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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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TELECONFERENCE

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THURSDAY,

DECEMBER 18, 2008

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The meeting was convened telephonically at 1:00 p.m., Leon Malmud, ACMUI Chairman, presiding.

MEMBERS PRESENT:

LEON MALMUD, Chairman

RICHARD VETTER, Vice Chairman

DOUGLAS EGGLI, Member

DARRELL FISHER, Member

DEBBIE GILLEY, Member

RALPH LIETO, Member

STEVE MATTMULLER, Member

SUBIR NAG, Member

ORHAN SULEIMAN, Member

BRUCE THOMADSEN, Member

WILLIAM VANDECKER, Member

PRESENT (cont.)

MICKEY GUIBERTEAU, Diagnostic Radiologist

NRC HQ STAFF PRESENT:

CHRIS EINBERG, DFO

JAMES FIRTH

CYNTHIA M. FLANNERY, ALT DFO

DONNA-BETH HOWE

SOPHIE LE

ROB LEWIS

GRETCHEN RIVERA-CAPELLA

ASHLEY TULL

GLENDA VILLAMAR

DUANE WHITE

RONALD ZELAC

NRC REGIONAL STAFF PRESENT:

COLLEEN CASEY

JACKIE COOK

SANDY GABRIEL

PATTY PELKE

TOM THOMPSON

OTHERS PRESENT:

CHERYL BIEGEL, NIH

LUCA BRIGATTI

CLARA C. CHEN, NIH

WILLIAM DAVIDSON, University of Pennsylvania

JEFF HEIER, NeoVista

JOHN HENDRICK, NeoVista

PETER HERSCOVITCH, NIH

KAREN LANGLEY, University of Utah

MIKE PETERS, American College of Radiology

BARRY SIEGEL

MIKE STABIN, Vanderbilt University

CINDY TOMLINSON, Society of Nuclear Medicine

BILL VERMEERE, NeoVista

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P-R-O-C-E-E-D-I-N-G-S

(1:02 p.m.)

MR. EINBERG: I'm going to open up the meeting. As the Designated Federal Officer for this meeting, I would like to welcome you to this teleconference public meeting of the Advisory Committee on the Medical Uses of Isotopes.

I am the Chief of the Medical Safety and Events Assessment Branch. I have been designated as the federal officer for this Advisory Committee in accordance with 10 CFR Part 7.11.

Present today as the alternate designated federal officer is Cindy Flannery, team leader for the Medical Radiation Safety Team.

This is an announced meeting of the Committee being held in accordance with the rules and regulations of the Advisory Committee Act and the Nuclear Regulatory Commission. This meeting was announced in the September 22, 2008, edition of the Federal Register, Volume 73, page 54635.

The function of the committee is to advise the staff on issues and questions that arise on the medical use of isotope material. The committee provides counsel to the staff but does not determine or direct the actual decisions of the staff or the

Commission. The NRC solicits the views of the committee and values their opinions.

I request that, whenever possible, we try to reach consensus on the procedural issues that we will discuss today. We also recognize there may be a minority or a dissenting opinion. If you have such opinions, please allow them to be read into the record. At this point, I would like to perform a roll call of the ACMUI members that may be participating today.

Dr. Leon Malmud, Chairman, Health --

CHAIRMAN MALMUD: Here.

MR. EINBERG: -- Care Administrator?

CHAIRMAN MALMUD: Here.

MR. EINBERG: Dr. Richard Vetter, Vice Chairman, Radiation Safety Officer?

VICE CHAIRMAN VETTER: Here.

MR. EINBERG: Dr. Douglas Eggli, Nuclear Medicine Physician?

MEMBER EGGLI: Here.

MR. EINBERG: Dr. Darrell Fisher, Patient Advocate?

MEMBER FISHER: Present.

MR. EINBERG: Ms. Debbie Gilley, State Government Representative?

(No response.)

I just understand Debbie will be joining us late.

Mr. Ralph Lieto, Nuclear Medicine Physicist?

MEMBER LIETO: Present.

MR. EINBERG: Mr. Steve Mattmuller, Nuclear Pharmacist? Is Mr. Mattmuller there?

MEMBER MATTMULLER: Yes, I'm here. Sorry.

