and which should have correspondingly dramatically different criteria, judging sufficient evidence for making that particular indication-based claim, represent a huge step forward.

What I'm worried about is that if we insist on always showing rigorous data regarding the application in a specific clinical context, then aren't we really saying that we're always insisting on falling back to either the diagnostic category or the outcomes category of the indication, and I think we are saying that if we insist on that, aren't we?

I personally object to that. I think the whole point of having these different categories of indications is to permit drugs to be approved, marketed and used on label for things other than diagnosis and outcomes initially. It's the same thing with the development of CT NMR, where the applications and the evidence and the categories that you describe came after its approved use, not before its approved use.

DR. TULCHINSKY: Before we hear about MR and how that was cheated in the discussion, let me address the comments previously made by the two speakers.

To start with, this discussion has happened already, and the Congress directed us to take the functional indication and run with it. This has already

been addressed, and if you take the Congress as the voice of the American people, then the American people told us it's okay.

If you review the 1997 Act, it is in there, I believe. I would -- it is not? Ms. Axelrad is shaking her head.

MS. AXELRAD: I don't believe that it's in there.

DR. TULCHINSKY: I do believe that there is. While we're looking, I do believe that there is indication towards the functional use of those tracers. I think we need to keep that in mind if indeed that is true.

But if it is not, that was the basis of the move that brought the nuclear medicine community to Congress to seek this legislation. So that's one point that I wanted to make, and I think what we're doing today is a major milestone as far as the difference that has taken place in the way we assess those tracers.

It's in a way paradoxical to me that in the past, physicians sought less bureaucracy on the side of FDA in approval process and in the past have fallen on a deaf ear. Today, we see the reversal of things. I hear physicians objecting to a more scientifically-based, more creative approach to looking at diagnostic methods, and that is just an interesting observation personally.

Have we figured it out, Ms. Axelrad?

MS. AXELRAD: What I think what you were referring to is the reference in Section 122 of the Modernization Act.

DR. TULCHINSKY: Exactly.

MS. AXELRAD: On the requirements for radiopharmaceuticals.

DR. TULCHINSKY: Exactly.

MS. AXELRAD: Not for PET specifically.

DR. TULCHINSKY: That's correct.

MS. AXELRAD: And what --

DR. TULCHINSKY: Radiopharmaceuticals.

MS. AXELRAD: Right. But this was a separate section. PET was addressed in a separate section of the Modernization Act and was specifically excluded from the radiopharmaceutical section.

DR. TULCHINSKY: Understood. But PET choices are radiopharmaceuticals.

MS. AXELRAD: Right. But we were talking about what Congress did or didn't intend in the Modernization Act, and it was not addressed in the radiopharmaceutical section, but that being said, let me just read what the statute said.

It says there's a special rule in Section 122(a) that says, "In the case of a radiopharmaceutical,

the indications for which such radiopharmaceutical is approved for marketing may in appropriate cases refer to manifestations of disease, such as biochemical, physiological, anatomic or pathological processes, common to or present in one or more disease states."

Then it defines the radiopharmaceutical as "an article that is intended for use in the diagnosis and monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei," and it goes on with this other stuff.

DR. TULCHINSKY: Right. Therefore, I would stand with my statement that that's what they intended, for us to look at the physiology, biochemistry and so forth, across diseases, not specifically narrowed to one indication, one disease and how that changes things.

We ought to keep that in mind because that is the starting point for our discussion today. Without that, this discussion today would not have happened.

DR. LOVE: If I could just get in for just a second. A moment ago, I certainly hope I wasn't defensive. One of the concerns that we had when we were looking at the guidance document to discuss some of these issues is when you have a functional indication, what is the clinical setting in which that indication is going to be used, and that gets back to some of what you're talking about in

terms of the relevance to an individual patient.

Some of the things, principles we talked about there, are the apparent need to study at least the spectrum of patients, maybe those who are moderately ill or very severe if you're only going to look at a certain thing, like ejection fraction. If you're looking at a situation here where you have cerebral perfusion, it's going to be evaluated in a wide variety of patients as Dr. Conti presented, looking at a number of different things.

So what kind of information would be needed to show that there is relevance in this type of population? Is it studying a few? Looking at sensitivity and specificity? That might be an approach. Is it studying looking at a clinical outcome? That might be an approach. There might be others that would be relevant to provide the data to answer that question.

So I'd like to hear what the panel feels would be relevant in this kind of a consideration, both now today given the database that we have, and then if something else is needed, what would that be?

DR. RAMSEY: Dr. Choyke, did you have a comment?

DR. CHOYKE: Thanks. Yes. I agree actually with a lot of what was said. I didn't mean to appear to be reacting, but I think this is a kind of a unique situation

we have here. We have an agent that's been around for a fairly long time, and we have a huge track record. We have a mandate of some sort from Congress, and so it's very unusual, but in the future, if a sponsor came before us with an agent that promotes a functional assessment, I think what we'd really like to see is the theoretical underpinning, the animal models where you can do things you can't do in people, and then some clinical-based evidence of an example in essence of where the application looks strong, and from that, you can't obviously do those kind of complicated studies in a huge population of people, but in essence what we're doing here is taking a model of disease, the kind of evidence that you look at, and extrapolating from that to other kind of entities that are similar, and I think that's a very reasonable approach overall, and I think if a sponsor successfully documented the theory, the animal background and then one or two examples where it was convincingly similar to an animal model, that they would have a functional application that would be acceptable. So I'm very content with that kind of model.

DR. TULCHINSKY: I think that's a very well-positioned argument, and it is interesting that other imaging modalities would certainly derive a clear benefit from what has transpired.

The Congress specified those positions for PET

and radiopharmaceuticals. As we look at the draft document, and I hope that those committee members that came today have looked at that very carefully, and the draft guidance is for the imaging pharmaceuticals, not to radiopharmaceuticals.

I see Ms. Axelrad looking at the book again, and I think that that is very useful for the imaging community in general. On my personal level, I'm very pleased to see that.

DR. PONTO: This radiopharmaceutical represents a tool. It's a tool to measure blood flow. We already know that blood flow is a relevant parameter in the brain or we would not have approved HMPAO and ECD. We would not be using that.

So we need to look at the effectiveness of this particular tool to measure blood flow, and as anybody that's looked at my CV, you'll know that probably 90 percent of my papers have been written on O-15 water, and they have not been limited to the brain only.

I have published work on the use of this tracer looking at blood flow in the bone marrow in normal patients and in people with leukemia and also in solid tumor, and I would advocate that looking at the mechanism of action, you presented a myocardial justification for a cerebral measure of blood flow, that if we could limit this indication to

looking at blood flow and then use it wherever it's relevant.

DR. TULCHINSKY: I would like to echo that comment and say that it would be appropriate in my view to specify that this tracer is useful for assessment of blood flow, including special clinical situations that it would seem to be demonstrated useful and list those. That would be by far more fair and coherent approach with what the statute is telling us in my personal belief as a professional.

DR. RAMSEY: Dr. Conti?

