from the test would be greatly influenced by the level of accuracy.

DR. SOX: One possible approach would be to evaluate the treatments, start your model, plug some numbers in for test performance.

DR. ZARIN: How good the accuracy would need to be to make this.

DR. SOX: Exactly. And then sort of, that would inform the degree to which you really want to

split hairs on diagnostic test performance.

DR. ZARIN: I actually agree with that approach, because I think that for example, we could look at the range of reported sensitivities and specificities and see whether, you know, being more precise about pinning down the exact numbers would actually end up mattering. And that also deals with the issue of which machine, and then you can say if the machine changed it this much, it might make a difference, but if it's within this general range, our conclusions would be about the same.

DR. SOX: Other comments on that strategy? Alan?

DR. GARBER: Well, this is a related issue, I don't know if it falls exactly on the topic, but as part of this exercise course, you'd have to figure out the effects of the treatments of the alternatives diagnoses, and I think this falls into your option one, two and three camp, where option three would be a primary literature review saying something like the effects of treating multi-infarct dementia. But I think your analysis will really only

be useful if you, will only be fully useful if you can say a little bit about correctly diagnosing someone with multi-infarct dementia rather than

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Alzheimer's disease.

And again, I think using the same principle you enunciated before, you can probably use summary estimates from the literature. Hal's question and mine, Hal's probably thinking the same thing as me. The last time I reviewed that, there was no direct evidence that treatment of multi-infarct dementia made a difference, but that may have changed. But in any case, you have to at least put in some number there to show what would happen if you improved the diagnosis of that disorder too.

DR. ZARIN: It's also, I gathered from my cursory review, a little more complicated in that many people seem to have both Alzheimer's disease and multi-infarct dementia.

DR. GARBER: That's one of the reasons it

doesn't seem to make a difference.

DR. ZARIN: Right. And when you decide they have enough infarcts to cause the dementia as opposed to just sort of background infarcts, so it gets very complex.

DR. SOX: I would like some comment on the question of the diagnostic problem to focus on. We heard earlier from Dr. Albert that she thought that

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the money so to speak, was in the presymptomatic and the very early cognitive impairment group of patients, and I would like the panel's opinion about that as guidance to Deb and the EPC. Any thoughts about that, where to focus the effort? Bob.

DR. MURRAY: I think that you have to take whatever data is available, but clearly the early preclinical studies, the studies of preclinical patients is where the money is, and it's also where the money is going to be. If it's classified as a screening test, you know, then it's a different coverage issue. However, presumably every patient being seen and being tested would have some level of

MCI that would justify the treatment.

But going back to answer your question, I think while the data is probably going to be sparse, that is whatever data is available should certainly be included.

DR. ZARIN: That population I think is where there will be the biggest mismatch between treatment data and diagnostic data, so there might be some diagnostic data, but there's some clinical trials going on. I'm not sure how much data we will find about treating people who are asymptomatic, you know, the high risk people who are in those trials

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now, and that's where we might have to model that.

DR. FRANCIS: That's also where I'm most worried about the psychosocial stuff. So whatever there is out there, you have to look at.

DR. TUNIS: One thing on the table is that I think we can't frame the coverage question as completely asymptomatic patients or patients with a genetic predisposition because it's not a covered

benefit under Medicare at all, so we couldn't actually approve it for coverage as a screening test in asymptomatic or predisposed patients. The only population, the next population I would guess would be mild cognitive impairment or some degree of early suggestive symptomology, but I think the others are off the table.

DR. SOX: So perhaps the person who is worried about forgetfulness, that would be --

DR. TUNIS: We would have to have some definable entity as mild cognitive impairment.

DR. SOX: Well, have we run dry on comments and advice?

DR. ZARIN: I feel like I'd better get going on this.

DR. SOX: You'd better get those folks started the afternoon.

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DR. ZARIN: This was very helpful to me, so I hope you all will remember this discussion when we come back to you with the assessment.

DR. SOX: I think it would be really

helpful to us Deb, when you get home and write this up for the EPC, to copy us, so as the panel then sees the product, they will be able to know what we focused on, what our concerns were, and focus their attention accordingly.

DR. ZARIN: And I would like to put in a plug, this actually was very helpful and I think that when we are addressing complex questions, as diagnostic tests tend to be, and certainly others as well, if we could have the opportunity to get the thinking of the Executive Committee prospectively, that would help us.

DR. SOX: Great.

DR. MCNEIL: Just to add to that plug, I personally benefitted enormously from Dr. Albert's presentation, so to the extent that for future activities of this sort, somebody like her provide an overview might also be useful.

DR. SOX: Well, we'll thank you very much and excuse you.

DR. ZARIN: Thanks for changing the time

of the agenda.

DR. SOX: Great, wonderful. We will take a break at this point, then come back and offer opportunity for public comment on this discussion and then see if there is any wrap-up discussion.

(Recess from 10:55 to 11:18 a.m.)

DR. SOX: Let's resume. The next item on the agenda, or the schedule, is an opportunity for comment from anybody in the audience about the discussion that we just had about framing the PET scan analysis for dementia. So, is there anybody in the audience who would like to step forward? There being none, I will then ask whether anybody on the panel would like to make any further comments, conclusions, regarding the discussion that we had before the break. Tom?

DR. HOLOHAN: Just as a matter of information, the VA owns more PET scanners than any other system in the world, and our current guidelines for the evaluation, diagnosis and treatment of Alzheimer's disease specifically do not recommend the

use of PET scanning. The guidelines state that the utility of PET scanning is as yet undetermined.

DR. SOX: Leslie?

DR. FRANCIS: I'd just like to make a

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comment about the prior public comment period, which was how helpful I thought Dr. Albert was. And it was really through the efforts of the Alzheimer's Association that she was brought here, and I thought that was very nice.

DR. SOX: Ron.

DR. DAVIS: Just following up on Tom's comment, I thought you might elaborate on the basis for that opinion from the VA.

DR. HOLOHAN: It basically stems from, the VA has a series of very active clinical guideline projects, probably extending at least back until, at the time Ken Kaiser had arrived as Undersecretary for Health, and guidelines have been developed, some jointly with the Department of Defense, but most internal to VA in many areas, and I won't go through

the list, it's extensive and covers mental health, it covers treatment, evaluation and treatment of ischemic heart disease. Usually they are done in conjunction with other professional organizations, and the geriatrics strategic health group or geriatrics clinical program in VA, commissioned the development of a set of guidelines and I think the University Hospital Consortium was a contributor, and it was done basically using mechanism of review of

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published articles, expert clinical opinion, whatever inputs most guideline processes have or don't have, and the conclusion was that PET scanning was not of demonstrated utility in the diagnosis of Alzheimer's disease at the present time.

DR. DAVIS: Was that recently, and have the results of that review been made available to HCFA and the AHRQ so they can use it in their study?

DR. HOLOHAN: We can do that. That was done in 1996, but they update every two years and the recommendations have not changed.

I should also note that at the 2001

meeting of the American Geriatric Society, there were 53 presentations on Alzheimer's disease, none that related to the use of PET scanning for diagnosis.

DR. SOX: Well, before we go on, I would just like to find out whether anybody on the panel has serious concerns about the direction that the analysis of the PET scanning and Alzheimer's is taking. Are we all kind of on the same page in feeling that the approach that AHRQ is tasking the EPCs to perform is on the right track? Speak now or forever hold your piece. Okay, good.

MS. RICHNER: I have a process question, I'm sorry, but we've written operations and I want to

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know if we can meet the timings associated with the November MCAC panel discussion of this. I know Sean, at one point you said that perhaps we should extend this, but if we look at what we've written in terms of what has to happen next, I wonder, are we going to apply this to what we've asked them to do with the reviewers. We have that the panel chair assigns two

panel members, the Executive Committee assigns two primary reviewers, we have the Executive Committee choosing a small number of expert reviewers, we have the reviewers submit a written report to the panel executive, we've got all these different steps. Are all those going to happen before the November MCAC panel review?

And if we find this too cumbersome, which I think it is, should we rethink all of this? It seems to me that if we're going to do this, we're doing part of it, you have asked the panel to help you form the questions, which we've done, so now what else are we going to do in this list of operations guidelines?

DR. TUNIS: To just separate the question into two parts, I think we, it did seem to me the way we ultimately ended up potentially scoping the EPC report, will hopefully be doable in this sort of four

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months that's available. I'm sure I will hear back from Deborah and others if they took a different message away from this discussion.

As far as the -- so, in that time frame of aiming towards a November panel meeting, I think we're still on for that. I guess in terms of the other list of procedures that are, that's part of the EC operating document, I guess I would sort of hand that over to you Hal in terms of whether we want to go through some of those things now or do it outside of the context of a meeting, or however you want to do it. We certainly shouldn't just ignore it.

MS. RICHNER: One of the issues is what Dr. Holohan just brought up, there is VA information that's available, and according to this, there would be an opportunity for that to be part of their evidence report, and so that seems to me that's very important then. And there is also other opportunities that we've written in here about supplying other evidence, other public comment, getting content experts as part of developing the evidence report, so you know, we should give this every bit of weight that we have put into our guidelines.

DR. SOX: Well, the guidelines that we

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wrote and approved several times represent our best thinking about how to proceed, and we really won't have an evidence base for modifying them or discarding parts of them until we do them, so I personally believe that we should carry it out according to the way that we said we were going to do it, and then debrief ourselves about what made a difference and what didn't. But right now, what's in the interim guidelines represents the consensus of this group about the right way to go, and you were a major contributor to that.

MS. RICHNER: Right. So working back from November, you know, we have a lot to do here in terms of appointing committee members and reviewers and all that kind of stuff.

DR. SOX: Alan.

DR. GARBER: Well, Randel, I wasn't sure whether your point was that what's been proposed is too cumbersome and will take too much time, or that you're afraid we're going to slip and not do the

reviews and everything else that was called for in the guidelines, but whichever was the point you intended, I'd just like to make the observation that sometimes we will be dealing with technologies where it's truly a life or death issue or something that's

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really important like, you can imagine, we might hear about a treatment for Alzheimer's disease that really worked well, was incredibly effective but also very toxic, and it will be important for HCFA to assess the evidence and make the coverage decision rapidly.

And in other cases, the magnitude of benefits, potential benefit we're talking about will be much more modest, and now we're presented with a technology which is very complex in the sense that it's not that easy to figure out how big of impact it has on health outcomes, and would require substantial effort. And where frankly, the initial evidence seems to suggest its benefits will be modest, because it's not a treatment, it's a diagnostic test and a lot of people get treated anyway, and I would argue

that HCFA should have some flexibility about timing.

In a case like this, I think it's more important to get the answer right, to do a proper study and to get all the relevant information even if it means some slippage in the schedule. In the case where we have something that's dramatically effective or potentially dramatically effective, then we really need to adhere to a rapid schedule and get things done quickly.

So, basically, I agree with Hal. I think

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it's important to follow the guidelines in terms of being very complete in this process, and let's see how long it takes. This will be a very good test case.

MS. RICHNER: Fine.

DR. SOX: So in that respect, the possible action that we might be taking now is to schedule an alternative date for the panel, say six weeks or two months from the current schedule as a fallback, in case we do run into trouble. Ron, did you have something?

DR. DAVIS: I think Bob was first.

DR. SOX: Bob, please.

DR. MURRAY: Just a comment in support of Randel's observation. These guidelines were written as I recall, or they were at least initiated after the first two panels had met and the panels had been presented with, from my recollection, a rather disorganized packet of information that each panel member was expected to synthesize into a coherent logical analysis, and the step by step process was an attempt to deal with that so that the whole process would become more efficient. So, I would support Randel, that I think it's always subject to review, and just as we have updated these recommendations

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from time to time, I think that since we have seen a very thorough AHRQ or EPC analysis with each of the susequent issues, I think that will change, you know, how rigidly we feel we have to adhere to the process that we set in place initially.

DR. SOX: Thank you. Ron?

DR. DAVIS: I agree too with the thrust of Randel's comment, and to be a little more concrete about it, the interim guidelines, I don't know how long we're going to call them interim, but they state that, as Randel was touching upon, that the panel chair shall assign at least two panel members to work closely with the authors of the evidence reports, and I'm not aware that this has happened yet. I know in the evidence reports that I have seen either on the EC or in our own panel, I am not aware that there has been an opportunity for panel members to work with the authors of those evidence reports, so it's possible this is the first opportunity that we have to get panel members involved on the ground floor in the preparation of this evidence report.