MR. EINBERG: Okay. Thank you. And Dr. Subir Nag, Radiation Oncologist? Dr. Nag?

(No response.)

Dr. Orhan Suleiman, FDA Representative?

MEMBER SULEIMAN: Yes, here.

MR. EINBERG: Dr. Bruce Thomadsen, Medical Physicist Therapy?

(No response.)

Dr. William VanDecker, Nuclear Cardiologist?

MEMBER VANDECKER: Here.

MR. EINBERG: Dr. James Welsh, Radiation Oncologist?

(No response.)

Okay. I believe we have a quorum. Dr. Mickey Guiberteau is representing the Diagnostic

Radiologists. Dr. Guiberteau does not --

THE COURT REPORTER: This is the Court Reporter. I'm having a difficult time hearing you due to the static.

(Whereupon, at 1:06 p.m., the proceedings in the foregoing matter went off the record briefly, during which time the static problem was corrected.)

MR. EINBERG: Okay. Let me just -- the Court Reporter indicated that he was having some trouble hearing me. I'll repeat some of it.

Dr. Mickey Guiberteau is representing the Diagnostic Radiologists. Dr. Guiberteau does not have voting privileges, but he will speak on behalf of the Diagnostic Radiologists. I would like to thank Dr. Guiberteau for acting in this capacity.

I now ask NRC staff members who are present to identify themselves. I'll start with the individuals in the room here, and then we'll turn it over to the other NRC staff members on the phone.

MR. LEWIS: This is Robert Lewis from FSME.

MS. FLANNERY: Cindy Flannery, FSME.

MR. FIRTH: James Firth, FSME.

DR. ZELAC: Ron Zelac, FSME.

MR. WHITE: Duane White, FSME.

MS. RIVERA: Gretchen Rivera, FSME.

MS. VILLAMAR: Glenda Villamar, FSME.

MS. LE: Sophie Le, FSME.

MS. TULL: Ashley Tull, FSME.

MR. EINBERG: Okay. Now, for regions, anyone from Region I?

MR. THOMPSON: Tom Thompson in the Commercial Branch.

MS. GABRIEL: And Sandy Gabriel.

MR. EINBERG: Okay. Thank you. Region III?

MS. PELKE: Patty Pelke from the Materials Licensing Branch.

MR. EINBERG: Thank you. Region IV? Okay.

DR. HOWE: And Donna-Beth Howe from Headquarters.

MR. EINBERG: Okay. Thank you, Donna-Beth. Is that it for the NRC staff?

MS. COOK: Jackie Cook, Region IV.

MR. EINBERG: Okay. Thank you.

Next, I would ask members of the public who are participating on the phone if they would identify themselves, please. For the Court Reporter,

if you could please spell out your name.

PARTICIPANT: My name is -- oh, you're going to spell the name for the public?

MR. EINBERG: Okay. Yes. Ashley Tull here is saying that you don't need to spell out your name.

MS. TULL: If you have notified me via e-mail previously, I have your name on the list already spelled for the Court Reporter.

MR. SIEGEL: Okay. This is Dr. Barry Siegel. I'm here.

MR. VERMEERE: Bill Vermeere from NeoVista.

DR. BRIGATTI: This is Dr. Luca Brigatti. I'm an ophthalmologist.

MR. HENDRICK: John Hendrick from NeoVista.

MS. TOMLINSON: This is Cindy Tomlinson from the Society of Nuclear Medicine.

DR. HERSCOVITCH: This is Dr. Peter Herscovitch from the NIH, Bethesda, Maryland. And in the room we also have Dr. Clara Chen from Nuclear Medicine at the NIH, and Cheryl Beegle from the NIH.

MR. DAVIDSON: This is Will Davidson from the University of Pennsylvania.

MS. LANGLEY: Karen Langley, University of Utah, Salt Lake City.

MR. PETERS: This is Mike Peters, American College of Radiology.

MR. STABIN: Mike Stabin, Vanderbilt University.

MR. EINBERG: Okay. Is there anybody else on the line who has not announced their participation?

MS. CASEY: This is Colleen Casey, NRC, Region III.

MR. EINBERG: Okay. Very good. We'll move on.

Dr. Leon Malmud, ACMUI Chairperson, will conduct today's meeting. Following the discussion of each agenda item, the chair, at his option, may entertain comments or questions from members of the public who are participating with us today.