DR. CONTI: Two quick comments. One, I want to go back to what Dr. Choyke mentioned a few moments ago. His statement should be reread to the committee because I think this is the most key aspect of where we want to go with these types of radiopharmaceuticals.

These are inherently safe drugs for the most part, and the fact is if we can use animal data theoretical as a foundation for evaluating these drugs and cite examples, they don't have to be extensive examples in terms of outcome data necessarily for radiopharmaceuticals, again they are safe, if they do mimic what we've already proven in a validation study in animal models, then we should go ahead and approve these pharmaceuticals and get them out into the community so the data can be generated following

approval, much the same way as we do in devices.

So I think what he stated in his comments a few moments ago should be taken to heart by the committee and by the FDA.

The second point I'd like to make is that we were reluctant to pursue a general perfusion application for this pharmaceutical because of the limited nature in the body applications, but I actually believe that that's the appropriate way to go because this is a perfusion tracer that can be used in the heart. It can be used in the brain, and the data support it. It has been validated in a number of situations, and the data would support its use as a general perfusion imaging agent, and the community would support that.

DR. KONSTAM: You know, I actually am looking forward to us discussing the data. It sounds like we're spending an awful lot of time discussing whether it's relevant to discuss the data, and I'm frankly finding that discussion extremely disturbing.

I think that personally, I don't care what's in the law. Personally, I think comments like it's safe, I find very disturbing because the burden on the FDA is not only to show that it's safe but also to show that it's effective, and, you know, again I'm going to keep coming from a very different perspective, which is that I don't

think any of the physicians around the table really believe that we are in this business to treat biochemical processes or physiology, and therefore the public health really demands that we seek a standard of documenting that we're making a difference in patient care.

To me, the argument here is very different. To me, the argument here is to what extent are we willing to compromise on that standard because we know so much about the biochemical process or the physiologic process that we're studying, that we're fairly certain that if we study that process, we will make an impact on care, even though we haven't studied it.

Now, in this case, again I come in with a good deal of ignorance because I don't know much about the fields being discussed today, but I find it -- so maybe that's the limitation or maybe that's an asset because I find it personally very difficult to make the leap to simply say because I know something about cerebral blood flow, I know I have helped myself in managing the patient.

Now, I guess to me, I think really that's where this discussion sits. How much do we really know about the physiology? How much do we know about this agent's impact on the physiology, and on the basis of that, how much are we willing to compromise on the usual standards of holding an intervention or a drug to an extremely high level of

standard, to say I am impacting on care, the drug is doing clinically what I think it's doing, and I think that's where we're going to have to identify a compromise.

I think we're going to have to come out and say, well, in such a circumstance where the physiology's very well known and the agent on a physiologic basis is very well known, then maybe we don't need two 2,000-patient randomized clinical trials, each with a P value of less than .05 showing an effect on survival or something like that.

But we've got to decide what is the standard. There needs to be some clinical standard, and I look forward to discussing the data here and seeing whether the data here reach some acceptable level of standard based on what we know the agent does physiologically.

DR. TULCHINSKY: My light was first. Thank you.

I think the comment is well made, and you're right. Your ignorance has helped us today as we discuss different aspects of this matter, and specifically what you're bringing up is, the question is, is it effective?

One way to look at that same question is, is it effective in demonstrating blood flow in general, and I think that FDA has posed a very voluminous body of literature that points to the answer, yes, it is effective

in demonstrating blood flow. It's as close to the nature as you can come to demonstrating blood flow.

Now, is it useful in specific conditions? I think if you're looking to the package insert in finding that answer, you are simply looking in the wrong place. That belongs in the textbooks. That belongs in current articles, and that belongs also in some part to reside in your clinical judgment.

If you ask yourself, and I hope you will -- you might answer aloud so we can all hear. Among the medications that you use clinically, how many times out of all prescriptions that you write is it for package insert-directed indication, and if your answer is 90 percent, I'll be stunned. If it's 50 percent, I'll be surprised, but I'll believe it. If you say it's about 25 to 30 percent, that to me might be closer to the norm.

But what that tells you is that I think as the science progresses, that you modify your applicability of a particular medication, and it's specifically true for diagnostic agents, and that's how you practice medicine, but I think the way that we approach radiopharmaceuticals, and the way that has been discussed many times over and over again and very well put in written word is that I think we need to start thinking, as Jonathan was saying, about functional application, list specific conditions

where it has been shown but not limit the physician to that, and follow the data-driven therapeutic position or Harrison's textbook or whatever the specialty textbook that you have and your clinical judgment.

On that, I'll close.

DR. RAMSEY: Dr. Ziessman? I'm sorry, Dr. Houn. I know your light has been on for awhile, and I'll call on you next. Oh, okay.

DR. ZIESSMAN: I'm sympathetic with the FDA today because they're trying to find their way in how to look at a new approval process for radiopharmaceuticals, in this case particularly radiopharmaceuticals, and I think what's becoming evident is that I think most of us appreciate the data is there for approval of this radiopharmaceutical for blood flow, is the presentation, I think, today that has us bothered because I think your concern's appropriate, that we haven't discussed the data, and that the data that was presented probably isn't adequate for our approval. But I think we all know that it's there, and that's the problem I think we face.

I don't have a quick answer how we should proceed as a result.

DR. RAMSEY: Dr. Houn, I think, is next.

DR. HOUN: I just wanted to say that across the Center for Drugs, drugs are developed in a manner where

preclinical studies in animals are done first to try to assess safety and appropriate dosage and get an idea of what is the pharmacologic action of this drug. Then they're assessed in small numbers of humans for safety, and then larger numbers in terms of trying to test a hypothesis in terms of the drug action. So what was said by Dr. Conti really is not different from the drug model.

I think the reliance purely on biochemical information, I mean, we know sudinitil citrate inhibits degradation of CGMP. That's a biochemical indication. What does it do? Well, it's believed it vasodilates, and that's why it was being developed as a drug for hypertension. It turns out it causes erections. It's now, you know, Viagra. This is how, you know, biochemical activity needs to be tested in humans to define relevancy, and I don't think people are saying we're not going to be doing human drug trials.

I just want to emphasize how important that part of the information is for the drug development process.

DR. RAMSEY: Dr. Links?

DR. LINKS: I thought that Dr. Konstam beautifully identified what the central issue is we're discussing and bringing it back to the specific case we're trying to look at this morning.

It seems to me that if you have what I'll call a functional indication that it measures cerebral blood flow, then the primary evidence that should be presented to support that indication is evidence about the tracer's ability to measure blood flow, such as the dog heart study that was shown but obviously going beyond that single study.

Now, fortunately, in the literature, there are examples for O-15 water in other organs, in other species, that go beyond the dog heart. But if we're truly to embrace the new final rule that allows these different types of indications, then the primary data on which to support or not support the indication must be data having to do with that indication. So that's the first point I'd like to make.

The second point I'd like to make is that I really like the use of the word "example" that I think Dr. Konstam used, Dr. Choyke used. Obviously, it's insane to propose a drug for which there's no clinical application, and it's not helpful to not present any evidence clinically that the drug is making a difference in patient management one way or another.