And Frank, are you the chair of the diagnostic imaging panel? So I think the point is, picking up from Randel's comment, is that now is the time and maybe Frank has already thought about this,

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where two members of the panel should be assigned to work immediately with whoever is doing this work on

this evidence report, and that could begin I guess as soon as tomorrow or next week.

DR. SOX: And I guess, just to put a little more pressure on you, Frank, I think the committee is basically saying let's do it the way we said we were going to do it, and I guess I hold you and Barbara and Sean, and the executive secretary of the panel, to do it.

DR. PAPATHEOFANIS: Right.

MS. RICHNER: Exactly, that's the point, to see if this works. I mean, when I tried the last time in February to outline the process, I didn't see how it could possibly work, so this is a good idea to try it, and see if we should modify it. I mean, we really should think about if this is indeed logical or sensible to have all of these review upon review, and this kind of thing.

I mean, even though it's not life threatening, even though we know that there's going to be a robust body of evidence, et cetera, et cetera, let's work with something that's

reasonable so that we don't continually get the reputation of being obstructive and taking too long.

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DR. SOX: Barb?

DR. MCNEIL: Well Hal, maybe I could ask Frank this, or Sean. The PET for breast is meeting on Tuesday, and the question would be, there is an evidence report and we are going to discuss it, and what would we want to do next with regard to the process that Randel is talking about. I don't believe we assigned two panel members to review it. On the other hand, I'm not even sure that would have been a helpful step to be honest, because it was reviewed by the group that did it, AHRQ or their subcontractors had outside reviewers review it, and I'm sure that those outside reviewers were much more tuned in to the clinical details and the technical details of the project or the technology than on average, a diverse group like this would be.

MS. RICHNER: There's some really good components of this in terms of getting the kind of people you need to get information and provide input.

DR. MCNEIL: The question is how many reviews, and I was just raising this one on Tuesday, and Frank, what do you think?

DR. PAPATHEOFANIS: I think Randel brought up the point that this is really the first time that we're going to actually get a chance to work through

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the complete mechanism. Both times prior to this, the PET, which would fall under the purview of the Diagnostic Imaging panel have come up, they've come up because other sorts of interest from the Agency and have really been guided by Sean's group. I think that as you said Hal, now the onus is on us, Barbara and myself, to pull this thing together in an appropriate way, and I think we can give it a good shot.

DR. MCNEIL: Can I just follow up though? Do we need to do anything for the technology that's coming before us next Tuesday? That's really what I was asking.

DR. TUNIS: Yeah. I'm not aware of

anything that is in the interim guidelines that is now a step that we can take between now and next Tuesday that we are sort of missing.

The other thing to point out, and I think we talked about it in February when these were presented, the EPCs do have their own very formal and explicitly defined process for developing a core technical advisory panel, a broader advisory panel and the whole sort of mandatory extensive outside review process. And what I don't believe we did since February was to see in what way the operational

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things described in your guidelines are either redundant to or coordinated with the EPC standardized process. So I think after this meeting, we will need to look at both of those things and to maybe come back either with a conference call of this group, or for our next meeting.

MS. RICHNER: I mean, if HCFA chooses 100 percent of the time to go with AHRQ and using that model, then this, we need to put something in here to reflect that. If you're choosing ECRI or other

technology assessment bodies to do your evidence reports, then it may need something a little more.

DR. TUNIS: Right.

MS. RICHNER: But I don't how you choose who's going to do your evidence reports.

DR. TUNIS: At this point we are doing a hundred percent of our evidence reports now through the relationship with AHRQ.

MS. RICHNER: A hundred percent ongoing?

DR. TUNIS: Right. We are not doing any separate contracts with other providers. In fact, just since we're on it, what AHRQ is actually in the process of doing is setting up one of the EPCs to be, I don't know what the title of it is going to be, but sort of a rapid response TEC assessment group, who

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will be able to do much shorter turnaround TEC assessments, on the order of two to three months, in order for internal HCFA use as well as for things that are going to come to MCAC, but it will still all be done through our relationship with AHRQ and their

relationships with EPCs using kind of standardized EPC processes.

MS. RICHNER: I wasn't aware of that so that's helpful, thank you.

DR. SOX: I think Alan was next.

DR. GARBER: Well, you may know, the Medical Surgical Procedures panel had worked with previously written reports that were done under the EPC arrangement, or that were done by two evidence based practice centers, ECRI and Blue Cross/Blue Shield, so there was no opportunity to participate in the review because these had been previously completed. But I think that this point that we need to, basically the implication of Randel's and Ron's comments, I think is that maybe this process is redundant if they have gone through the full EPC review, and I think that it will be very helpful to see what your experience is with this upcoming one, where you will have the chance to apply it.

And again, the interim guidelines were

meant to be advisory and there is a certain amount of

common sense involved here. I was the co-author of an EPC report that had something like I think 40 reviewers, 30 or 40 reviewers, and they included people like the people around the table, people in the clinical area and so on, an yes, to some extent it's very likely that two reviewers from the panel are not going to contribute a whole lot that's new.

On the other hand, HCFA may sometimes want to work with existing evidence reports that are tweaked in a particular way to address a coverage question that might have been a little different from what the EPC had originally went to look at, and that's a situation where presumably having another review through the panels would be very valuable.

So at this point, I agree with Randel's suggestion, we need to collect the data and find out how this works, but at the same time I think everybody on the Executive Committee felt that some aspects, particularly the operational aspects, are going to have to be changed as we get more experienced with it, and I hope that everybody views

these as just broad parameters to work with, that you may have to bend a little bit. Now this does not mean that we bend a lot in something like whether to

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use evidence and the adequacy of evidence criterion. We're talking about things like timing, who does the review, and so on.

MS. RICHNER: One of the key points that I don't want to give up in these operations is the public input in here, and also making sure that there is the opportunity for industry or clinicians or whatever, that have data that may or may not be published, that was one of the discussions we had in February, that could be included within the accumulation of evidence for the report, and so that step to me is very critical that we remain, keep that pure.

DR. SOX: My view is that what we have written down is the default and if you want to depart from that, you need to have a good reason and if you think it's appropriate to discuss it with Sean or myself, just to kind of reassure yourself that you're

on target.

DR. PAPATHEOFANIS: Just to reassure Randel, as far as the breast cancer PET topic that we will be reviewing next week, I think it's fair to say that whatever questions we had, the Agency was very responsive in addressing it on short term, and there was more than ample opportunity for public and

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industry to provide comments, so even if the letter of the guidelines wasn't followed, in a practical sense, there were opportunities.

DR. TUNIS: Just to point out that some of the reviewers for that particular evidence report, we asked Sam Gambhir to be one of the reviewers, who was one of the requesters of the original PET coverage document at UCLA, and we also gave it to Ellen Feigal and the folks at NCI to find a reviewer, of the actual EPC document, so I do think we're very guaranteed when we go through the EPC process, you know, of comprehensive review. And maybe it would help at the next EC meeting if we actually had

somebody closely associated with the EPC, either Deb Zarin or the person who actually runs it to actually walk you all through exactly what the process is, and you can see if there is any steps left that you still think this committee would have like to have as part of their deliberations.

For example, I don't believe standard EPC reviewers typically have industry reviewers, in part because if you have an industry reviewer, it's very hard to make sure that you have every potentially affected industry reviewer, and so I think they have taken the position not to have any industry

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reviewers, but that may be something that you would want to modify for this process.

DR. SOX: Barbara?

DR. MCNEIL: I like that idea, Sean. Just from the phone call we had with some of the members, or all of the members of the Diagnostic Imaging panel this week, there was some, I think confusion is the right word, about what the criteria were for evaluating evidence from the original

articles by individuals who were on the panel, but probably weren't as familiar with the EPC approaches to things. I certainly felt very comfortable with what the contractor had done, and had set up the tables absolutely beautifully, and I think Frank did as well, but I'm not sure that everybody on the panel was totally tuned to their modus operandi, so this is to say, maybe if we had them come to the Executive Committee, we might want them also to say a few words at each of the committee meetings, so that everybody is on the same page.

DR. TUNIS: In fact, the EPC has commissioned a separate subgroup just to look at the issue of how evidence is rated, and so they could talk about -- that's a standardized methodology across all the EPCs and they could certainly describe

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that.

DR. PAPATHEOFANIS: That would be very useful.

DR. SOX: Ron?

DR. DAVIS: I wanted to return to this question of two panel members being assigned to work with the authors of the evidence reports. Barbara and Alan in their comments implied that the purpose of assigning these two panel members to work with the authors of the error was so that they could provide additional technical input, but that's not what I recall the main purpose being when we drafted this thing. I thought it was mainly to insure that at least two members of the panel would really be in tune to the material in that evidence report, akin to the NIH study groups where each grant proposal gets assigned, for example, two primary reviewers.

That guarantees that two people on the study group will really know the ins and outs of that particular grant proposal. Similarly, here, we will be assured that at least two panel members will really know the guts of the evidence report. So I see that as the greatest gain from this, and if they could provide some technical input that helps the contractor at the same time, then great, that would

be icing on the cake.

DR. SOX: Alan.

DR. GARBER: Ron, just as a point of clarification, I agree with what you said. Actually, there are two aspects of this. One is the time at which they review it, and my expectation is that we always would have two panel members assigned to take primary responsibility. The question is, do they need to get involved at the time the EPC report is being prepared, and that's what is kind of an innovation in the process, to get them in that early in the development of the evidence report. And that's where I thought you would draw more on technical and clinical expertise at that part, but my expectation, and Hal, correct me if I'm wrong, is that we would always have two panel members take primary responsibility at the panel meeting for being intimately familiar with the report.

DR. SOX: Yeah. Actually, the innovation of having two panel members get involved was actually stolen right out of the play book of the U.S.

Preventive Services task force, where it has been extremely valuable to have task force members, usually two, involved with the EPC members in framing the questions, making sure the thing is clinically

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relevant and representing the, actually representing the EPC at panel discussions. It's a way of really us taking more responsibility, rather than just simply turning it over to somebody and then hoping it comes back in some kind of condition. It maximizes our chances that we will be able to do our best for the public.

DR. DAVIS: And I think there is a huge difference between that process and simply getting an evidence report at the end of the process. I mean, just reading a report at the end as opposed to being involved in its development, I just think that's a very positive innovation and a big difference.

DR. SOX: This stuff is our responsibility, not HCFA's responsibility.

DR. TUNIS: Just to be sure I understand, would it be then, the chair and the vice chair of the

respective panel will be the two people who will be assigned to work with the EPC on the evidence report.

DR. SOX: I think they could assign themselves or they could assign somebody else.

DR. TUNIS: From their panel?

DR. SOX: From their panel.

DR. PAPATHEOFANIS: And I think from a practical sense, from our conversation with our

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panel, there may have to be some translation of issues to the methodologists that make up the EPCs, because I sense from our panel that maybe their clinical knowledge would be useful, but their methodological understanding may not be up to par, so that may be just a practical issue, so it's either the chair and co-chair, or someone who is able to translate the methodology of the EPCs to somebody clinical.

DR. SOX: I think somebody has to take responsibility for making sure that you start to have some telephone conference calls involving the two of

you and the team, and that it happens regularly because my opinion is it's a good approach, but somebody has to take the lead to make it happen.

DR. PAPATHEOFANIS: We will try to take this for our next meeting and run with, and let you know how it turns out. But up to now, even regular conversations with the full panel on the line has been pretty rare.

DR. SOX: Well, we're getting pretty close to calling a break for lunch, but if there are any other comments on processes, they have been really quite valuable and I don't want to cut them off.

DR. FRANCIS: I guess I wanted to say just

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briefly that one of the reasons why I like the interim guidelines is that I do they allow a lot of opportunity to get the question framed in a way that we really want to get responses from the public broadly, and so truncating it seems to be a bad idea, if that's what the drift of Randel's comments were.

And I was going to say something earlier, and I was delighted to hear from the two of you and

from Sean that there has been a lot opportunity for folks who might be interested in commenting to have a good sense of what those questions are, or at least we perceive right now that's the way you guys proceeded, so that it would be useful, I think as the meeting happens, to try to keep your blinders up to see whether that's actually happened, because it seems to me that we think now that there has been good groundwork laid, and I hope, you know, I hope that transpires, and so it would be nice to keep your ears to the ground, and see if that's really what happens.

DR. SOX: Well, we'll take up our task at one o'clock.

(Luncheon recess from 11:53 a.m. to 1:27 p.m.)

DR. SOX: The next item on the agenda is a

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discussion of ambulatory blood pressure monitoring. The Medical Devices and Prosthetics Panel, which I chair, met to discuss this topic and made a

recommendation that's now up for consideration by the Executive Committee.