At this point, I would like to turn the meeting over to Rob Lewis, who would like to make a few opening comments. And then, we will turn the meeting over to Dr. Malmud.

And just one last reminder, for those people who joined us late, please press star 6 to mute your phone if you are not speaking.

Thank you.

Rob?

MR. LEWIS: Thank you. Good afternoon, everyone. I would like to just bring the committee up to speed on a couple of activities occurring within NRC that are getting a lot of attention, the first of which is the national source tracking system. We do have a regulation which requires all licensees to enter the sources and the transactions of sources for IAEA Category 1 and 2 sources -- so, basically, the increased controls licensees -- into the national source tracking system by January 31st of 2009.

The system has received its authority to operate, which is a step under federal information security requirements, and is available at this point. In order to use the system, you have to go through an extensive credentialing program and receive tokens that you plug into your computer to make sure that the users have proper credentials and are actually the users. There is a very high level of security for a federal information system.

And, in all honesty, the credentialing process is not going very smoothly at this point. So for those of you that are in the meeting that are licensees, I would encourage you to get involved with that early. There is currently NSTS training going on

around the country, and the credentialing process itself is rather onerous. But it is nothing that we can control from the program office perspective. So it is difficult, and we are working through issues.

We underestimated the precision with which applicants need to enter information. For example, if you enter your licensee name and it doesn't match a database of companies that the credentialing contractor uses, then you will get rejected from the system. If you enter "corporation" instead of "inc," if your official company name is Something Something, Inc., you would be rejected.

So things like that that we need to work through, and we are working through, but the regulation is set. And the compliance with the rule is mandated as January 31st people -- licensees need to be entering their source information.

Now, using the NSTS website is only one option for compliance with that rule. There are other options of providing the information by fax or e-mail to NRC or an agreement state. So those options exist, but we want to create a situation where people want to use the NSTS because it is efficient once you get into it. Getting into it is the trick.

The second topic area is safety culture.

The NRC has several activities underway regarding safety culture, both internal safety culture for the agency and external safety culture for licensees. I would like to touch a little bit on the second piece of that, the external safety culture.

Our safety culture is basically a corporate attitude from the worker all the way through senior management that is a personal dedication and accountability towards safety issues. And it is often synonymous, for example, with Safety First attitude, willing to stop work if they think something is unsafe and the management would support them, willingness to stop it.

It is a concept that has been around for reactors for maybe 10 years now, but it really caught a lot of focus after the Davis-Besse vessel head erosion that occurred about five years ago. And the Commission has directed the NRC staff to look at extending safety culture into the materials area and extending safety culture concepts into the source material security issue, or just security area in general, or a security culture if you will.

The staff are working on those assignments from the Commission, and in the near future we will be engaging the committee more on our efforts to get user

feedback on how safety culture could be applied to materials, including medical applications.

There is a public workshop currently planned for January 28th at NRC Headquarters on this area. The main focus is soliciting input from the stakeholders and the public. The workshop will just be one opportunity for NRC to obtain the views of the stakeholders.

We will be engaging the committee in the next several months, next few months I should say. We owe something to the Commission in about four months, not the final answer but our initial proposals to the Commission. So more to come on that topic, but it is an emergent issue that will need some attention in the near future.

And, finally, I want to thank the committee members for completing the information security training. We do have several periodic trainings throughout the year, various -- invariably, they have bad timing of when they are announced, and this one happens to be due over Christmas and New Year break. But I appreciate what you did to get -- make sure that you did your part as committee members.

That is a requirement placed upon NRC, as is many of the other periodic training requirements.

I realize that you have to take time out of your busy schedules to do those. But the management of NRC is held very accountable to making sure everyone has jumped through all the hoops on all of those periodic training requirements.

At this point, if Dr. Malmud will indulge me, I would be willing to take any questions from the committee members before we get started on general topics.

CHAIRMAN MALMUD: Are there any questions? This is Malmud. Are there any questions?

(No response.)

MR. LEWIS: Thank you, Dr. Malmud. I will turn the meeting over to you.

CHAIRMAN MALMUD: Thank you. We have the next item on the agenda, which will be Cindy Flannery. Am I correct, Cindy?