What I'd like to emphasize, however, is that at least to me, the degree of evidence required for an example is significantly less than the degree of evidence required

if your indication is diagnosis- or outcome-based.

So the studies presented this morning in my opinion absolutely satisfy my criteria for example, whether or not they would be sufficient to satisfy the criteria of evidence if the indication itself was based on diagnosis or outcome.

DR. RAMSEY: Dr. Konstam?

DR. KONSTAM: Well, you know, I worry about the word "example" because I'm not sure what it means, and I mean, we've seen some beautiful examples of cases today, and I think they were very helpful to me because I've never seen them before, and again I don't know too much about it. So they're very helpful to me in terms of putting this in perspective and bringing this down to the real world.

On the other hand, I was very worried watching them because in my former days as a radiologist, I've seen many presentations of examples of cases, and people show their best cases, and even if they're not showing their best cases, what does it mean, and how do you translate that into statistics? How do you translate that into what the impact is on the patient, and so I don't know what example means.

I guess I think that -- well, I guess maybe we need to ask ourselves that question. If we say, well, the example is the Grubb study, it's not an example of a case

report. It's an example of a potential specific clinical indication. What's that indication? Prognosticating in the presence of carotid occlusion for subsequent stroke. Well, I think we actually should look at that article and start talking about that right now or soon because I have a 1:00 flight, because to me, that was the closest thing in the data set that was actually evidence that the agent used for the biochemical or the physiologic indication that is being requested will mean something clinically.

I think we should tear apart that article and examine the statistics in it and examine the population and examine the validity because that's the one that will help me make a decision whether I think this agent should be approved or not.

I think that the rest of the body of data that Dr. Love presented, you know, I feel was really fairly weak. I feel that the supportive studies to the Grubb study seemed weak to me. They seemed duplicative. It's not clear that they're separate populations.

I think that the sickle cell case is exciting and interesting. It doesn't quite make it for me because it's not clear to me how that translates into influencing care, and so I get the sense that this could be a useful agent, but when it comes down to me asking the FDA to say this is safe and effective and ought to be used in clinical

practice, I want more than that, and, yes, physicians are going to use their own judgment and are going to use off-label applications all the time, but that's not the FDA's problem.

The FDA's problem is to declare that something is safe and effective, and so I think we'd better look at the data and ask ourselves whether it's safe and effective for examination of cerebral perfusion based on a clinically-relevant application.

DR. PONTO: I understand completely your concern. If this is all I knew about O-15 water, I would not want to approve it. The trouble is, I have a file drawer this big that literally has hundreds of articles in it. Dr. Herscovitch has done a validation back in '83, wasn't it, of this whole process, and knowing that, that's why I expressed confusion at why we were looking at these particular articles to approve this particular drug for this indication, and if we only had this data, I would also have the same concerns that you have.

DR. TULCHINSKY: But given the data we do have, again it's a good suggestion. We should look at the article, and I have looked at the article. We're talking about Grubb's article, of course. It's again in our hand-out, Volume 5, and what I'd like to hear instead of a general comment, what is the concern that you have about

that article?

DR. KONSTAM: Well, I don't have any concern.

DR. TULCHINSKY: So what is the comment then? I think it was very well presented by the FDA representative.

DR. KONSTAM: No, I guess my concern is that we're not discussing it. That's my concern.

DR. TULCHINSKY: That is our homework, is to look at it. If you have a concern, address it.

DR. KONSTAM: I thought you were saying that we don't even need to look at it.

DR. TULCHINSKY: Oh, no, no.

DR. KONSTAM: I thought you were saying that all we have to do is know that it has a physiologic effect and that's that.

DR. TULCHINSKY: Then my comment was taken out of place. My point is this, that you have a tracer that has a physiological indication. Say, like this one. You document that it's safe, and you study it in animals, then you proceed to the clinical model, and that has been done.

DR. KONSTAM: Right.

DR. TULCHINSKY: Hasn't it? I mean, this tracer went on to the clinical arena. Then it has shown to work in certain scenarios, not maybe to the same rigor as a commercial product that has a sponsor because again the

financial power to show that is just not behind that drug.

However, the scientific studies were well done. The Grubb article was published in JAMA, a publication that I hope will grow into respect tremendously. I'm not saying you should not show that it's useful in some clinical situations. It does show the blood flow in clinical scenarios in humans. No, that is not the point.

But the point is that once you have shown it in a number of clinical scenarios, that it does demonstrate the cerebral blood flow, then you approve it for cerebral blood flow, including situations -- and that's what I think I said in my first comment, including the situations in which it has specifically been studied, but --

DR. KONSTAM: Now, this is very --

DR. TULCHINSKY: -- don't the other one to it.

DR. KONSTAM: No. This is very helpful. So maybe we could, based on what you're saying, maybe you could or others around the table could quantify for the FDA a little bit more clearly, you know, in this circumstance, what are the standards of clinical data that we'd like to see? And then maybe we could look at this data set relative to that.

So for example, let's take the standard and work backwards from it. You know, the standard for drug approvability is two randomized clinical trials with P less

than .05 with the data set in hand by the FDA, that it's being used in a population, that it's been studied in the population in which it's likely to be used, that the data set is clean, that there was a preset protocol established, and that it was adhered to, and that we have good evidence that it was adhered to, and that the data set has validity and integrity.

So those are the starting points. So maybe you could articulate in this case which of those specifically would you be willing to compromise, and what specifically would be the standard of clinical investigation specifically that you would say that, short of that, that you would say when we come back and look at this data set, we could say yes, we can approve this agent?

DR. RAMSEY: Excuse me. I'm going to take the chair's prerogative. Dr. Herscovitch?

DR. HERSCOVITCH: Yes. I have a few comments, some of which may be repetitive, but I think have to be said, is that, firstly, in terms of O-15 water as a cerebral perfusion agent, it is an extremely good agent, probably the best agent there is on the basis of a tremendous amount of experience.

Secondly, I will say that none of that experience and none of those data are in this package. So I would have to disagree with Mark Tulchinsky who said that

this package shows that it's useful for measuring CBF. I would say that this package does not show that it's useful for measuring CBF at all, and this in part, I think, reflects to the approach that the FDA probably felt they had to use, especially not including all the animal validation studies, and also to their very restricted, perhaps unfortunately restricted, choice of papers, not doing a full literature search as was done yesterday with the myocardial blood flow agents and fludeoxyglucose.

I think the question is to a certain extent what is the question? For example, looking at the question we have to answer, Number 4, based on the presented review. Well, even forget about that. Just in general, the question is, do you think water is safe and effective to measure cerebral blood flow in patients with a variety of cerebral vascular diseases?

Well, the answer, I feel, is yes, because O-15 water gives you excellent maps of cerebral perfusion. So is that the question? The answer is yes. It gives you excellent maps of cerebral perfusion in virtually any disease. So if that is the question, then a proposal could be designed to answer that.