So what I'm going to do is present briefly our findings and our rationale, and then we'll have committee discussion, an opportunity for members of the public to comment, more discussions, and then we will take our votes.

Now, first a process note. For this discussion, the committee borrowed another play out of the play book of the United States Preventive Services task force and used what the task force calls an analytic framework, which is basically a way of dissecting out the problem of trying to understand the impact of the technology on health care outcomes, and then to look at the evidence for each one of the sort of nodes in the analysis. And if everything lines up nicely, then you've got strong evidence for a favorable effect on health care outcomes.

As a procedural note, I found that not only was this approach very valuable for steering the discussion, but it was also very helpful in drawing up my official chair's report of the discussion, and

I think it, in my opinion, it leads to a pretty good way to track what the committee's thinking was and how well it used the evidence in trying to come to a conclusion.

And so what we're going to do is to walk through my report following the nodes of the analysis that we did. Now we focused almost all of our time on the issue of using ambulatory blood pressure monitoring to try to identify people whose blood pressure was abnormal in the office but normal at home. And the question for these patients is whether, if you can identify people whose blood pressure is normal most of the time, whether perhaps they require no treatment or less treatment.

So, we parsed the problem the following way. Suspected white coat hypertension, which you might suspect on the basis of high blood pressures in the office but then the patient reports that when they take blood pressure in their home environment that it's normal. Then performing APBM. And then

there are basically two sort of ways you could go.

The first would be to ask, is doing ambulatory blood pressure monitoring, does it affect health care outcomes? And in order to draw a conclusion about this sort of direct line between

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doing the procedure and health care outcomes, you would do some sort of controlled trial in which some patients got the procedure, others did not, and then you measure health care outcomes downstream. There have been no studies which in fact tried to test whether APBM reduces the frequency of stroke, coronary artery disease and other complications of hypertension.

So instead, we followed this inner line of reasoning and first said, does APBM in fact identify people who have high blood pressure in the office but normal blood pressure at home? And that leads to key question number one. Then, given that you can identify patients who have a normal blood pressure at home but not in the office, do physicians actually change the management of these patients, and if they

change the management of these patients, what is the effect on intermediate health care consequences of hypertension such as left ventricular hypertension or the development of atherosclerotic plaque in the large vessels. And finally, if such effects do occur, what are the health care outcomes under these circumstances, so is there link between these intermediate outcomes and more distal health care outcome. So that's how we parsed the problem.

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I organized my report basically to touch on each of these key questions. The first question, we basically took as a given, relying upon the responsibility of the Food and Drug Administration to find out whether a technology in fact does what it's supposed to do. So we took that truth as a statement, as a given.

The second question is, do physicians withhold treatment from patients who are found to have normal blood pressures at home, or who meet the definition of white coat hypertension?

And perhaps I could take a moment to comment that the definition of white coat hypertension varies a great deal from study to study. Some studies, a person with white coat hypertension would have a blood pressure of greater than 90 in the office and a blood pressure of 85 or lower diastolic at home, whereas in other studies the definition of white coat hypertension would be a diastolic blood pressure of less than 80 at home. So there was a considerable heterogeneity in the definition of white coat hypertension.

Well, there's not much information about what physicians do when they find out that somebody has white coat hypertension. There was one UK study

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in which 80 percent of patients who had white coat hypertension in fact had no change in their treatment, and as far as I know, that's the only source of information we have on that score. If physicians ignored the findings of APBM, that would clearly undercut the value of the procedure.

The next key question is, do people who

have untreated white coat hypertension have intermediate health outcomes that are the same as people with normal office blood pressure? And what we found in looking at probably 15 different cross-sectional studies which simply looked at people who either had sustained hypertension or people with white coat hypertension, and looked at the frequency of thickened left ventricle, carotid artery plaque and the like, and what we found was that most of the studies showed that patients with white coat hypertension had these intermediate measure of health care outcome that were somewhere between people who had normal blood pressure all the time and people who had high blood pressure all the time, and the prevalence of these intermediate outcomes varied between studies, in general correlating with how high they set the definition of white coat hypertension. So a study that defined white coat hypertension as a

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diastolic of 85 or less at home would have a higher prevalence of increased LV mass than a study that

defined it as 80 millimeters of mercury or less.

But, sort of getting back and looking at it at the 30,000 foot level, it was pretty clear that the majority of studies showed that patients with white coat hypertension have a greater prevalence of these intermediate outcomes, in other words, white coat hypertension is not necessarily a benign condition, and there needs to be concern about what you should do with these people and what level of diastolic blood pressure it would be appropriate to reduce or even stop antihypertensive medication.

Now, the key question number four, the patient with untreated white coat hypertension and intermediate health care outcomes have final health care outcomes that are the same as patients with normal office blood pressure. And there we really only had one study to rely on which was a cohort study in which they found that the stroke incidence in patients with white coat hypertension was similar to that of normotensive people, and much lower than patients with hypertension at home on ambulatory blood pressure monitoring. So, stroke rates more

similar to normotensive people than to people with

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sustained hypertension.

The problem with this study was that it wasn't clear to what degree the patients with white coat hypertension were on treatment, some were on treatment, some weren't, and it was really not possible from the data presented in the study to link the presence or absence of treatment or withdrawal of treatment to the health care outcomes.

Also, it was a short-term study that looked simply at the amount of medication the patients were on, rather than long-term outcomes. So it really didn't test the hypothesis that we were concerned about.

Now, we had quite an extensive discussion of these data. It appeared that white coat hypertension is not a benign condition but it's simply not clear how treating patients on the basis of their ambulatory blood pressure at home, what effect that has on health care outcomes. So the data

set in some senses is seriously missing key items of information that relate the treatment or the management of patients with white coat hypertension to health care outcomes.

We were aided in our discussion of this problem by several national world experts on

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ambulatory blood pressure monitoring, and although they were people who subscribed to consensus statements that advocated ambulatory blood pressure monitoring and they also, their clinical expertise, I think made a quite a strong impression on our committee.

In the event, we eventually had a motion on the table, and I'm going to read that motion. The panel believes that the evidence in cross-sectional studies indicates that people with white coat hypertension have intermediate harmful health care outcomes as compared with normotensive people. So again, white coat hypertension is not a benign condition.

Although higher quality evidence is

lacking and data on true health care outcomes such as mortality and cardiovascular disease morbidity are sparse and of relatively low quality, the panel believes that the use of ambulatory blood pressure monitoring in diagnosing white coat hypertension can help individual treatment of patients with white coat hypertension, which may in turn improve health care outcomes. Therefore, the panel supports ABPM for the diagnosis of white coat hypertension in patients suspected of this, if guidelines are developed for

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selecting patients for APBM, for monitoring, and for deciding when to treat and when to withhold blood pressure medication from patients who prove to have a lower blood pressure in their home setting than they do in the office setting.

And finally, the panel recommends that studies be done to better define white coat hypertension, and to identify patients with white coat hypertension who are at relatively low risk of developing cardiovascular disease side effects.

So, we had a discussion of this, we made some modifications, and eventually this panel voted unanimously to approve this motion, which was Ron Davis's contribution. If you look closely, I think what happened in this discussion, it's pretty clear that the evidence base leaves some of the links in this logical train of thinking pretty open, that is to say unproven. The committee's decision to ultimately endorse, if you like, ambulatory blood pressure monitoring, I think was partly the influence of the experts who came both to advocate but also to help us think about the problem. And we became convinced that if physicians knew how to manage patients with white coat hypertension and actually managed them thoughtfully and cautiously, that health

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care outcomes would be improved and costs might be lowered.

However, I think it's fair to say that those two events, that is appropriate management of these patients, really remains in the hope category rather than in the proven category. And so the final

bottom line as I interpret it was, we became convinced that ambulatory blood pressure monitoring had the potential, as yet unproven, to improve health care outcomes in patients with white coat hypertension if physicians are selective in choosing patients for monitoring and cautious about altering treatment after diagnosing white coat hypertension.

I think the process that we followed in coming to this conclusion was in my opinion a good process. We dissected out the problem, we had good information about the evidence, we heard from a number of expert clinicians with a lot of experience in the field, and ultimately the panel made its call.

So, with that as a rather lengthy introduction, the first step in the discussion will be to hear from the panel. Who would like to start the discussion. Ron.

DR. DAVIS: I'm on the panel with Hal, I am the vice chair of the panel, so perhaps I will add

a few comments to provide a little bit more

information. I think Hal did a very nice job in summarizing the deliberations of our panel. I think what was most persuasive, without repeating much of what Hal said, was that there is evidence that white coat hypertension is associated with intermediate health outcomes, which are intermediate in occurrence between normotensive people and people with sustained hypertension, so that was compelling to our panel. And I think it was a feeling of the panel that even though those were not what we refer to as true health outcomes, that there is likely to be a relationship between intermediate health outcomes like left ventricular hypertrophy and risks of more serious adverse health outcomes.

We also did hear testimony which I think was compelling to the panel that APBM is useful in clinical decision making. And some of that was presented to the panel in the public comment period and submitted beforehand as well, and I think we went through a real educational process, I know I did, and learned a lot about this issue, even in some conversations with some of the experts during the

breaks and the panel deliberations.

The end of the statement that the panel

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approved I think is important. It offers a few caveats, and those caveats were put in there because of concern that this policy, if put into place by HCFA, this recommended policy if put into place by HCFA could lead to some abuse. Certainly we didn't think it would be appropriate that every patient who is hypertensive in the doctor's office be put on ambulatory blood pressure monitoring, so in an extreme case, this could get out of hand. So we thought if we added the caveats to the policy statement that we were adopting, that that would mitigate against that problem.

And those caveats are, as Hal mentioned, that guidelines really should be developed for selecting patients for ambulatory blood pressure monitoring, that's number one, and number two, that there needs to be the development of guidelines for managing people who are diagnosed with white coat

hypertension.

Just to give you an example, talking with one of the experts, how do you select patients for ambulatory blood pressure monitoring? One of the experts mentioned to me for example that you could have somebody who gets his appropriate three independent measurements of blood pressure in the

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office and then might be recommended for blood pressure measurement outside the office, not continuous ambulatory measurement, but through a home device or some other device that we see in shopping malls or the like, and for example, there could be a requirement that the person have three independent measurements outside the office which are normal, which might then lead to a diagnosis of white coat hypertension. So that might be a criterion for diagnosing white coat, for provisionally diagnosing white coat hypertension, which then would be confirmed by ambulatory blood pressure monitoring. I'm not sure that that's reflected in policy from any organization but that was how one of the experts

approaches it in his own office, so that's an example of how such a guideline could be developed for determining how to select people for ABPM, first require three independent measurements outside the office that show normal blood pressure before doing the continuous ambulatory monitoring.

Then on the second caveat, how does one manage white coat hypertension, one of the experts told me that his approach, if I remember correctly, went something like this. If there was no sign of end organ damage, no nephropathy, retinopathy and so

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on, then he might be inclined to monitor the person's blood pressure, monitor the person for the development of end organ damage and not treat with medication in the interim, but then at the first sign of end organ damage, then begin treatment. Again, there might not be much data for that approach, it might not be a policy that had been enshrined by any medical organization, but this is the guideline that this particular expert follows in his own office.

So, I think it was the panel's feeling that we need to at least develop consensus guidelines for how to do these two things so that the whole process doesn't get out of control.

So that, I think provides a little bit more of the thinking of the panel that went behind the adoption of this statement, which I look at as kind of a compromise statement that the panel adopted to bridge between positions that might have gone toward rejecting any sort of use of the medical technology versus something that would have been much more permissive. Thanks.

DR. SOX: Okay. So our goal is to have a discussion, hear from members of the public, more discussion, and then take a vote on whether to endorse this recommendation or not. Alan.

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DR. GARBER: I should preface my comments by saying that I was a member of the medical advisory panel for the technology evaluation center that reviewed this same topic and determined, the panel had voted that it did not have adequate evidence to

support its effectiveness. I think that your panel did a really excellent job of finally drafting this and I think it's important to understand why people might come out differently on this issue.

And to my own mind, if you look at this case of white coat hypertension in particular where the outcomes are intermediate, most of my colleagues, I believe, treat those people as though they are hypertensive, and don't worry about doing the ambulatory blood pleasure monitoring, figuring that the risk is elevated, and I'm sure there are other physicians who choose not the treat, and the crux of the issue is that we don't really have definitive data to tell you which approach is right, and if you confirm the diagnosis of white coat hypertension by doing the ambulatory blood pressure monitoring, we just have a very sketchy evidence base on which to determine the optimal treatment.