MS. FLANNERY: Yes. Cindy Flannery. The topic of this first discussion is NRC's position on the applicability of the medical event reporting criteria for an event that was reported to the NRC involving an infiltration of F-18 of FDG.

NRC staff's objective here today is to get ACMUI's input on whether NRC staff should pursue a change to our current position on the lack of

reportability of infiltrations of dosages that may result in doses that exceed the dose threshold in the medical event reporting criteria -- that is, 50 rem to an organ or tissue.

An event was reported earlier this year as possible medical event. 3.6 millicuries of F-18 FDG was infiltrated into the anacubital dermis adjacent to the left elbow. The dose of the tissue was estimated to range somewhere between 200 millirem and 96 rem, and it was based on assumptions such as the entire dose was infiltrated into a tissue of 60 cubic centimeter volume sphere using a soft tissue density of 1.06 gram per cubic centimeter with a range of mean resonance time of .006 to 2.6 hours.

So just a little bit more background on this, the needle was carefully checked for infiltration using a 10 milliliter flush and a 100 milliliter infusion prior to injection of the F-18 FDG. The infiltration was discovered upon image acquisition one hour after the administration, and, unfortunately, the biological parameters were not measured, so it lead to a very large and varied absorbed dose estimates, as listed in slide 3.

But there were no identified adverse effects. There was nothing to suggest any kind of a

radiation injury.

The licensee did file a report 30 days after the event, and they stated that, "Because the technologist noted the fuse localization of the F-18 FDG, it seems likely that much of the administered dose did not -- or, I'm sorry -- did get into the vein, leaving less than 3.6 millicuries to irradiate the local area."

NRC's internal dose assessor did review the licensee's dose estimates, as provided on slide 3, and found this to be reasonable. Using a different method, NRC's calculations were slightly lower, but, as I said, they were certainly reasonable.

Now, as far as the outcome, the event was later retracted because NRC staff determined that an infiltration does not require reporting as a medical event. Based on some supplementary information that supported the previous equivalent regulation -- 35.33 -- which states -- and it's in 45 Federal Register 31703, May 14, 1980, "Extravasation is the infiltration of injected fluid into the tissue surrounding a vein or an artery. Extravasation frequently occurs in otherwise normal IV or intra-arterial injections. It is virtually impossible to avoid. Therefore, the Commission does not consider

extravasation to be a misadministration."

So based on these excepts from the statement of consideration that I just quoted, it was staff's determination at that time that this case did not qualify as a medical event. It has always been NRC's position that infiltrations do not constitute a medical event.

But that position has been based on the fact that diagnostic dosages, like technetium-99M, that were typically used in nuclear medicine at the time are gamma emitters of relatively low energy and low risk and wouldn't exceed the dose thresholds that are in the medical event criteria.

The language in the FRN is not really based on a distinction between diagnostic and therapeutic administrations, but, rather, on the fact that some of that, such as infiltrations, are an integral part of the procedure, and so their occurrence must be viewed as expected.

At the time that this FRN was published, higher energy radiopharmaceuticals, like PET radiopharmaceuticals, were just not being used. This is from 1980, as I mentioned before.

F-18 is a diagnostic administration, but because of the higher energies that can now result in

a dose to the surrounding tissue exceeding 50 rem, when doses are infiltrated, NRC is trying to determine whether there is any justification based on safety significance to change NRC's policy for these new NARM materials, which are now under our regulatory authority, and also the applicability of the medical event criteria for infiltrated dosages.

And just to take it one step further, should there be a requirement for reporting an infiltration of a therapeutic administration, that is something that also has not been considered before.

So that concludes my opening of the discussion.

CHAIRMAN MALMUD: Thank you, Cindy.

Any comments or discussion regarding the issue of infiltration of F-18 FDG? I heard someone click on or click off.

MEMBER THOMADSEN: That is Bruce joining you. Sorry I am late. I had a patient who was considerably late today.

CHAIRMAN MALMUD: Thank you for joining us. Cindy just presented the material regarding the infiltration of F-18 FDG and therapeutic radiopharmaceuticals. I was asking the group if there are any comments regarding her presentation.

VICE CHAIRMAN VETTER: Dr. Malmud, this is Dick Vetter.

CHAIRMAN MALMUD: Dr. Vetter?