Then there is another question. Is the assessment of cerebral blood flow by O-15 water or other methods useful in the diagnosis and management of specific

diseases, and surprisingly, the answer is not very many, and even in diseases like cerebral vascular disease, when the problem is by and large in the plumbing, isolated measurements of cerebral blood flow, either quantitatively or just a map, are not particularly useful in terms of making a decision about what to do with the patient.

The only other comment I'll make is concerning the Grubb paper which we seem to be giving a lot of stock to in this process, is that my opinion, and I think we should discuss it, is that's an extremely well-done paper, probably one of the best papers showing the clinical application of PET, but, on the other hand, it is not particularly relevant to deciding whether CBF is a useful perfusion agent because the main outcome measure there was the oxygen extraction fraction that was measured with a different tracer in conjunction with CBF. Actually one can even show, I believe, that if the CBF is off, it kind of cancels out, and you still get a good measure of the oxygen extraction fraction.

So if we were discussing the utility of those three O-15 tracers that one needs in this case to measure the oxygen extraction fraction, the Grubb paper is an extremely good place to start, and I would contend short of the NDA-type study that you mentioned, this is probably the best paper in the literature to meet requirements of a

committee such as this.

Unfortunately, I don't think it meets the requirements to answer the question about O-15 water. So I think we are really in a conundrum. We are in a philosophical conundrum about whether we are approving a perfusion agent or something that is useful for the diagnosis of a specific disease, and we are also in just a bit of a logistical conundrum because the FDA experts, unfortunately, and I think but for reasons which I totally understand, did an assessment which doesn't necessarily provide us with all the data we need. So we're really stuck here.

DR. RAMSEY: I just want to make one comment which I've tried not to make comments, but as a neuroradiologist, I know my surgeons do respond to the data obtained by regional cerebral blood flow when they look at those patients, and they use it to make clinical decisions, but that said, I thought at this point, I would jump in here and just read the question since we've alluded to it several times to see if we can then direct our attentions to that.

It's Question 4. "Based upon the presented literature review, do you think water O-15 injection is safe and effective in positron emission tomography (PET) imaging to measure cerebral blood flow in patients with

cerebral vascular disorders associated with ischemia, hemodynamic abnormalities, occlusion and other vascular abnormalities?"

DR. KONSTAM: Ruth, before we get into the question, I don't know whether this is appropriate or inappropriate, but I personally would like to hear some discussion on the panel with respect to the question I asked, which is, in this circumstance where the principle motivation for approvability is as a physiologic marker?

If we accept that people use the word "example," I think -- I don't like the word, but if we're to accept that even in those circumstances, we need to document that the agent has a role to play clinically, based on data that can be analyzed statistically and meaningfully -- I mean, I think it's worth having some discussion about what people think that means in terms of criteria.

Does it mean a single study? You know, what are the standards of that study? You know, what do we mean when we say example, and I for one would like to see -- let me throw something out. I'd like to see one extremely good study where the basic findings are beyond reproach based on, as best we can tell -- now, here we have, you know, an article in the literature. Ideally, the FDA would have the data set and the original protocol. So that's not here,

but those would be ideally.

Ideally, you'd have a study. You'd have the data. You'd be able to validate the data. You'd be able to validate the statistical approach, and that the study has some clinically-relevant impact on something, prognosis, relative to some other diagnostic method that we are very confident has a major impact on clinical outcome.

That is to say, what I'm trying to approach is to say basically this is analogous to having a process/outcome link, basically. It's saying that we're going to go through the process of measuring cerebral blood flow. What we really want is better patient outcome, and we're going to wind up being very confident that if we measure cerebral blood flow well, and we have the data to know that we were measuring it well, then that will impact on outcome.

I guess that's what I'm looking for. So now go back. A single study that does that, that somehow permits us to make that process/outcome link, to say yes, if I measure cerebral blood flow by this agent accurately, I will to a fairly good degree of confidence know that I have impacted on clinical care in some meaningful way.

Is one study enough? I'd probably like one study and at least a fair amount of support around that from other studies that may not be quite as good but at

least point in the same direction. Internal consistency within the study would be another thing that would be useful.

So that's my throwing out the idea about what I'd like to see, and maybe we could measure this data set against it. Maybe it meets it, maybe it doesn't. I don't know. I haven't decided yet, but maybe we could have some reaction of that.

DR. TULCHINSKY: I totally agree with the comment made, and that is, some standards need to be developed, and clearly there is great deal of room for making the process better.

This is just really a first step. I consider it to be a step in the right direction and a very good step. FDA has done an exceptionally good work, and with all due respect to the comment that maybe not all the papers were submitted, but please do realize that if all the papers were submitted, and Dr. Ponto pointed out that she has a whole drawer full, I would never be able to physically make it to this meeting.

I had a hard time dragging the five volumes, but I think as a member of the panel, one ought to look at what has been submitted, and if one looks again carefully at what has been placed in our package, there are references, although not xerox copied for us, but there are

references to fairly good number of basic papers, and it's a good array of papers.

If you look at the reference that has not been xeroxed, it has the original articles by Bergmann, for example, on Page 6 of the initial section in Volume 5. I've looked at that paper. I didn't have to have FDA make a xerox copy of it for me. I'm sure that there were some things missed.

Again, using my intellectual ability to synthesize, it seems to me that what has been proposed is very reasonable. What are the criteria, though? I think a separate meeting probably is worthwhile to talk about the criteria. I don't think we're going to resolve it today, but one good paper -- what is good? How many patients? How well would one statistically analyze it, and what are the methodologies to be applied?

It's all excellent questions. I think we need to spend some time thinking about it. 50 patients at least to make it a good paper. Statistical analysis, and that's a discussion that probably deserves different time and different place.

DR. AMENDOLA: Can I make a small comment? I was wondering why some of the seminal papers were not included in the review, and I was wondering if looking at these papers, they are fairly new, and I wonder if that is

because maybe 10-15 years old, that is the reason that the FDA didn't include it.

Looking at the Grubb paper, another thing caught my attention, that they had to end the study early because of lack of funding, and I was wondering if that, the lack of funding, is something that has to do with the dearth of material presented, that some of the other studies that didn't reach that critical number of 50 patients to be accepted for the FDA review.

DR. RAMSEY: Dr. Conti?

DR. CONTI: Again, two quick comments. One, I wanted to just state as far as the literature was concerned that what was submitted to FDA from the ICP were representative articles, not the entire world's literature on O-15. So this is an important distinction.

Secondly, I want to remind the committee that there are a number of perfusion-related agents that are currently with label. Okay. These are approved radiopharmaceuticals for perfusion imaging. There is precedent. There is data that supported those initial perfusion imaging agents for their approval.

I would also like to stress that there are other modalities that use the concept of perfusion imaging. So again, I don't think the committee, from the public's perspective, should spend a great deal of time on focusing

on the concept of whether or not perfusion is an important clinical question. This has already been addressed through other discussions with other approvals, but to focus on the equivalency of this particular tracer that has been validated in animal studies and has been shown in a number of representative articles to be clinically useful, that's where the focus should be.