I think that was very influential in the TEC program's medical advisory panel's conclusion

that the evidence was not adequate, and I think that reasonable people might differ, and your panel's decision to craft the indications as narrowly as it did, although I don't entirely agree with it, I think was a very well considered response to this issue. But the bottom line for me is that, although I may disagree with the conclusion from all that we've read in the minutes and so on and all that we've heard, the panel really did follow the procedures that were prescribed and I don't think the role of the Executive Committee is to second guess the conclusion. The role of the Executive Committee is to decide whether the panel followed the procedures that would lead to an evidence based conclusion, and it seems to me that it very clearly did do that.

DR. SOX: Thank you. I think that's an important statement for us to remember. If we depart from procedure in a way that could lead us to make a wrong conclusion, that is an indication perhaps for the Executive Committee to send it back basically, but otherwise, I think we put the evidence out there and we trust our colleagues to do the best with the

evidence. Barbara.

DR. MCNEIL: I agree with Alan. I have one quick question actually, maybe to Sean. I think

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you did a great job with this and it's clear the data are lacking. Would it every be possible to send a message to the Heart and Lung Institute that as part of their ongoing funding of the Framingham study, which I think that they are still doing, they identify patients with white coat hypertension, and then send them on to some kind of approach similar to one of the ones that Ron suggested, and then just follow them? Because it would be a very small amount of money added on to a quite large -- the amount of money they would have to pay would be I think quite small, because these patients are already in the system, having been evaluated, and are being followed forever as far as I know, and this might be one way of actually answering the data limitation that you have.

DR. TUNIS: Well, interesting. Actually,

one of the points we will talk about briefly later in terms of the future roles of the Executive Committee, one of the ideas I wanted to put on the table for your discussion was almost precisely this, which is essentially the Executive Committee identifying critical research priorities related to coverage issues that do get discussed here, and it sounds like that essentially what you're identifying, and not

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only a priority research question, but also a potential platform of existing research on which that can be done.

As you know, we don't have any particular leverage to influence funding decisions by NHLBI, but you're welcome to recommend them to anyone you see. But, in terms of how we actually could go about turning that into something that occurs, other than to have this body endorse that as a recommendation, I think would be of some value.

DR. SOX: Any other comments? Tom.

DR. HOLOHAN: Was there any evidence presented to the panel or the issue ever raised about

the relative utility of patient self monitoring versus APBM?

DR. SOX: That's a crucial question. In other words, what does APBM offer at the margin as compared with simply taking your blood pressure at home with a cuff that you buy at the local five and dime store, or I guess 25 cents and dollar store.

DR. GARBER: Would that be where Wal-Mart steps in?

DR. SOX: And I don't recall that we saw any studies that addressed that question, which is such an important question, I think I would have

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remembered it if there had been. Frank, do you?

DR. DAVIS: I don't remember that information being presented to us either.

DR. HOLOHAN: Following on that same track in a sense, the key question one said the panel took the truth of this statement that it does detect patients who have normal BP at home as a given, relying upon the FDA PMA process, that these devices

are accurate. The only information I found in the package sent to me from Space Labs said this was a 510.K approval by the FDA, which ordinarily requires no clinical evidence, all you have to do is demonstrate it was equivalent to a product that was on the market before 1976.

The reason I bring this up is the British Hypertension Society and AMI I guess, together recently had a couple of publications, one in Lancet, that looked at accuracy standards for home blood pressure monitors, which essentially are also marketed without significant clinical evidence, and found that many of them didn't meet the British Hypertension Society's accuracy standards. So if Medicare or HCFA is the going to pay for the use of APBM, would there be any requirements that those specific devices should have paced the AMI or British

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Hypertension Society's specs?

I know the VA is right now, we pay for home blood pressure monitoring cuffs for our patients and we have done a review and found a lot of the

devices that we have been buying did not pass the British tests for accuracy. Kind of a long convoluted question, but I think it gets to the issue of whether the measurement in the office and a measurement somewhere by something at home allows you to come to a rational conclusion about the true existence of hypertension.

DR. TUNIS: I think one of the speakers that's going to come up here in the public comment period represents Space Labs and I think can sort out the 510.K issue in terms of the clinical data. My recollection of the TEC assessment report and other information we reviewed internally, was that the FDA does apply very good technical standards in terms of accuracy and reproducibility of the measurement, as measured against the gold standard, but doesn't require the clinical data in terms of does the use of the device make a difference in terms of patient outcomes. But I think Grant can speak to that issue a little bit more.

And I don't know if there is anyone in the

audience that recalls, I thought there were some studies that looked at self monitoring of blood pressure with a cuff versus the ambulatory blood pressure device, but I don't actually remember the design or the results of those studies.

DR. SOX: I have some faint memory of that going back to when the ACP actually reviewed the subject. And my recollection actually was that home blood pressure monitoring with a regular cuff looked pretty good, but I don't remember the data.

MS. MARX: There were several patients who testified before the panel and talked about ambulatory blood pressure monitoring detecting high blood pressure that they had while they were sleeping, so clearly they wouldn't have been able to detect that themselves.

DR. SOX: Thank you. Ron?

DR. DAVIS: I just wanted to comment on this key question number one as a follow-up to Tom's question, and even though your write-up, Hal, says the panel took the truth of the statement as a given,

I do remember looking for an answer to this question as we went through the various studies, and there were many studies that did allow us to answer this yes, even though we more or less took it as a given.

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So there are I think substantial data to allow us to answer that key question number one as yes.

DR. SOX: Leslie.

DR. FRANCIS: I just wanted to be sure I understood this recommendation, because the idea is this is supposed to serve as a recommendation that will be helpful to people, right? We don't have to listen to it and it's not binding, but it would be helpful. And when I first read this, and your comments were helpful but I just want to be sure I really understand this, when I first read this, what I asked myself was, does this mean that what the panel was really saying was unless guidelines get developed, don't move forward, and when they do, move forward. Or was what the panel really saying, HCFA, you know, go ahead and cover it, and we kind of are

making a strong recommendation to you that it would be a good idea to cover with guidelines. And I was just trying to figure out how strong or weak or what -- I'm really thinking about -- see, I am a philosopher, so I'm really thinking about whether you wanted guidelines to be a necessary condition.

DR. TUNIS: And by the way, I was going to ask you all that question before you were done, which is exactly that question, were you saying that we

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should essentially, when we have treatment guidelines and when we had a definition for suspected white coat hypertension then we should cover, but you weren't going to offer us either of those?

DR. SOX: Well, Ron will probably have his recollection of those events and then I will try to see if ours match up. Ron?

DR. DAVIS: Yes. Well, I don't recall that the panel really laid it out all out in terms of what it meant by this language, but I can tell you what was going on in my mind as I put this language together and then threw it out to the panel, which as

Hal mentioned, did amend it in a few ways. My thinking was that if HCFA agreed with this approach, that HCFA might make a policy decision that would go something like this, the Agency has reviewed this issue, it's heard from MCAC, it agrees, it would like to cover ambulatory blood pressure monitoring consistent with its statement. We do think we need to have some limitation on its use, as indicated by this statement, and we invite public comment on what would be an appropriate guideline for selecting patients for APBM and managing white coat hypertension. And my guess is that the experts who deal with this situation would very quickly submit a

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guideline that had somebody's imprimatur, which would then allow HCFA to go forward. So I think if HCFA would announce some agreement with this approach, then guidelines which at a minimum would be consensus based guidelines, would be developed rapidly.

DR. SOX: I didn't agree with the motion as originally stated and either went along with this

amendment or made the amendment, I can't remember, but my concern was trying to minimize potential collateral damage from the enthusiastic use of ambulatory blood pressure monitoring and then wholesale discontinuing medication of patients whose blood pressure was lower at home than it was in the office, which could lead to a long-term harm, as our experts testified. And our experts basically said the way we do this, if somebody's blood pressure at home is 80 or lower, then we start to cut back the medication, and actually use APBM to monitor their response to reducing medication, and to reduce medication only to the point where blood pressure below, diastolic below 80 is sustained, which seemed to me a very prudent approach and one that would minimize any collateral damage from a more widespread use of this technology because it was now being paid for.

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My personal take is that it's up to HCFA to decide what they want to do with this advice, but we voted to support this motion, and it has that

condition in it, and let HCFA decide what to do.

DR. GARBER: I'm still not sure that I understand the answer to Leslie's questions. Ron, you're saying you expect guidelines to be developed soon, but until they are developed, does that mean that you're recommending HCFA cover in the interim or not?

DR. DAVIS: I would say no. Again, this is just my own thought process. I envision that if HCFA agreed with this approach, they might make a public announcement that we would like to offer coverage of this device if it's used in appropriate circumstances, and we would feel much more comfortable moving forward if we had guidelines in place that could be used by physicians who treat patients with white coat hypertension. And that if the coverage was somehow tied to the development of the guidelines, then my guess is the guidelines would be developed and approved by various professional organizations fairly quickly.

As I mentioned earlier, the experts have

their own guidelines that they follow in their own

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office which seem to make sense to me, so I would think that it wouldn't be a huge leap to bring together others and develop consensus based guidelines.

DR. SOX: Bob and then Barbara.

DR. MURRAY: Question, Ron. Your statement just now and previous statements earlier a few minutes ago seemed to indicate a broader scope that the precise language of the motion and the approval. In the written approval, the panel supports ABPM for diagnosis, not diagnosis and treatment, but just diagnosis of white coat hypertension, dot, dot, dot. If guidelines are developed for selecting patients for APBM and managing, so I mean, there is confusion in there, and what I heard Hal say is that he supported the use of ambulatory monitoring for the management, for the treatment of patients.

So, was the intent that HCFA, or the recommendation, was the recommendation that HCFA

approve coverage for this broad range to include diagnosis and management of these patients? But my bottom line is the same as Hal's; I think the committee did a good job and we're not here to apply our judgment, but just a question.

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DR. SOX: Well, before we go on and hear from Barbara, I would like to try to wrap this discussion up fairly quickly, unless there is somebody who really disagrees strongly with Alan, Bob and myself, that we followed the process and that we ought to ratify this, and then we can hear from the public and then we can have our wrap-up discussion and vote. I want to make sure that we leave enough time for discussion of the interim guidelines and that's why I'm pressing just a little bit. Barbara?

DR. DAVIS: Could I just -- I'm sorry, Barbara, to interrupt. Can I just answer Bob's question?

DR. SOX: Please.

DR. DAVIS: My impression is that the

panel was focused on diagnosis, use of the ambulatory blood pressure monitoring for diagnosis of white coat hypertension, as opposed to management as Hal was getting into.

DR. MCNEIL: This could be the most trivial comment on record, but if to get to Leslie's question, you took out the comma between hypertension and if in that second to last sentence, there would be no ambiguity about what you meant.

DR. SOX: Uh-huh.

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DR. MCNEIL: That's my editorial, because that would really mean that you approved it if and only if.

DR. DAVIS: I personally don't think it makes a difference, but I would be happy for the comma to be removed.

DR. SOX: Id would certainly reduce ambiguity and I think make it a little bit more clear what I think the panel had in mind.

DR. GARBER: How about changing the if to a when?

DR. SOX: Well, it's within the framework of this committee looking at this from a distance, greater distance than the panel, to make such a recommendation as a formal motion and we can vote on it, but we're not to that point at this point, we are still in discussion mode.

Well, I'm going to open the meeting now for public comment and call upon Grant Bagley to come forward, please identify yourself for the rest of us, Grant, and we're looking forward to hearing from you, and feel free to use this if you wish.

DR. BAGLEY: Grant Bagley. I'm with the law firm of Arnold & Porter in Washington, D.C., and I assisted Space Labs in bringing this request

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forward. And I am not sure I can add very much about how the panel discussion went, because it has been reported fairly accurately. I would only say that it really was two different panels going on at the same time. I think Dr. Sox was doing a tutorial on how to evaluate a diagnostic modality, which was quite

appropriate, and we did it in the framework of ambulatory blood pressure monitoring, which I think was also appropriate, because it is a technology which has come a long ways over the span of the last 20 years since HCFA really last visited it, and it was one that does have a large volume of research and evidence out there, much of which is not quite focused the way it should be based on the way we are looking at evidence based medicine.

Space Labs brought this request forward, and Space Labs is by no means the only company -- you might wonder why they have a lofty name like that by the way, and it really came from that program; Space Labs was an outgrowth of the NASA efforts to develop instrumentation during the early astronaut program, and Space Labs makes ambulatory blood pressure monitors among other kinds of physiologic monitoring equipment.