VICE CHAIRMAN VETTER: I just wanted to point out that there is -- it's a bit old, but there is a publication that looked at infiltrations of radiopharmaceuticals back in 1994, Castronovo, et al., and the -- they looked at infiltration of various volumes, various volumes of tissue, etcetera.

And just as an example, maximum specific activity for a thallium -- let's see, infiltrations of thallium at the maximum specific activity available in two gram volume of tissue, worst case possible, would produce skin radiation burden of 417 to 463 rads. If you look at the table in that particular publication, which I can share with the staff if they don't have it, the doses range from about 40 rads to over 500, almost 600.

So the doses from infiltration are potentially significant. In fact, they are quite a bit higher than that particular PET issue that she outlined.

CHAIRMAN MALMUD: Thank you.

MEMBER NAG: Hello. Sorry to be late on the phone. This is Dr. Nag calling in.

CHAIRMAN MALMUD: Thank you, Dr. Nag. We just discussed the infiltration of F-18 FDG therapeutic radiopharmaceuticals. And Dr. Vetter responded that this already had been discussed about 10 years ago or so in a publication by Dr. Castronovo, where the infiltrations resulted in, if I am quoting correctly, an even greater radiation burden than these mentioned. Am I correct, Dr. Vetter?

VICE CHAIRMAN VETTER: Yes, that is correct. Yes, that's correct.

CHAIRMAN MALMUD: And, therefore -- this is Malmud again. And, therefore, the issue really was presented, dealt with, and probably need not be dealt with again. Is that your feeling, Dr. Vetter?

VICE CHAIRMAN VETTER: Well, I wouldn't necessarily say it doesn't need to be dealt with, but it has been dealt with in the literature in the past. I don't know if the NRC has ever looked at that literature, but it has been dealt with in the past in the literature, and the doses reported are considerably higher than that particular case that was outlined.

So I wouldn't view that particular case as being particularly egregious when compared to what apparently happens routinely in the injection of

radiopharmaceuticals.

CHAIRMAN MALMUD: This is Malmud again. Therefore, Dr. Vetter, what would your response be to the question raised by Cindy Flannery? And the question in the last slide is: considering the higher doses from the use of NARM, should NRC change its position to now regard infiltrations as MEs if the resulting dose exceeds the dose limits of 10 CFR 35.3045.

VICE CHAIRMAN VETTER: My opinion is that the -- that the practice should not be changed at this point in time. However, with the increased use of therapeutic radiopharmaceuticals, I think it is a subject that should be investigated, but nothing changed at this point in time.

MEMBER NAG: This is Dr. Nag. My viewpoint would be that this is somewhat akin to the seed migration issue for permanent implant. And that if in the -- if the injection of radioactive material, whether it's 125 ccs or, you know, NARM, if it is routine that some of it infiltrates out, and that this is something that happens in the normal course of a medical event, it should not -- I mean, the normal course of a medical administration, this should not be viewed as a medical event.

CHAIRMAN MALMUD: Thank you, Dr. Nag.

Dr. Vetter, do you wish to make your recommendation into a motion?

VICE CHAIRMAN VETTER: I would be happy to do that. I move that the ACMUI recommend that the NRC not change its practice regarding the definition of infiltrations as medical events at this time.

CHAIRMAN MALMUD: Thank you.

Dr. Nag, are you seconding that motion?

MEMBER NAG: I will be seconding that motion, but I want to make sure that the following definition says that infiltrations are not medical events. I want to confirm that, please. Can someone confirm that?

CHAIRMAN MALMUD: I'll ask -- this is Malmud. I'll ask Dr. Vetter to confirm that in his motion.

VICE CHAIRMAN VETTER: Yes, I would accept that as a friendly amendment to the motion. But I think Cindy Flannery can confirm that that is the practice now.

CHAIRMAN MALMUD: And I'll ask Cindy, is that the practice now from your view?

MS. FLANNERY: Yes. This is Cindy Flannery. Yes, that is NRC's position based on that

supplementary information.

CHAIRMAN MALMUD: Thank you, Cindy. Therefore, Dr. Vetter's motion stands, with Dr. Nag's seconding. Is there any discussion of the motion?

MEMBER EGGLI: This is Doug Eggli. I'd like to speak to the motion.