DR. RAMSEY: Dr. Links?

DR. LINKS: In that regard, if we cast our mind back to previous agents that we've considered in this committee, what I would call the standard, even if you're just going to focus on diagnostic accuracy, the standard has changed from agent to agent because the context in which the agent was to be used has changed, and the competing choices were of either good quality or poor quality or non-existent in the different scenarios.

So I'm personally a little loathe to talk about standards of any type in that regard because, for example, it would only be natural to say, well, unless the indication is a diagnostic accuracy indication, unless the diagnostic accuracy is X, we're not going to approve it, and we've approved agents whose diagnostic accuracy was relatively low by most conventions but was sufficiently high to make a difference clinically because there was nothing else available to compete with the information.

In the same way, I'd be loathe to talk about P values, sample sizes, et cetera, for any kind of paper. For instance, let's say that we're talking about a perfusion agent, and the issue is one of a change in management based on the outcome of the imaging study.

I pose the question in what fraction of the patients would the management have to be changed in order for you to say that the agent was a useful agent? That would be a very --

DR. KONSTAM: Any patients. But I look to any patients. I mean, you could say one in a thousand. I mean, this is --

DR. LINKS: Then we're together.

DR. KONSTAM: Just a second. I don't think we are because this isn't a discussion about cost effectiveness. We're not getting into costs here.

So if you knew for sure that an agent was going to influence therapy one in a thousand cases, I think that that to me -- I don't know what the cut-off for that would be, but that would satisfy me.

The question is how do you know it? How do you know from a study of 50 patients or a hundred patients or a thousand patients or 10,000 patients that therapy was influenced in one of a thousand patients?

The way you know that is by statistics. That's

how you know that a finding is valid and correct. So the level of impact is not what we're discussing here. The issue really is -- and I accept Dr. Conti's point. I will state his point a different way.

I think what he is making a plea for is to say that, you know, we know so much about the impact of cerebral blood flow measurement and how that impacts on outcomes, that we don't have to remeasure outcome with this agent. Okay?

Now, I would challenge that that's really true, but then again I don't know anything about it. So maybe it is true. But I really am concerned when you say I don't need a P value because you do need a P value because if you don't have a P value, you don't know that the study is very likely to be correct or not.

DR. LINKS: Well, let me rephrase it then. Let's say that I do a study with 50 patients, and the outcome is changed in one. I can certainly express a confidence interval of what in the overall patient population the most likely or the range of percent of patients in which the outcome would be changed is, but a P value per se is not necessarily the most meaningful statistic.

In other words, maybe we're just quibbling, but I don't want to have standards that are so explicitly

defined for certain paradigms, that there's no way of fitting another paradigm into it. So if by P value, you're really not talking about necessarily a P value but rather some way of characterizing confidence, then we're together.

Even in a case like that, I would hope that we don't have to agree on a minimum fraction in which the outcome would be changed or a minimum diagnostic accuracy. Obviously we want to characterize the certainty with which we're saying that the outcome will be changed by thus and so or the accuracy is thus and so. We have no disagreement there, but the statistics they are characterizing are certainty rather than providing some sort of threshold operation for action or no action.

DR. RAMSEY: Ms. Beaman?

MS. BEAMAN: Well, I'm still floundering over here between the information that's presented and the information that may very well be out there.

From what I've read, the agent perhaps does indeed measure blood flow. It's a diagnostic tool, to be used as the diagnostic tool. There may be volumes upon volumes of information out there, some of which I'm sure people around this table have some knowledge of.

It isn't here. It wasn't presented, and from what is presented and even looking further into some of the indications referenced here, I didn't find some answers,

and one question that is still there is, if it's used as a diagnostic tool, is it necessarily of sound clinical application at the expense of the patient? So you know the blood flow, the degree of blood flow. What do you do? How do you use it? From a quality of life standpoint, please help me out here.

DR. TULCHINSKY: Yes, that's a tough question to answer. I don't think anyone around the table would have a clear-cut answer for you, but again, I would support my earlier statement that studies to show clinical effectiveness to that degree as to improving the quality of life are very energy- and finance-intense endeavors.

Not many medications that we use today would have that information in it, but I think it would be a good start to look at what we have in front of us and either agree or disagree. I personally agree that it does measure blood flow, cerebral blood flow in this case, and one would have to rely on clinical judgment as to how it will be used along with the information provided.

It will not be unlike 95 percent of what we do today. It will be very much along the lines of our medical practice, but it is not to say your question does not need one seeking answer. I think we are in pursuit of that answer, but the lack of it today at the table in my view should not preclude us proceeding.

DR. RAMSEY: Dr. Conti?

DR. CONTI: I apologize for having to walk a distance here, the delay, but I want you to ask the patient who had transfusion therapy and sickle cell whether it made a difference to that particular patient that we did a test on that child or his or her parents, and I want you to look at the data in the sickle cell paper and use that as an example of altered management.

A patient received a specific therapy on the basis of the PET findings. It's a very tangible evidence that that did occur. It's published.

I also want to point out that this committee, as far as I remember, yesterday approved a perfusion imaging agent for the heart called N-13 ammonia. So keep this in mind when you're doing these evaluations and keep in mind, as I said earlier, that perfusion imaging and perfusion-based assessments, whether it be with PET, SPECT, MRI, ultrasound, transcranial doppler, for example, are in fact there. They're approved, and they're used clinically, and decisions are made on them every day.

DR. AMENDOLA: I think that if you look at the Grubb article which I think most of us, if not all, agree that is a very sound article, it provides the answer to your question. They identify the set of patients which are at high-risk category of stroke, and their assessment of

these patients going to have surgery.

I think that if you read the other articles, I agree with Dr. Conti's opinion that this agent has a really valuable indication many times as an important impact on clinical decisionmaking.

DR. CHOYKE: Can I make a comment about, you know, this discussion, and, you know, I started out fairly happy with the evidence until I heard two O-15 experts say that they didn't really see the evidence here for cerebral blood flow, which is what the question talks about.

Yet, you know, we know they both -- I hasten to add that there's voluminous data outside this room that exists, and, you know, so, where my own thinking is, is that are we that rigid that we can't bring in expert opinion that hasn't been presented officially here?

I really think this agent should be approved, especially in view of what we did yesterday to be internally consistent, but on its own merits, I think it should be approved based on what I've heard and other comments, but, you know, I think we may be getting into almost a legalistic rigidity in terms of just considering what we have before us, and I think the common sense decision is to go forward with O-15, but, you know, legalistically, I don't think we have it. So that's where I am.

DR. RAMSEY: Dr. Ziessman?

DR. ZIESSMAN: Yes, I think that's right. I mean, I think the problem today is the process, and we're just trying to figure out and learn the proper process to approve radiopharmaceuticals for these new indications, and I think we all agree that if we had to do this over again, this would not have been the way we would have looked at this radiopharmaceutical today. We would have had stronger and more appropriate basic science information, more appropriate animal studies, and it seems to me then if we presented clinical data, I think we may have our own standards, but I don't think the standard has to be very rigid.