18 years ago HCFA wrote a policy saying

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ambulatory blood pressure monitoring is not covered, it's not covered because the equipment is not

standardized and we don't know what it means, and there is no evidence that it performs any utility function in deciding how to manage patients with hypertension. That was 18 years ago.

Now in submitting that request, there was a large volume of evidence submitted which HCFA did not send on to the panel, which dealt with the issue of standardization. There are voluntary standardizations that have been adopted by the British Hypertension Society among others, which deal with ambulatory blood pressure monitoring as opposed to home monitors, which also have standards. So there are well accepted voluntary standards within the industry of ambulatory blood pressure monitoring.

It's interesting in that the standards are so well accepted that the drugs that you're using for hypertension, the ones we're talking about not knowing how to make a decision on based on ambulatory blood pressure monitoring in fact have been tested with ambulatory blood pressure monitoring, which is the method which FDA now requires antihypertensives

use at some point in their studies for approval. So ambulatory blood pressure monitoring is the gold

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standard, at least by which antihypertensives are measured by the FDA.

So I think the standardization and the accuracy of the methodology is, was at least convincing to HCFA, and the more pressing question, what is the utility of this test, was presented to the panel and underwent the analytic framework that we went through.

The panel did look at the evidence very critically, but I think as Dr. Sox mentioned, I think what was persuasive to the panel is that there were clinicians who have a lot of experience in this and talked about how they personally use this technology.

There were also, as Sandy Marks mentioned, some patients. There were Medicare beneficiaries. There was a patient that said, I was thought to have hypertension in the office, it was not sustained, it was white coat hypertension, I wasn't treated, that was confirmed a few years later, and now as of last

week I am now hypertensive, but I wasn't treated for the last four or five years, and I avoided that treatment, I avoided that cost, and it was a positive decision for that Medicare beneficiary.

And what was perhaps even more telling is that the Blue Cross/Blue Shield TEC which Dr. Garber

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participated in evaluating, which was done in 1999, and was updated at HCFA's request in 2001 to develop an evidence report for this panel, was presented and looked very critically at the evidence, and said yes, the evidence making that final link in how do we use this and what is the link in treatment, do we have final evidence, when Frank Lefevre presented that he said no, we do not have evidence to show that white coat hypertension has the same risk if untreated as normal tension, that specific question.

But it was very telling and it was very persuasive to me that during the public comment period, Frank Lefevre on his own initiative got up to the microphone and said, I want to say that as a

part-time practicing physician, I used to order ambulatory blood pressure monitoring even though I have done both these technology assessments. After having done the update in 2001, I order it more than I used to, and I admit that the evidence is not all there, but I am taking care of patients.

I think that was persuasive that there is a place, it's just that we need to define the place. As I interpreted the panel from the audience, and far be it for me to tell the panel what they meant or said, but as I interpreted it the panel said we

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believe from this clinical information that there is a role for ambulatory blood pressure monitoring in white coat hypertensive patients, whatever that definition is, and we think the standards need to be developed to control the use in that population, I interpreted that to mean that in HCFA, in order to implement that coverage for white coat hypertension, would need to develop coverage criteria that would then guide them to prevent overutilization.

And I also listened to the same experts,

have spoken with them since, and talked at great length and asked them the same question the panel did, and have gotten vague answers also. So how do you know, and of course most clinicians will just say well, I just know. But in parsing it out and thinking about this, I said what criteria would be reasonable and how does HCFA get its arm around a problem like this, because standards have been developed.

You know, the National Heart, Lung and Blood Institute has had six national panels on hypertension, and the sixth panel did recommend that ambulatory blood pressure monitoring had limited use within certain concluding for white coat hypertension. The American College of Cardiology has

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developed recommendations which they presented to the panel, but in terms of how HCFA could deal with this, and the advice of the experts and with the panel, you know, you heard from Dr. Davis. A patient with in-office elevated readings, which clearly tells us

we should look to that patient as a hypertensive who should be treated, and that same patient in whom you may have recommended, or on their own have taken home readings or had readings from an office nurse, had readings in a pharmacy, whatever, have said I have normal readings out of the office.

And there is some research which shows that home monitoring, home blood pressures and layperson blood pressures are not particularly accurate, but they're indicative, so a patient with in-office blood pressures, perhaps two, perhaps three, on two or more occasions each visit, with reported out of office normal blood pressures, would be an appropriate patient to have ambulatory blood pressure monitoring, but I would submit perhaps only if another criteria is added, and that criteria being that the physician at least believe that that information is useful to guide therapy.

Now Dr. Garber might not order that test, and might believe that every in-office hypertensive

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measurement should be treated, although most

hypertensive guidelines would say be sure the patient is really hypertensive. But if the physician believes that it's going to guide therapy, and says I need to know, and I have a reported hypertensive in the office and out of the office, then I need to confirm that.

And again, the research that was presented to the panel, and all of the experts made it clear, this was not going to become the cell phone of the future, this was something we were going to see on everyone's arm going down the street. This is something that is done very seldom and it is done perhaps only once in a hypertensive's treatment history, and certainly not very often in a hypertensive's history. So I think the experts may it clear that this was for some patients in some circumstances and that's it, and that perhaps the proper criteria ought to be suspected white coat hypertension by elevated and normal reading by whatever criteria we use, and additionally, that the physician plans to use that for a treatment decision.

HCFA uses such criteria for a number of things. Magnetic resonance angiography of the head and neck definitely has a utility for evaluating

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surgical patients, but has very little utility in treatment otherwise, and HCFA covers it only for patients who are surgical candidates and plan to use the results in the decision for surgery.

The recent decision on PET scans for staging cancer have a similar prohibition, it's covered only for evaluating the stage of cancer when it has treatment implications. That's up to the treating physician to decide, and that's maybe as it should be in the absence of evidence.

Maybe when we get more evidence we can tell the treating physician how they should also treat, but we aren't there yet with this therapy. But I would just like to finish by saying it was a panel which I would, in your leisure moments I would suggest you go back and look with great depth at the transcript, because it was a tutorial on diagnostic tests, and I think it was the wave of the future on

how they should be looked at, and I want to congratulate Dr. Sox for the job he has done.

DR. SOX: Questions for Dr. Bagley?

DR. HOLOHAN: Grant, did you, did I interpret correctly your statement that the FDA now requires for any NDA on antihypertensive that ambulatory blood pressure monitoring readings be

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required on the clinical side?

DR. BAGLEY: FDA is using ambulatory blood pressure monitoring at some point in NDAs for new hypertensive drugs. In fact, FDA is involved in the collection and aggregation of that data in evaluation of new hypertensive drugs with accreta, with outside parties that are evaluating that data. But yes, in fact there is a meeting going on next month in which Dr. Lapicki is going to report on FDA experience in using ambulatory blood pressure monitoring in evaluating the hypertensives.

DR. HOLOHAN: My question really was, is it mandatory?

DR. BAGLEY: It's my understanding it is mandatory that they validate the antihypertensive effect at some point in their protocols, and at which level of the studies it's required, I do not know.

DR. SOX: Thank you very much, Grant. Anybody else from the audience wish to come forward and speak? Please identify yourself and your affiliation.

MS. MARX: Sandy Marx from the American Medical Association. First I wanted to just comment briefly on the discussion you had just prior to the open public comments about kind of what comes first,

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do we provide the coverage or do we get guidelines developed. And I think HCFA has at least several times if not more over the last few years had the experience of working with physician organizations in developing the conditions of coverage that they then put in their coverage decisions or coverage rules. This was in the diabetes self management final rule which recently came out, the bone density measurement rule, and the coverage decisions that you worked on

related to urinary incontinence treatments.

So it can be an interactive process, you don't have to say we're going to go out and get guidelines and then we're going to come up with a coverage decision. It's really part of HCFA's development of the coverage decision to seek input from the practicing community on how these things are used and under what circumstances the particular technology should be covered or should not be covered.

On other point I wanted to make on the issue of the Executive Committee providing advice to HCFA about research priorities or things for Medicare patients where research funding should be sought or even where Medicare should directly fund clinical trials, the AMA thinks that is highly appropriate.

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Dr. Janelle from our Council on Scientific Affairs testified to that point before an AHRQ hearing last fall. So we're encouraged that you're thinking about that, and we hope that HCFA will consider your advice

on research priorities. Certainly when there are conditions that are very important problems for the Medicare population like urinary incontinence, like hypertension, where you find that more research or better evidence is needed, then we think it would be a very good role for the Executive Committee to play in advising HCFA about what research questions need to be answered.

DR. SOX: Thank you very much. Anybody else wish to speak?

In that case, it's time to entertain a motion. I think the comment was made that a slight change in fact would be appropriate, and if there is a motion that was specific on that matter, we could take it up.

MS. CONRAD: Let me make a statement for the record first please. At today's committee meeting, voting members present are: Thomas Holohan, Barbara McNeil, Leslie Francis, Robert Murray, Alan Garber, Frank Papatheofanis, Ronald Davis, and Joe Johnson. A quorum is present, no one has been

recused because of conflicts of interest. Now, Dr. Sox.

DR. SOX: Alan?

DR. GARBER: Before anyone makes a motion, could I just ask another wordsmithing question of you and Ron? And it has to do with the if comma, if no comma, on the guidelines. Is there any qualification that the panel had in mind on the guidelines, I mean, any old guidelines will do, or is there any sort of guidance, do you want to leave it completely open?

DR. SOX: I think if there were some language that encouraged formation of evidence based guidelines, which in this case may actually be unrealistic, but some kind of process or else some body doing it that really carried a lot of weight, that might be helpful.

DR. DAVIS: Well, I think that putting evidence based in there might change the whole thrust of this thing. We could come up with modifiers like thoughtful or appropriate, or whatever, but I think we would be best to just leave this in HCFA's hands.

And when I spoke earlier, I was referring to guidelines that might come from the medical profession but as Sandy from the AMA was mentioning, this can be done as a collaborative thing.

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Dr. Bagley was mentioning that HCFA might develop some guidelines internally, so whether the guidelines will be developed internally, externally or collaboratively, I think it will get done right, and I personally don't think we need to clarify this any further than the way it appears now.

DR. SOX: Maybe I could ask Sean to comment about whether language, more specific language would be helpful with respect to the issue of who develops the guidelines or what sort of standards the guidelines might have to meet, or is that something that's sort of, you could fend for yourself on?

DR. TUNIS: I think that producing the concept of some sort of agreed upon guidelines without stating the source or the nature of the evidence I think is an adequate platform for us to

move forward at HCFA.

DR. GARBER: Does that mean you want a modifier or you don't want a modifier for the guidelines?

DR. TUNIS: I think we don't need a modifier.

DR. SOX: Alan, do you want to make a motion?

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DR. GARBER: Well, I move that we ratify the recommendations of the panel with the word substitution, if I can find that place where it had the comma, to eliminate the comma and if, and substitute the word when.

DR. PAPATHEOFANIS: Second.

DR. SOX: Any further discussion of the motion? In that case, it's time to take a vote. Connie, do you want to administer the vote?

MS. CONRAD: Let me repeat the motion first. You recommend that you ratify the recommendations substituting the word when for if,

and removing the comma after if.

DR. HOLOHAN: Before if.

MS. CONRAD: Before if, okay. Those in favor.

DR. DAVIS: We're just voting on the amendment at this point; is that right?

DR. GARBER: No, we are voting on the amended recommendation.

DR. DAVIS: Then maybe we should just get a quick indication of whether people agree with the amendment, just for the sake of parliamentary procedure, and I think we could just do that with a quick show of hands.

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MS. CONRAD: Okay.

DR. HOLOHAN: I thought he made a motion and it was seconded, so we're voting on the motion.

DR. GARBER: Yeah. If you don't like the amendment then you can vote it down and somebody can make a substitute motion.

DR. DAVIS: That's fine.

DR. GARBER: But I suggest at this point,

if there's something you don't like about the language.

DR. SOX: Or perhaps if anybody feels strongly that we're doing the wrong thing by this vital piece of wordsmithing, it would be good to try to persuade the rest of us that we shouldn't vote for this motion and if I don't hear from anybody, I assume that nobody wants to persuade us of the potential error that we might be making.

DR. TUNIS: Could I just then say, are we then to understand the intention of this wordsmithing is really to say that the Executive Committee supports the panel's recommendation for coverage but only at the point where we have undergone some process to develop treatment guidelines and a definition for suspected white coat hypertension? That's sort of your recommendation, and you're trying

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to make that stronger by removing the common and saying when.