I think if we had expanded on what Dr. Conti presented, for example, had multiple experts come in and give us information like that or reviewed literature that gave similar type of information, that we had multiple examples that showed us how it impacted on clinical care, that that would have satisfied us for these -- they would have satisfied me for these indications, but I don't think we ought to penalize this radiopharmaceutical because of what's happened with this process because of the situation that we're floundering in trying to find the proper way to do this.

I think the radiopharmaceutical ought to be

approved. I think we all understand that this is an excellent radiopharmaceutical, that it has clinical utility. The process is what has suffered today.

DR. RAMSEY: Dr. Love?

DR. LOVE: If I could offer an approach that might help. We've certainly been talking ourselves on what is the best way to proceed that would help us in this, and I think it's quite clear that there are other data out there from your comments.

Yes, the committee is free to consider other opinions and information discussed on the panel. Obviously from our perspective, if you wanted to make some sort of conditional or preliminary type of vote, that would also be acceptable to us on perhaps the condition that these other articles are reviewed, and we can either get that information to you or develop some other mechanism, if you wish, if you want to see it, or you can give us a preliminary assessment and whatever recommendations you have for us in terms of looking at the other articles that are available.

So there are a number of other options that the committee could choose to follow, other than a strict vote.

DR. PONTO: I would like to propose a change in the question. I would say based upon the literature, do you think O-15 water injection is safe and effective in

positron emission tomography imaging to measure blood flow? Limit it to that.

DR. RAMSEY: Mr. Hammes?

MR. HAMMES: I've just been sitting here taking this all in and trying to digest it, and what I call us to personally, you know, I believe, and I've done some literature review in this through the years, that oxygen-15 water does measure blood flow.

I don't see that data here, you know, and based on the presented data, I couldn't say that's the case, but I do believe that's the case.

But, overall, when I look at the presentations yesterday and our deliberations and all the evidence, I had a comfort level in what we were doing yesterday that was orders of magnitude stronger than my comfort level with this drug today, and I just don't feel comfortable based on what I have to, say, answer this question yes, you know.

Laura's proposed question, I'd feel a little more comfortable with, but, you know, you still have to see the data, I guess. Without seeing the data, it's hard to say yes, and this is compounded somewhat by the knowledge that I have, that, hey, we have other cerebral blood flow tracers. I don't see the drastic need for approval of a third cerebral blood flow tracer based on flimsy evidence. So I feel uncomfortable with it.

DR. RAMSEY: Dr. Tulchinsky?

DR. TULCHINSKY: It would help me, I guess, with pondering myself on that same question, it would help me to understand why is it that we around the panel, people that are considered to be knowledgeable or should be knowledgeable in this topic, you may correct me at any point here, but we're supposed to be knowledgeable on the topic, and we have personally reviewed the data.

Now, I have reviewed the data. It didn't stop here. Dr. Ponto has reviewed the data, and that data is your baby really, quote unquote, not literally speaking. You want to say yes, but you are saying no. It sounds fairly schizophrenic to me for the lack of a better correlative term.

Now, if we have studied the data, we've worked with the drug, and we are comfortable with what the question is posing, why simply not answer the question? Why does it have to be the volumes right here piled up on the floor? Is there a particular point I'm overlooking? I'd like someone to point it out because we have looked at the data. We individually and professionally reviewed it. Some of us have spent a number of years writing about it.

What makes today different as far as you answering that question? In one situation, having that pile on the floor with those articles, and in the other

situation, not having that pile on the floor with the articles but just having -- being reviewed by your own self?

I'm lacking an understanding of this critical difference perceived by others.

DR. RAMSEY: Ms. Beaman?

MS. BEAMAN: I'll answer that by saying because this is not the Psychic Hotline. That's why.

DR. TULCHINSKY: Could you clarify?

MS. BEAMAN: You said, yes, the volumes may be out there, but why do we have to have them stacked here, because there are those of us who are not psychics. That's one reason why, and it is the responsibility of the presenters to have that information before us at some point if indeed we're going to be expected to act up on it.

We're seeing a perfect example here when specific guidelines are not set forth for recommending approval of drugs what can happen. Statements such as you recommended approval of ammonia yesterday, why not this one today. As long as we don't have some specific guidelines, and we have multiple interpretations, we're going to continue to have these kinds of dilemmas, and I'll follow that by also stating in reference to the gentleman here.

DR. LOVE: Dr. Sancho.

MS. BEAMAN: Dr. Sancho. I think it's pretty

elementary that there is some expected blockage and blood flow issues with sickle cell patients, and that also transfusions are indeed a help, a tremendous clinical help. I am a person who gives space to the patient as a cancer survivor here. I didn't quite follow your point as to thanking that patient who got a transfusion as a result of your use of this drug.

DR. LOVE: That was actually directed at Dr. Conti, not Sancho.

DR. RAMSEY: Dr. Tatum? Oh.

DR. CONTI: Peter Conti from USC. My point was simply to give you an example from the literature of how patient management was altered on the basis of the information provided from the diagnostic test, that there was question brought up within the committee discussion about outcomes and effect on patient management, keeping in mind, of course, that the word "alterations in management" may mean something simply from preparing the operating room for a potential bleed-out from a biopsy all the way down to something such as survival.

If something has been altered or changed in the work-up, the day-to-day activities of managing a patient, those are the things we need to be looking at, and those are very difficult necessarily to quantify with P values and specifics within the manuscript, but you can at least

glean from the literature, at least the perfusion literature, that there are changes in how we manage patients on the basis of the imaging data that's provided.

DR. LOVE: If I could interject, the discussion that has been taking place is very valuable to us, and we certainly appreciate it, and I think it's clear to us from listening that there are a number of different perspectives on the committee, and that it's mixed, and what I would ask the chair, your feeling, but we would be comfortable pulling the question at this point in time, not going forward with actually getting an answer and coming back and representing this at another advisory committee meeting.

But I certainly want to thank everybody for this discussion. It has been extremely relevant and helpful to hear the different perspectives.

DR. RAMSEY: I think Dr. Hertzberg was first. Well, actually Dr. Tatum, but --

DR. HERTZBERG: I happen to have some knowledge because I serve on an NIH study section where I was last week, through some of my relationships there, that one of the patient management aspects that they're going after, the Powers group, which Grubb and et cetera are members of, is they're going to be looking at bringing back EC/IC bypass in this specific group of patients that show this particular pattern in PET, and so I think that this

publication was just last year.

They're just now girding up to procure the funding to go investigate this, but I think that that's the kind of thing that you can see in terms of a change in patient management that will result in this.

DR. RAMSEY: Dr. Tatum?

DR. TATUM: This gets back to Dr. Love and yesterday. I think it's a good for clarification points that what I understand about how this process is going forward. This is like doing a step to bring forward sponsors, and my understanding was that what's going to go in the Federal Register is going to be based on what we basically have here.

Therefore, trying to introduce documents or other information that is not part of this would not include necessarily in what's going to go forward. Therefore, we do need to do, I think, what you're saying, so that that information can be included in what I understand the process to be.

DR. LOVE: Right. We would have to have the additional literature in order to move forward to reference it in the FR notice.

DR. RAMSEY: Dr. Ziessman?

DR. ZIESSMAN: As I understand, we are just an advisory committee, and the FDA can take our advice or not

take our advice.

I think that we can give advice to say that we don't feel we have the data to approve this radiopharmaceutical based on what was presented. Many of us have the feeling there is the data out there and would say if the FDA would review that data, we think they would find that this is approvable and therefore take it from there without having to come back to the advisory committee.

DR. LOVE: That would be at the committee's pleasure. We certainly do intend to review the other data, but whether it comes back is the committee's pleasure.

DR. TULCHINSKY: Right. As a note, I would like to make a small one here, that I believe that FDA, as this process began, I'm talking about two years ago and up to date, and if you look at the November meeting notes, one of the potential mechanisms of dealing with this same situation of non-supported drug application, no sponsor for the drug application.

One suggested approach was to have an organization actually review the literature and present that at the FDA meeting. If you'll recall the November meeting in 1998, that was a favored approach, and the thought back then was let's see how it works, if FDA would do it, as a first step and maybe that can be generalized

later into us professionals doing this with FDA having the final look-over and checkmark.

I do believe today we are a bit reverting, and I personally would favor to proceed today with voting on this question. I do feel that the members have been irreversibly altered by this discussion, and I'm not ignoring the comments made by the patient advocate.

I think those comments are very appropriate, very good, and those comments do pertain to everything we've done yesterday, and I'm not saying do it just because we did it yesterday. I think we did yesterday the right thing. Let's do the right thing today is my simple point.

I'll give the floor to Jonathan.

DR. LINKS: Well, it's up to you to give the floor to me.

DR. RAMSEY: I'm not sure who was next. I think Dr. Hertzberg, actually.

DR. HERTZBERG: But, yesterday, with all due respect, I think we had a different standard of evidence. We had different quality of evidence in terms of what was presented, and that's why it was right to do it yesterday, and that's why it is questionable whether it would be right to do it today at best.

DR. LINKS: For all of us who love nuclear medicine, it seems to me that if the only way the

literature that we know for 100 percent certain is there and supports the use of this tracer, if the only way for that literature to get into the FR is to do the process Dr. Love suggested, then especially if you love nuclear medicine, we need to follow that process.

DR. TULCHINSKY: It's not going to get in there. The literature will not decide it.

DR. LOVE: No. We will have literature references listed in the FR notice.

DR. TULCHINSKY: In the FR?

DR. LOVE: Yes, and so the basic --

DR. TULCHINSKY: This entire literature list?

DR. LOVE: Not all of it.

DR. TULCHINSKY: Okay.

DR. LOVE: Those references --

DR. LINKS: Only if we don't act on it will it get in there, right?

DR. LOVE: The references that are forming the basis of the decision would be the ones that are listed. There are a couple of approaches that we could probably take at this point in time.

One is what was mentioned. We can not vote today, look at the rest of the information, bring it back to the committee for presentations. The other would be whether or not we wanted to do the review and send it to

the panel without a full meeting, and each of you can send back your individual comments to us. That's another approach, without actually doing a meeting.

Someone on the committee could review the rest of the information. That's an option. There's several ways to approach this without having to take a vote today, and it seems to us from what we're hearing, is that there is a mixed sense on this, and clearly that there are other data that were not considered, and we're perfectly happy to do that.

DR. MALCOLM: May I? We're going around in circles. May I make a motion, please? May I make a motion, number 1, that this question today be pulled? We get that answered, and if we can get a vote on that.

PARTICIPANT: Second.

DR. MALCOLM: Okay.

DR. RAMSEY: Discussion? We had the discussion on whether it should be pulled or not. I guess we vote.

DR. TULCHINSKY: As a preponderant for not pulling it, I would say for the sanity of this meeting, yes, that will be fine.

DR. RAMSEY: So the question before us is if we should pull the question for the present time. All those in favor?

(Show of hands.)

DR. RAMSEY: Opposed?

(No response.)

DR. RAMSEY: None opposed.

MR. MADOO: Question pulled.

DR. MALCOLM: Okay. The next is how do we handle this?

MS. AXELRAD: Let me address that for a second. I do not think it's a good idea for us to simply pull literature together and submit it to you and get comments back in the mail. I think that this needs a public airing, especially given the different views expressed by committee members.

So what I would suggest is that we review the literature. We may ask the Institute for Clinical PET to provide us a better selection from the literature, and we'll do a review like we did for FDG and ammonia, and we will present it to the committee at a future meeting.

DR. RAMSEY: Dr. Herscovitch?

DR. HERSCOVITCH: Perhaps we should stress that the different views expressed by committee members related more to the process and the evidence that was presented and not to the nature of the tracer which I am convinced when we do have the data will demonstrate that it is an excellent perfusion agent and perhaps just a minor point, but picking up on something the gentleman said down the

way, that although there are other perfusion agents, such as HMPAO and ECD, which have been approved, they really don't do the job for at least one of the applications that was discussed, and that is functional brain mapping as a prelude to surgery and defining eloquent cortex. That really can't be done. So even though there are other perfusion agents which might do the job in certain types of cerebral vascular disease, there isn't an agent which does the job in functional brain mapping.

Finally, not to anthropomorphize this agent, but Dr. Ziessman did already, it really is too bad that the agent is being blamed because of the nature of the presentation and the difficulty of clarifying the process, but I do have to agree with everybody who did say that they feel uncomfortable approving it because they feel they didn't have the literature, and perhaps I was in a somewhat better position to be very optimistic because I am more familiar with the literature as is perhaps Dr. Links and Dr. Ponto.

DR. KONSTAM: You know, I agree with what we've decided to do, and I also agree that I think it would be a mistake just to send this out and get our comments back. I think we need to reconvene. I think there's a dynamic here that has to be fleshed out, and I think that would be very valuable.

I do think I'm still a little bit stuck, and I wonder what to do to unstick myself and perhaps other panelists regarding, you know, defining a little bit more clearly what is the standard of evidence that we'd like to see here, and maybe this does exist in terms of criteria, and we haven't looked at it carefully enough or thought about it carefully enough, but listening to my colleagues around the table, I think we've been applying very different standards across the table, and I think it would be worthwhile taking a shot at agreeing about what that might be.

Again, I think the goal is going to have to be if we're going to approve an agent for a biologic process, physiologic process, biochemical process, you know, to my mind, we're going to need to do that on the basis of a very strong data set supporting what I will continue to call a process/outcome link, and that is that if we use a particular agent to measure a particular process, we'd like to have some way of coming to a strong conclusion that that will influence patient care, and I don't think that's a lot to ask.

I think there are a variety of different lines of evidence that can be brought to bear on that type of subject. For example, I think to me in this particular case, other evidence related to the impact of cerebral

blood flow measurement on clinical outcomes or patient management with other agents, I think, could come to bear on this discussion.