DR. GARBER: Yeah, but I think it's

important to underscore one point. My intention in making that change in wording is not to try to get the panel to say something different, it's a response to the perceived ambiguity in the language that the panel used. We are trying to make it as clear as possible what the recommendation, what we interpret their recommendation as being. Again, I don't think we should try to overturn the decision of the panel, but solely trying to clarify the ambiguity.

DR. SOX: My personal belief is that the panel voted for this recommendation that has a slight ambiguity in it, but I believe the panel really believes that we ought to have guidelines in place for the use of this technology. Ron, how do you feel about that?

DR. DAVIS: I agree a hundred percent. I think this is fully consistent with the views of the panel and the panel didn't perceive any ambiguity when it adopted this language, but if others do, then let's clean it up, and that is fine.

DR. SOX: That's a good way of putting it. I think we're ready for a vote.

MS. CONRAD: Those in favor? Opposed? Okay. It's unanimous.

DR. TUNIS: Just to close this out and to make sort of one last observation related to this particular recommendation by the panel, as you know, for a good long time, and there continues to be some discussion about the extent to which both HCFA and the coverage advisory committee use expert opinion versus empirical scientific published evidence in the context of making coverage recommendations and coverage decisions.

And we just want to highlight the fact that in this case, particularly guided by Dr. Sox's analytic framework that allowed the question to be broken down into discrete pieces, for some of those pieces there was good quality scientific evidence and for some of those pieces, really the panel to a large extent paid a great amount of attention to the expert opinion and judgments of the clinicians who came and discussed the issue. And so, I think it's just worth

pointing out that I think we have reached a point where explicitly both expert opinion and scientific evidence are being considered by the panel in making recommendations to HCFA, and HCFA is considering those same sources of information, and it's not that

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one is substituting for the other but in a case like this, both sources of information are being used simultaneously, and that's consistent with the directives that have been written into the Benefits Improvement and Protection Act in terms of what they have asked for Medicare to consider in terms of information going into coverage policy. So I just wanted to underline that as representative and specific.

DR. SOX: And I have a process point, and just want to beat the drum again for some sort of explicit analytic framework for the discussion as a way to focus the search for the evidence, as a way to focus the discussion of the evidence, as a way to backtrack and try to figure out how a decision got made, and as a framework for making the report of the

chair to the Executive Committee. And I am certainly going to push when we do our next revision of interim guidelines for some sort of expectation that the EPCs will provide us with an explicit analytic framework, which I believe will be the intent for the PET scanning and Alzheimer's disease evaluation. It's very valuable at every step in the process, and I think the more that we can take advance of the work that we're about ready to discuss, the framework for

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evaluating evidence, and really hold our hands to the fire to use them formally, the less we will run the risk of the sort of chaos as we move from problem to problem, and the more accountable we will be for our decisions in the public record.

And with that, unless there is some comment, we will move on to the last part of the day, which is to talk about the interim guidelines. I just remind the audience that the committee discussed these revised guidelines at the time of its meeting in February, we spent the better part of an hour on

one particular point, which I will get to in a minute, but otherwise approved the guidelines in the way that they have been revised by the methods subgroup based on external comments as well as comments from members of the Executive Committee that have accumulated since the initial publication of the guidelines.

So there has been a fairly extensive process that went into these modifications. The only changes that have occurred since the last meeting were you know, literally a few words moved around and a little bit of reorganization, so this is really an opportunity for the public to have input and if we hear something compelling, we could change these

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guidelines on the spot, but otherwise, I don't believe that a vote will be called for at the end of the discussion period.

I thought I would briefly go through what I saw as the high points in the change of the interim guidelines published about a year and a half ago, and this is mainly for the benefit of the audience.

First, we inserted a section on the evaluation of diagnostic tests and you heard about that today in the context of the discussion of the PET scanning for Alzheimer's disease evaluation. We found that this approach was quite valuable for us in shaping the discussion around PET scanning and helped us to see the strength of the evidence at various points in the chain of logic that linked the doing of the tests to health care outcomes.

Secondly, we made some process changes to deal with the status of unpublished studies which were used by the EPCs to evaluate the technology. The issue was if the study had not been published in the medical literature, what would be its, would we then make it available to the public at the time we published the evidence report, and we felt that the overriding principle should be that the public should have access to all of the information that went into

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the development of the evidence report.

In the case of published studies, the

public can go to the published literature. In the case of unpublished studies it reviews in the development of the report, the public should have some other recourse, and so we felt that it was essential to make unpublished studies available to the public at the time that the evidence report was put on the web. And we had about an hour's discussion about that and eventually came to a pretty strong feeling that this is crucial, so that's another small but important change.

In general, I would say the tenor of the outside comments overwhelmingly was that our basic principle that we require some form of controls in order to evaluate evidence, that nobody really took issue with that statement of principle. The form of controls and the study design can range anywhere from randomized clinical trials to studies with much less satisfactory controls with much more potential for differences between the control and the intervention group that are not due to the intervention, but to differences in the selection of the two cohorts for study. We simply hold the panels accountable when

they use less suitable controls to make their

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reasoning clear as to why they thought those controls were reasonable.

And finally, we introduced a section, a fairly substantial section of what to do if the evidence is inadequate to try to guide panels into those circumstances, and parenthetically one of the things the panels could do when the evidence is inadequate is to rely on practice guidelines, which is in fact a way what we're edging toward in the discussion just completed.

So that's a summary of the major changes in the guidelines. And it's now an opportunity I guess for anybody in the public to stand up and give us some feedback. Yes, sir? Would you please identify yourself and your affiliation and so forth?

MR. ROBB: I am Greg Robb, I'm a consultant representing ACTA, the Advanced Clinical Technology Association. I would like to echo some of the points you just stated, commend HCFA for opening

the process and the resources, significant resources to do these sorts of meetings, and through all the transparency initiatives in the coverage process. I want to reference the guidelines that you have here and commend you for trying to make information available, using the Internet, et cetera, but in

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commending you I want to say it does get complex if you do follow the process.

Randel Richner this morning talked about her level of confusion on just what the steps were, where you have public input, who does what, when, what does the panel do, what does the Executive Committee do. You're working at it, keep it up, it is very hard to follow. You're having access to these briefing documents, we don't, so as you open things up and provide opportunity for public participation, it's very important to tell us just what you're seeing and how you want us to participate.

In opening things up, you are challenged with timing. The industry if it had one goal, is to

get a clear predictable timely process. It's opened up at HCFA, there's a level of predictability. There's still of a level of unpredictability with this open forum, and what I think Randel was pointing to was how does one add up the days? How can you squeeze all these process steps into a limited period of time, and still get a timely decision. It's a challenge. At every time that you have a decision point you do need the input from the public, so we will work with you and commend you for the effort so

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far.

On this process side as well, there is a level of confusion in the industry and in the decision making process on coverage, and this is probably directed more to you, Sean, than the Executive Committee here. It's when does the Executive Committee need to be brought in, when does MCAC need to be brought in, versus when do you need at HCFA technology assessment by itself.

I heard you reference a quick relationship

with AHRQ to pull in that information. A lot of interest for an industry on just how that will work and what the real function here on MCAC is on that. We're reminded of Jeff Kahn, who advertised MCAC quite a bit and sold it a few years ago. A slide he always used in the role of MCAC was consensus. It was on all the slides he handed out when he did his public relations on that issue and it was leading toward this evidentiary thing of getting consensus, getting practice guidelines, getting involvement from the public into the process, because the evidence was confusing, weak, not there.

So from process to evidence, a lot of interaction, and all I can say is we like where you're going. Dr. Sox, you did a great job in

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showing just what you do in a very difficult area. Thanks.

DR. SOX: Thank you very much for your helpful comments and for the bouquets. Other comments?

Would the committee like to raise any

issues that might possibly either now or later lead to changes? Yes, Ron.

DR. DAVIS: Hal, Leslie just brought to my attention that I think we neglected to act on those other recommendations.

DR. SOX: We will get to that as soon as we're past this, thank you. Barbara.

DR. MCNEIL: Hal, I really like this, I hope now final report. The question I have, would it help people who pick this up on the web to have five or ten references that they might go to if they wanted additional information. For people who aren't in the field, a handful of them might be useful.

DR. SOX: Good suggestion.

DR. TUNIS: You mean references in the sort of evidence based kind of reference, evidence based medicine, that sort of methodologic reference?

DR. MCNEIL: Yeah, not reference in the text, not saying see reference two, but just at the

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end, here are five general references that talk about

evidence based medicine or the evaluation of clinical trials, or the evaluation of diagnostic tests, sources of bias or whatever.

DR. TUNIS: One thing to mention in that regard is that we are very actively working internally now in actually developing guidance documents that we've been advertising for quite a long time that are under development, guidance documents which will have more detail and will be a HCFA document as opposed to an MCAC document, to talk about how we go about appraising evidence from individual studies, groups of studies, in both areas of diagnosis and in therapeutics, and I think that will be a much more heavily referenced document as well, but the time frame for those is to, we're sort of approaching having good working drafts and we're actually hoping to have the MCAC consider actually working with us to refine those, but ultimately those will be posted on the web and will provide some of that information.

DR. MCNEIL: That will be great.

DR. SOX: Any other comments?

In that case, I have to go back up to the transparency projector and we'll work our way through

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the other two recommendations about the use of the ambulatory blood pressure monitoring.

The second question that the panel addressed relatively briefly is the use of ambulatory blood pressure monitoring in patients who are under treatment for hypertension and whose blood pressure just won't go down to the normal range as measured in the office, so this is an issue of management, not an issue of diagnosis, of white coat hypertension. And we performed an analytic framework for this problem, unfortunately in which we first asked, does ambulatory blood pressure monitoring identify a group of patients on treatment with high blood pressure in the office but good blood pressure at home.

And we found in fact one study that addressed that in which patients with treatment resistant hypertension underwent ambulatory blood pressure monitoring and were then divided into three

equal size groups based on their home blood pressure. And the study showed that patients who had relatively good blood pressures at home had better stroke rates and other health care outcome measures than patients whose blood pressures remained high at home. So it's pretty clear that ambulatory blood pressure monitoring can identify a group of patients who are

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at relatively low risk because their blood pressures are well controlled at home, so this element is certainly a fact.

Next question as to whether physicians maintain treatment in patients with high office blood pressure but normal blood pressures at home, and we didn't have any evidence on this score, but we took sort of a best case scenario, which is that physicians would reduce blood pressure medication for patients or would not continue to add blood pressure medications for patients whose blood pressure was well controlled at home but not in the office.

And finally, the crucial and unanswered question is what are the health care outcomes in

patients who are managed, whose blood pressure is managed based on their home blood pressure as opposed to their office blood pressure. And on this particular link, we don't have any evidence about long-term health care outcomes in patients with treatment resistant hypertension who are managed either according to their office blood pressure or according to their home blood pressure, and the question felt that this was a crucial link and that without that link, we were not in a position to encourage HCFA in their coverage decision, and so we

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voted unanimously to approve the following motion:

The evidence is inadequate to determine the effect of using ambulatory blood pressure monitoring in patients with treatment resistant hypertension.

The last problem that we took up was the use of ambulatory blood pressure monitoring to try to make a diagnosis in patients who develop symptoms that sound like they might be due to low blood

pressure while on treatment for hypertension. The idea here is that if the patient's blood pressure went down at the time they had these symptoms, that one could then manage the patient in a more appropriate way, because you'd then have a diagnosis and perhaps could switch to another blood pressure medication. HCFA didn't provide us with any information pertinent to answering this question and so again, the panel voted unanimously to approve the following motion:

The evidence is inadequate to determine the effect of using ambulatory blood pressure monitoring in patients with symptoms of low blood pressure on medication.

So basically, for these last two, we said the evidence is inadequate to evaluate the problem.

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So, what I will be asking for is a motion to confirm the judgment that the committee made.

DR. FRANCIS: Can I just ask a question? Why didn't HCFA give you information? Was it just that there is no data or that it was imprecise,

because a negative judgment, the evidence is inadequate, is different from a judgment that nobody gave us any evidence.

SPEAKER: There was no data available to submit.

DR. SOX: Thank you. Bob.

DR. MURRAY: Did any of the experts or Dr. Lefevre say that they did use ambulatory blood pressure monitoring in these categories?

DR. SOX: I don't recall that they did. I think they --

DR. MURRAY: So the evidence and the experts were all consistent?

DR. SOX: It sounded like it was a question that didn't really come up in practice, not very often, and certainly doesn't come up in my practice. Well, could we, if there's no further discussion, could we have a motion to approve these two recommendations?

DR. GARBER: I move to ratify.

DR. MURRAY: Second.

DR. SOX: Connie.

MS. CONRAD: The motion is to ratify the findings of the device panel deliberation of ambulatory blood pressure monitoring. Did I miss something? Okay. Those in favor? It's unanimous.

(Dr. Holohan was absent for this vote.)

DR. SOX: Well, at this point I guess I will ask if there is any other business to come testimony before the committee.

Our last item is the future role of the Executive Committee. Dr. Tunis, do you want to lead that discussion?

DR. TUNIS: What I wanted to was run by a list of about six or seven sorts of advice assistance and activity that we would propose as possibilities for the Executive Committee to continue to work with HCFA once the function of formally ratifying the panel recommendations is completed. So what I would do is just run through all of them and then maybe we could have sort of a general discussion about which ones you think are good ideas, bad idea, or if you

have other ideas of your own. These were sort of generated from internal discussion within HCFA.

One thing I also did want to mention, kind

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of in relation to the future of EC is, I'm not sure, Dr. Sox, if we talked about some of the changes related to panel, given your new position at the Annals, but I just wanted to mention because Dr. Sox has been elevated to the lofty editorship of the Annals of Internal Medicine, I'm sure in no small part due to his role in the MCAC, plus a few professional accomplishments besides that, in any case, not only have we had to congratulate him, but we've had to figure out how to keep him on.

So, in order to do that and what the arrangement will now be is that he will be resigning as the panel chairperson for the medical devices panel and will not participate on any panel, but will continue on as the chairperson for the Executive Committee. And in that role he will continue not to have a voting role on any particular given motion.

For the medical devices panel, Dr. Davis has graciously agreed to be promoted to the chairperson of that panel, and Dr. Wade Aubry will be the vice chair for the medical devices panel, so there are just a couple changes to mention.

Okay. So basically here's the set of functions. The first one is, and very similar to what we did today, but basically we are still

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planning to have the panels when they consider particular technology to summarize their recommendations to HCFA very much in the form that they currently do. Those summaries, we propose, would still be forwarded to the Executive Committee for discussion but not formal ratification. And the purpose behind that would be that we would see the role of the Executive Committee as at least trying to insure that the panels are functioning according to the guidelines for evaluating effectiveness, so essentially would be a quality control function as opposed to a formal ratification function. And again, I think to some degree, that was the way the

Executive Committee operated today in relation to the ambulatory blood pressure monitoring panel, probably in deference to the fact that the chair of the Executive Committee was also the chair of the panel. But at any rate, that would be one proposed function.

A second function would be to continue to work on any needed updates or improvements to the guidelines for evaluating clinical effectiveness, including additional subcomponents. For example, last November, the methods working group developed guidelines for evaluating diagnostic tests and it may be that in the future there are categories of

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technology for which tailored guidelines would be necessary. I am imagining for example that genetic testing technologies may be coming forward to Medicare attention in the next few years for coverage policy, and it may very well be necessary to develop a framework for evaluating those sorts of things that would not necessarily be covered by the general guidelines, so continue basically to build on the

guidelines for evaluating effectiveness.

A third issue would be potentially to provide a forum here for discussing overarching technical issues that may arise in the context of one technology but have applications to a number of technologies. And here a good example I think is the issue of how we are struggling with how to deal with the gamma coincidence cameras versus the full ring PET scanners in terms of coverage policy, which raises a general issue of whether the Medicare program should be distinguishing within a category of FDA approved devices subcategories which would be eligible for coverage, as opposed to any FDA approved device within the category. So you can imagine for example, ambulatory blood pressure monitors might come in all ranges of accuracy and quality, and the minimum criteria for FDA approval might not in fact

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be the technical performance standard that would be necessary for clinical effectiveness from your perspective, and it seems that this body may be a forum to discuss that sort of overarching issue.

Dr. Brook, when he's here, always likes to raise complicated social issues related to coverage policy, and one of his favorites is the issue of technologies for which there are small but demonstrable benefits and extraordinarily large implications in terms of utilization, cost or other factors, and whether or not this committee would want to on occasion dive into that sort of complicated social, ethical, legal, allocation type issue. I'm not raising that to suggest that HCFA wants to get into considering costs in the context of coverage policy, but there ought to be at least a forum in which that sort of thing could be discussed.

DR. MCNEIL: I just wanted you to repeat it, Sean. So he's worried about high cost technologies that have a small number of potential beneficiaries?

DR. TUNIS: Or small but measurable benefits.

DR. SOX: Low benefits, high costs.

DR. TUNIS: Right. That's just an example

of a complicated social ethical issue that again, I'm just proposing these for your feedback and consideration.

Fifth, some sort of horizon scanning function for technology, potentially where we would present to you all a list of technologies that we're aware of that might be coming over the horizon, beginning to develop in stages of clinical research that we may be faced with soon, and getting some direction from you in terms of which ones we should be particularly ready to look for in terms of coverage, whether proactively considering early coverage for something that's promising, or at least being forewarned of things, so some sort of priority setting horizon scanning function.

Sixth issue, we talked about, Barbara, you raised identifying critical research priorities even in the context of technologies we are actively considering or ones that we should be.

And the last one that we have listed here was really what we just did earlier today, which was

helping to frame the questions for complicated questions such as are posed by PET for Alzheimer's disease, where we could once we've identified an issue, bring the issue here for discussion as we did

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today, identifying the questions in the analytic framework prior to even going forward with the TEC assessment or a panel discussion.

That's obviously not a complete list, it's a lot of stuff, and I just wanted to throw it open for your discussion.

DR. SOX: Well, why don't we discuss this, just work our way down the list and see where there are comments or concerns.

First, the issue of hearing the report of a panel not as part of the ratification process but simply to here how they tackled the problem, what issues they got into that might have more general implication for the policies used by all panels, and perhaps creating some sense of accountability on the part of panels and panel chairs and co-chairs to

follow the guidelines we have established and to tell us when the guidelines aren't working so we can change them.

Any comments about that one, one that will not delay the approval of a proposed technology, it shouldn't be a problem but it would nonetheless keep us essentially being a body to which the panels are accountable for how they operate. Ron.

DR. DAVIS: I support that function for

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the Executive Committee. I just wanted to throw out the idea also that at some point, maybe a year down the road, we might want to write up a paper that describes the whole MCAC process in the first several years of its experience, and how our process has evolved over time and where we think it's going, so that we could share that with the outside world beyond the fairly small group of people that monitor what we're doing. There might even be a peer review journal out there that might be interested in publishing a piece on this.

DR. SOX: Any other comments about the

first one? Frank.

DR. PAPATHEOFANIS: Just a quick comment. Something to consider as I've started to spend more time with the product, if you will, of each of the panels, I'm just curious whether there's a way to produce those summary documents in a uniform style or uniform format, so that one can't say, oh yeah, this one was written by whomever. I don't know if there is any interest from HCFA to do something like that, but I think the various TEC programs do a good job, you never know who wrote it, who was the key author, because there is a uniformity of style.

DR. SOX: Are you thinking about the

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evidence reports or about the report of the panel's deliberations or both?

DR. PAPATHEOFANIS: Both. Maybe it's just too hard to do that.

DR. SOX: Well, I again will repeat what I said earlier, which is this analytic framework is a nice framework for making the report of the panel to

the Executive Committee, and I hope that other panel members will try it and like it, and I guess it's sort of a question out there for further discussion when we're not at the end of the day as to whether we should require getting a more uniform format.

DR. TUNIS: Hal, I think your panel report was the first one that we've had since the request was made by the EC to try to have more comprehensive summary of what the panels had reported, and it may be that Hal's write-up of this could serve as kind of a de facto template for the time being. These aren't HCFA products, and it seems as though the chairs at least so far have been responsible for writing these up.

DR. SOX: I personally believe that the panels ought to be accountable to the Executive Committee for the process and the line of reasoning that is followed, and is part of this accountability

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function that we discussed earlier. Leslie.

DR. FRANCIS: I don't want to sound like I'm lazy or don't like to carry stuff, but it seems

to me that if the function of the Executive Committee is to try to help think through what was uniform or what wasn't uniform, or what can we learn or what can other panels learn from the panel decision, I am going to want to look at different documents or different things, from what I looked at for this meeting. For this meeting, when I was thinking about ratification, I really read the panel's decision, and then I read all this stuff as though it were an administrative reference, and I don't think I would want to read it all or need it all, but what I'd want to know are what were the real issues in contention at the panel, which I really couldn't figure out from this set of documents. So anyway, I don't know that that's helpful or not, but I do think that we might need to think through a little bit what we get or how to prepare for the meetings without the ratification function.

DR. SOX: I do think it's important that there are disagreements in the panel, not to paper them over, but get them out there for a discussion

and learning by ourselves and anybody who is a

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historian of this process.

MS. RICHNER: I have a question for Sean. Looking at, we have been into this now for two years, and looking at how the MCAC process is working and all this, I think what we are grappling with where are we in this evolutionary process and what do the panels do, what does the Executive Committee do, is there any way to look at how many decisions have been sent to which panels, and if it looks like it is heavily weighted to one or two panels, which I think it is, and is the, you know, essentially, what is the mix of the panels, is it the right mix, are we being as helpful as we can to HCFA in a sense with that type of panel structure and Executive Committee structure. I understand what you're getting here with this is to use us as sort of a think tank or policy kind of place to publicly discuss a lot of very difficult issues, and I agree with that, I think that is necessary.

However, I am just wondering if we are

doing the best job we can in terms of facilitating and expediting and efficiently helping HCFA in terms of making coverage decisions, so I just want to know, does this advisory committee process the way it sits work the best for you.

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And you know, I know you only send certain decisions to MCAC, that is still an unknown entity, which ones you send and which ones you keep, and that kind of thing. So this is the first time we have had a chance publicly to discuss this.

DR. TUNIS: Well, you know, that sounds like those issues you raise by themselves could be a topic for a session at a future EC meeting, all those things, including criteria for what does well to get send to MCAC and what does well to go for TEC assessment. I mean, those are decisions that we are still making on a kind of case by case basis according to our best judgment about the nature of the issue, the complexity, the extent of the issue, et cetera. I think that we're doing a lot of

thinking internally and this process is clearly evolving, the MCAC process, and becoming increasingly helpful, I think, and sort of synchronous or in sync with the coverage decision making process within HCFA.

I think we have just had a call for nominations on MCAC members, there was an extraordinary number of good candidates, and we're actually now talking a lot internally about what sorts of composition of, you know, how the

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composition of the panels might evolve, given the terms that are expiring and new folks that are available.

So, I think the process is working well, it's continuing to work better, and I am hoping obviously that the Executive Committee can kind of be working more with us in an iterative fashion to make the whole process even work better by addressing the kinds of questions that you just raised, because I don't think they are entirely questions for just me or HCFA, they are questions for you all as well.

DR. MCNEIL: I mentioned this following question to Sean before we started this morning and I don't know if it falls under the question, but if it doesn't, stop me.

And the issue is the following: We have been talking about coverage for technology in this particular context for which the data are either there or not there and we make a judgment about whether they are there or not there, and in some circumstances, like the blood pressure monitoring, we add on testimonies and say yes, let's go forward with it.

So the other question, and I understand how we can fine tune what seems like a pretty good

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process already, but the other question is, is there ever a time when HCFA is going to be considering doing conditional coverage pending data for something that's just the hottest new thing off the pipeline, and whether that should be part of the deliberations of this committee, whether we would be any use to

HCFA in that regard, or whether there are other people who would be better, or whether they would like to do it all themselves, or whether the entire issue is moot.

DR. HOLOHAN: Sound familiar?

DR. TUNIS: Well, it deserves a lot of discussion at a future meeting. I think everybody, there's a lot of folks incredibly interested in come variation of conditional coverage or coverage under protocol, or some way of getting past this catch 22 of you can't learn about something until it's covered, and you can't cover it until you have learned about it, so I think that there's a lot of interest in that.

Just in effect, we do have some quasiconditional coverage capabilities, although they don't have a lot of teeth to them to be honest, which is, we can cover something based on less than ideal evidence that you would want in a perfect world, and

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we have the ability to reconsider coverage at any time. Now, you know, the truth is to withdraw

coverage is a whole different animal than to grant coverage, but I think the points you raised are good, and I just think we need a longer period. That's one of those big issues that probably this group could discuss.

MS. RICHNER: I didn't set her up for that question.

DR. SOX: Well, let's continue to work our way through these suggestions. Updating the interim guidelines, it seems like we have to do that, the only question is how to try to be systematic about it, so that we revisit them periodically and don't allow them to languish. Any comments or discussions about that?