So if I were convinced that an agent was the perfect cerebral blood flow mapping agent and was safe, and I had an extensive knowledge base that measuring cerebral blood flow impacted upon patient care in some way, I would be much more lenient on the clinical data relevant to this particular agent. I still would like some, but I'd be more lenient.

So some of these ideas, I think, are worthy of being fleshed out and written down and agreed upon as we go forward with the discussions.

DR. RAMSEY: Dr. Tulchinsky?

DR. TULCHINSKY: I was wondering if it would be appropriate to make a motion to have ICP present the data for our next meeting. I would like to make that motion.

DR. RAMSEY: Is there a second?

DR. AMENDOLA: Second.

DR. RAMSEY: Discussion? Is that appropriate or I don't know what the rules are?

MS. AXELRAD: ICP can certainly make a presentation. In fact, they made a presentation here. I think that the FDA would also be making a presentation because what we're going to be asking you to vote on is our

assessment of the literature, and what we're going to be publishing in the Federal Register is going to be our assessment of the literature.

So while we could do that, it would be fine, but I think that we would intend to make an assessment and a presentation ourselves.

DR. TULCHINSKY: Oh, certainly. That goes without saying. The point is that why don't we have ICP compile the evidence, the one that was lacking today, and have the FDA review it, just like any other time that you have sponsored submission.

MS. AXELRAD: Right. That's what we were sort of hoping would happen in any event for the drug.

DR. TULCHINSKY: Well, I would like to formalize that.

DR. KONSTAM: Well, I think we have to remember that we are here at the service of the FDA, not vice versa, that the FDA is going to have to make this decision. As somebody pointed out, the FDA can in its wisdom choose to go against the panel under some circumstances.

We're here serving them. I think what they've expressed to us is their concern that they haven't provided us today with sufficient data to help them, and so I think the onus is on them to decide what they'd like to do to help us come to our deliberation, not for us to tell them

how to do that.

DR. RAMSEY: Could you maybe amend the motion in that way? Something like if they would like a presentation?

DR. TULCHINSKY: I'm not sure that it's necessary because, yes, we all understand that we're here to help FDA, and we're not serving them. Certainly we're serving to the public if you look at the things that you signed when you accepted this appointment, but I think it's appropriate to have ICP compile the literature in a way that they feel is complete, and just like any other time, radiopharmaceutical will be compiled, the literature, by the sponsor.

It would be fairly common process, and I think that the folks that know most about this tracer are members of ICP. Dr. Hertzberg.

DR. RAMSEY: No. My only concern is directing the FDA to have them make a presentation. I don't object to them collecting the information.

DR. TULCHINSKY: Even FDA can make the presentation. That would be fine. But I think the information needs to be collected and submitted to FDA by ICP in the form that they would feel would fulfill our overall requirements today for the lack of the literature, and FDA can either choose to have them present it. Again,

it's their prerogative.

The point is not who's going to be standing at a podium. The point is what's going to be in front of us as far as the data is concerned. That is the critical point, and I'll leave it up to the FDA to decide how they wanted it verbalized and flown out from that point on. But the key is it was felt that the data is lacking. All the experts is within the realm of ICP. They know all the data. I would suggest that we give them the opportunity to compile it, have the FDA review it as they always do, and decide who wants to present it.

DR. RAMSEY: Can we use that as the motion then?

DR. ZIESSMAN: Do we need a motion? I mean, the FDA knows what is needed.

MR. MADOO: Yes, I think it might be of benefit for just the lay audience, for people reading the transcript, if Dr. Conti could in a nutshell define what ICP is.

DR. CONTI: As the President-elect of the ICP, I probably should be able to do that. This is an organization primarily of nuclear medicine physicians who happen to use positron emission tomography. One of the founding purposes of the organization was to obtain reimbursement for PET radiotracers and was formed over a

decade ago to do that.

We're currently involved in a number of activities, including the working with the FDA to come up with an acceptable regulatory process as well as approvals of these clinical tracers.

In addition to obviously Medicare reimbursement, we're primarily interested in the primary sector reimbursement, and so we work with a number of insurance companies to educate the community on the value of these tracers.

I would like to actually begin our presentation for ICP for the approval of this drug by having our two experts, Dr. Ponto and Dr. Herscovitch, who are here, who are the world's experts on this tracer use. Dr. Herscovitch is actually a consultant for this medical advisory board. He was brought in specifically to look at these PET radiotracers, one of the leading experts in the field.

So I'm a little bit astonished that the medical advisory board hasn't taken advantage of this expertise in this deliberation.

DR. LOVE: Right. I think what you're talking about now is essentially what we would certainly be comfortable going ahead and completing the review, getting the other information. It's clear that Dr. Herscovitch and

Dr. Ponto have additional information, and I'm sure that ICP will work with them to get those other articles that they have identified as well, and I think we'll be able to bring back another review shortly.

DR. RAMSEY: I think Ms. Axelrad was actually first.

MS. AXELRAD: Well, I wanted to go back to several points earlier and address Dr. Konstam's point regarding the standards that would be used by the committee when we we make the presentation the next time, and I think that one of the things that hasn't been mentioned at all in the discussions is the final rule that was published on radiopharmaceuticals implementing the section of the Modernization Act that addresses the issues that Dr. Tulchinsky raised, and in that section, it's 21 Code of Federal Regulations, Section 315.5, it says that "the claim of functional, physiological, or biochemical assessment is established by demonstrating in a defined clinical setting reliable measurement of functions or physiological, biochemical or molecular processes."

So it does say that it has to be in a defined clinical setting, and we have, you know, the draft guidance document on medical imaging drugs that addresses what is meant in the rule by defined clinical setting.

So what I am thinking is that by the time we

finish doing the review of the literature of O-15 water, I think we will have also made a fair amount of progress in finishing up that draft guidance document, and that we may have the opportunity when we make the new presentation to clarify some of the thinking in terms of what the standards ought to be that should be used in evaluating these by the committee.

DR. RAMSEY: Dr. Herscovitch, did you still want to make a comment?

DR. HERSCOVITCH: Yes, and this is a totally personal comment which I feel I have to make. I have to correct the previous statement. I am not a member of the ICP, and although I appreciate your comment about my expertise in O-15 water, I came here and all my participation here was at the behest of the FDA, and all the questions that I answered or volunteered answers for were at the behest of the FDA as the government's employee. I am not associated with the ICP as a member or in any way as their representative.

MS. AXELRAD: Well, maybe either we or the ICP can take advantage of your expertise in conducting the further review of the literature. Maybe both.

DR. HERSCOVITCH: Maybe that's why we have lawyers, as yourself.

DR. RAMSEY: Okay. Any other questions?

Comments?

(No response.)

DR. RAMSEY: Well, I want to thank you all. I want to thank the FDA for a lot of work in putting the papers before us and doing everything in preparation for this, and as usual, Mr. Madoo, for getting us all together for this meeting, and I guess we'll see you all again, and have a good, safe trip home.

Thank you all.

(Whereupon, at 11:14 a.m., the meeting was adjourned.)

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