MS. RICHNER: I have to bring up that one sensitive paragraph again about never adequate. I thought we had decided that we would take never out of there on page 4. It's the one that has been bothering me for a year and a half. I understand that paragraph still says that you can use other controls, but I thought the last time when we

discussed this in February that we were going to use different wording than is never adequate, and I

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remember it very distinctly.

DR. SOX: Well, I think we have the transcript of that meeting, we need to go back and look at the transcript. I read about two-thirds of the transcript very carefully, but I probably didn't look at the relevant part, it was about another discussion. I think I would have remembered it, I think it would have been a real vigorous discussion if we had it. Alan, do you remember a discussion about that?

DR. GARBER: Well, we've discussed this on at least two occasions and my recollection is that at one point we were going to strike the word never, but then we had put in, and here I may be confused about the order in which these things occurred, so I too would like to look at the transcript, but we put in the extra language explaining what we meant, and then left in the never adequate, because we thought that was circumscribed enough. That was my last

recollection, but I would have to admit, that could be faulty.

MS. RICHNER: I don't remember either, I'm just trying to get back to that one again, because it always comes out glaringly as such a strong statement that can be interpreted two different ways.

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DR. SOX: Barbara?

DR. MCNEIL: I'd like to make one suggestion about this subject. I think we can spend a lot of time updating these guidelines every single meeting, and I'm not sure that's the most productive use of our time. I would like to make a suggestion that we make an informal deal that maybe every year, or after so many evaluations or so many new pieces of data coming in for evaluation that we look at these. Otherwise, I'm just worried that we are going to find, I'm going to find some more commas, and Alan is going to find some more words.

DR. SOX: In fact, I believe the thrust of the suggestions was that as suggestions accumulate,

as comments from outside the committee come in, that we will let them accumulate and at some point, probably on an annual basis, look at them and respond.

Next item is to allow the Executive Committee to serve as a forum for discussion of technical issues, particularly those that might have an application across panels. In a way, it's sort of related to updating the interim guidelines, that when such issues come up that apply to several panels, we need to have, I believe we need to have them sort of

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in the formal record of our processes and procedures. But anyway, that one is open. Alan, do you have a comment?

DR. GARBER: Well, just about the whole set of things that Sean described. I thought all of them sounded reasonable and it's hard to imagine us saying no, the Executive Committee should not consider these things, because we should be a sounding board for them, and it might include even the things like new technologies where there isn't

much data, and so on. So these are, it's hard for me to see any controversy. I think the issue, and this is really an issue for Sean, is how best to use the limited time of the Executive Committee. There should be some prioritization, and it seems to me that the broad issues that concern the operations of the panels collectively are the main things that the Executive Committee should be spending time on, but beyond that, it's really your call, Sean.

DR. TUNIS: So maybe, you know, if there is a sort of the sense of the panel, of the committee that sorts of thoughts that we raise in terms of the function, you know, that all of them seem in the right spirit in terms of what this committee should do, then that's fine, and unless people want to make

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specific comments we'll just go and assume we have the right idea about what we should use you all for, and so whatever comes up at a particular time, we will do that.

And maybe the only one that I would just

want to sort of get specific endorsement for is whether you do or don't as a committee feel that this area of sort of social policy, you know, the large cost, small benefit, whether you want to avoid those issues and stay more in the realm of testimony on the technical, analytical and methodologic issues.

DR. HOLOHAN: Who else would address them though?

DR. GARBER: The secretary of HHS.

Sean, I think this is sort of vague, and if you take it to the fullest breadth of what it might mean, it's overwhelming. And I think that basically the way we are constituted and they types of people we have here, we are best at issues of evaluating evidence, I think.

I in particular am very comfortable with looking at utilizations and those broader issues, but I don't know whether that's what we're convened to do as a body. But I don't think you would be likely to use us inappropriately either. I trust your judgment

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about that.

DR. SOX: If you brought something before the committee that nobody on the committee had any real confidence on, that we were functioning as a citizens panel, that would decrease our credibility, so I think we should advise Sean that we'd like to be used but that there ought to be, the topic ought to be related to areas that we have special confidence in, but that clearly extend well beyond just evaluation of evidence.

DR. TUNIS: Randel, industry perspective?

DR. HOLOHAN: Hal, let's suppose you had a peculiar circumstance where there were two equally effective treatments, let's say two forms of the same pharmaceutical, and one was far more expensive than the other, and there was no evidence there was any difference between the two. Do you believe that the panel or this Executive Committee should ignore that fact?

DR. SOX: Speaking as a private citizen, no, I don't think we should be. Sean?

DR. TUNIS: Well, thinking of you as a

private citizen, I don't think you should avoid it either. Can you say a little more about the question?

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DR. HOLOHAN: Let's take a hypothetical case where a panel is evaluating a technology, whether a pharmaceutical device, even a procedure or service, and the data are fairly clear that there are alternative methodologies of providing that technology or that service, no evidence of difference in clinical effectiveness but a striking difference in the cost. Should the panel and the Executive Committee ignore that fact? I mean, I understand we don't want to end up becoming cost accountants or cost effectiveness experts but --

DR. GARBER: God forbid.

DR. HOLOHAN: Even though we're called to do that in our other jobs, should that be ignored where there is clear evidence of a disparate cost effectiveness?

MS. RICHNER: Go right ahead, Tom.

DR. HOLOHAN: I mean, I hate to sound like

Rob Brook, but at one of the earlier panel meetings, he pointed out fairly strongly, as Rob is inclined to do, you can't ignore this, I mean we can pretend we're ignoring it but ultimately it can't be ignored.

MS. RICHNER: It's never ignored. What our mandate is essentially to evaluate the technology and the benefits on health outcomes, and essentially

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counsel HCFA in terms of how the evidence supports that. So then beyond that, it goes to HCFA administratively, they make the decision whether or not it's to be covered.

DR. HOLOHAN: I know how HCFA works, Randel.

MS. RICHNER: Then we have a system where we have to negotiate for payment on a whole different side of the equation and in that forum, on the cost side and the payment side is where those kind of issues are definitely played out in every possible way you can imagine. So costs are definitely considered, there is no question that they are

considered, but they are considered on the payment side, and we fight that battle every day with our hospitals, with Part A, with Part B, with everyone else, so all we are doing here is we are an expert advisory committee here to evaluate whether the technology is, whether the evidence supports that technology and that's what we're supposed to do, so cost is definitely a part of the equation, but it's something we are not mandated to address specifically.

DR. FRANCIS: We do have a category which is equally good, but with disadvantages, if you look

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at the variety of ways of assessing it.

MS. RICHNER: Of course there is.

DR. FRANCIS: And there are a lot of ways that various things can have disadvantages, including that they make people uncomfortable or that they make people poor.

MS. RICHNER: I mean we were discussing it today with ambulatory blood pressure monitoring, I mean, what's the issue, is the issue that it's going

to be used so widely that it's going to break Medicare's budget?

DR. HOLOHAN: I don't think that was discussed at all. I think the major issue was the statement in the panel's report that 13 of the 15 studies of white coat hypertension indicated that patients with white coat hypertension had worse outcomes, regardless of their blood pressures at home or on ambulatory monitoring.

DR. SOX: Alan, do you want to comment on Tom's provocative question?

DR. HOLOHAN: Thank you for calling it a question and not a suggestion.

DR. GARBER: I just want to make a simple point. Obviously the issue of how, where, when, whether to include costs is a very controversial one

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and it's not as though we are entirely free of controversy even ignoring costs. I think at this point, it is quite clear that there is a lot of information we can provide that HCFA doesn't easily

get by other means, and it includes everything that Tom mentioned short of costs, which actually you don't get that much, like whether two treatments are substantially equivalent, what the criteria are for that, whether the studies are adequate to even make a statement about that, and we can do a tremendous service for HCFA and if your goal is to improve cost effectiveness, which I agree has not been the charge of this group in any respect, but if your goal is to assess cost effectiveness and that's being done somewhere else in HCFA, we ought to be able to provide them with very extensive information about the effectiveness side of the equation and effectiveness always means comparative effectiveness.

And I think we will look to you for guidance, and you drafted that notice of intent how long ago was it now, about a year?

DR. TUNIS: May 2000, yeah.

DR. GARBER: So we'll see what happens with that, because we are in service of the coverage and analysis group in the coverage process, you tell

us at what point any kind of assessment on the part of MCAC would be useful in your deliberations.

DR. SOX: I think another way of putting that is that this committee is still only a couple years old, it probably shouldn't be the point person in establishing a beach head for costs as a consideration, that we should stick with the job we were tasked with. My reaction, Tom, is caution, not taking on too much, until we have the weight that would command a real audience, which we don't, we're not really well established yet.

DR. TUNIS: I would agree with all that. I think obviously the notice of intent, the notion of added value as a criterion for coverage was floated and evoked a substantial amount, although no consensus, but a substantial amount of controversy, and so I think we don't have clear marching orders that that's the direction we should be going in terms of coverage policy making. So I would say what Alan had to say is right, that there's a lot that this committee can contribute in terms of focusing on the

clinical effectiveness issues and for the time being that's where we are.

DR. SOX: The only other one of these suggestions that seems to for me at least require

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some comment is the last one, the one we just did, which was to essentially help frame the analysis before it starts. And my concern is that if we limit our input to topics where sort of timing works well in respect to our meetings, then we are only going to be doing some of the problems. On the other hand, if we take a chance on delaying the process by waiting until a meeting, then we're introducing delay, which is not good, and if we're going to take on this task, we are going to have to find some way to operate outside the framework of our regular meetings in order to have this input but at the same time not slow up the process, so we may be in for some conference calls for this purpose.

DR. GARBER: Sean, was your intent to use the Executive Committee to consider every question sent to panels or to use it selectively when as in

the case of PET, there are some fundamental issues about the structure of the method and the question?

DR. TUNIS: I think it would be selective and I think there are unusual questions like this one, although even in this case I think it would have been lovely to have had this meeting a month ago to go over this. So I think Hal's notion of if there is some thinking about some flexibility in terms of how

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we get input and when issues like this arise, you know, in terms of conference calls as opposed to meetings, we have obvious problems in relation to FACA compliance, so it's not clear that that's going to work for us, so we'll have to think it through.

DR. SOX: Well -- I'm sorry, Bob?

DR. MURRAY: We talked earlier today about the process that involved review of the evidence report and appointment of content experts to assist. I would be comfortable, speaking as the vice chair of the laboratory panel, if another member of the Executive Committee could serve as a content expert

or could assist with review of the evidence report to involve selective or certain members, one or the other member of the Executive Committee in the process leading up to consideration by the full panel when the panel meets, so that there is some Executive Committee involvement prior to the panel consideration.

DR. SOX: Good suggestion.

DR. MURRAY: I see that as just an expansion of Sean's reference to framing the question.

DR. SOX: Sean, any further? Have we addressed your questions about whether we think these

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are good functions for the EC?

DR. TUNIS: I do have a sense of it and I think maybe we'll write up some document that tries to sort of lay these out, and circulate it and make it sort of a more formal kind of a mission and functional statement for the post-BIPA Executive Committee.

DR. SOX: Well, before closing the

meeting, and asking for a motion to adjourn, I just want to note that Connie is going to be stepping down as our executive secretary, and as I gather, you're going to be actually leaving government service after 30 years at HCFA, which meant that you were here only about seven years after HCFA actually started Medicare legislation.

So we want to thank you, and offer you our best wishes for the next happy life, whatever it may be.

MS. CONRAD: Thank you, Hal, and all members, I certainly enjoyed working with all of you.

(Applause.)

DR. SOX: Any other new business or overlooked business? And if there isn't any, I will ask for a motion to adjourn.

DR. MURRAY: I don't know if this is the

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appropriate forum for asking the question, but I noticed that actually Sean referenced an announcement in the Federal Register, I think it was April 30th,

requesting nominations. Do we have any idea how long our term on the committee extends or are we going to get any advance notice, or just suddenly we don't get an invitation to come?

DR. HOLOHAN: No, they just won't pay your travel claim. That's how you know.

MS. CONRAD: We have a complete list of expiration dates of each member's term. Some of those terms have already expired and they are still here. The term of service continues until a replacement is named, and certainly we would not do that without telling anybody.

DR. SOX: I do think it's important for us to get some idea, because many members of the committee have other opportunities to serve and may take or not take depending on what other things they're doing, so if they know they're coming off, it helps in planning.

MS. CONRAD: I can do that.

DR. SOX: Motion to adjourn?

DR. HOLOHAN: So move.

DR. MURRAY: Second.

DR. SOX: We are adjourned. Thank you.

(Whereupon, the meeting adjourned at 3:38 p.m.)