CHAIRMAN MALMUD: Thank you. Dr. Eggli?

MEMBER EGGLI: There are -- infiltrations just always occur. If they were to become medical events, the NRC would be flooded with more medical events than it could manage. But, in addition, the radiation is a function of the volume of distribution. Obviously, the smaller the volume of the infiltration the higher the local radiation dose. In 30 years of clinical practice, I have seen lots and lots and lots of infiltrations. I have never seen an adverse clinical outcome.

Unlike non-radioactive iodinated radiographic contrast, which often has significant local complications when infiltrated, I have never seen an adverse outcome from a radiopharmaceutical infiltration in my clinical practice. And I strongly support the motion that they should be left in their current status as not medical events.

CHAIRMAN MALMUD: Thank you, Dr. Eggli. I

would second your observation, in that 37 years of nuclear medicine practice I have not seen a negative outcome as a result of an accidental infiltration of a diagnostic radiopharmaceutical.

Are there other comments or discussions regarding the motion?

MEMBER LIETO: This is Ralph Lieto.

CHAIRMAN MALMUD: Yes, Mr. Lieto.

MEMBER LIETO: I would also support that the current policy statement of the NRC be maintained. And maybe what we ought to do is just say that we reaffirm it with the, you know, current terminology of replacing misadministration with medical event.

The only thing I would maybe suggest in terms of change is that I don't think extravasation is a frequent occurrence in nuclear medicine. Otherwise, you'd have patients being repeated beaucoup times, and it is a very uncommon occurrence. So I would say that we just reaffirm the current statement as it -- that was postulated back in 1980.

CHAIRMAN MALMUD: This is Malmud. Mr. Lieto, are you willing to accept and support Dr. Vetter's motion?

MEMBER LIETO: Yes, because it basically reaffirms that.

CHAIRMAN MALMUD: Thank you.

MEMBER EGGLI: This is Doug Eggli. I'd like to comment again in response to Ralph's last statement.

CHAIRMAN MALMUD: Please do.

MEMBER EGGLI: I think that complete infiltrations are not as common, although I see them with some regularity, particularly if you have a very young technologist staff. However, partial infiltrations, as a needle flips in and out of a vein, are really quite common and have neither impact on the diagnostic quality of the study, nor long-term adverse impact on the patient.

MEMBER LIETO: I accept that clarification.

CHAIRMAN MALMUD: Thank you, Mr. Lieto.

Any other discussion of the motion on the floor?

MR. STABIN: Yes, this is Mike Stabin. I would note that even though this has been treated once or twice in the literature, it is very difficult in these situations to establish what you mean by "the dose." When you're talking about dose to a standard organ, it is pretty easy to define it.

But in these cases, as was mentioned by

someone else, it depends on the volume that you assume, the distance from that volume where you assign dose, and so there is not really a good standardized model for people to assign a dose to report.

CHAIRMAN MALMUD: Thank you. Are you also supportive of the motion?

MR. STABIN: I don't have a position on the motion. I just wanted to contribute that comment, that this would be difficult at the moment I think for people.

CHAIRMAN MALMUD: Thank you. I think we all agree with your observation. Are there any other comments?

MEMBER FISHER: Dr. Malmud?

CHAIRMAN MALMUD: Yes. Who is speaking, please?

MEMBER FISHER: This is Darrell Fisher. I would like to follow up on a question raised by Cindy Flannery and ask for your experience and the experience of others, Dr. Eggli in particular. She asked about the case in which a therapeutic administration goes awry in the same way with a high-dose radionuclide such as Yttrium-90, Iodine-131, or even an alpha emitter, when those infusions become more common.

And should the dose be very much greater as a result of an injection of this type? What would be your opinion?

CHAIRMAN MALMUD: Are you asking me specifically?

MEMBER FISHER: Yes. And Dr. Eggli.

CHAIRMAN MALMUD: Thank you. I have not had experience with an infiltration of a therapeutic dose. I have been fortunate in my practice in that the therapeutic doses that we have used have been carefully administered by experienced personnel, and, therefore, the therapeutic doses have not infiltrated.

Having said that, I would also comment that Dr. Eggli's observation is a valid one with regard to diagnostic doses, and they not infrequently partially infiltrate.

Now, getting back to the question of the therapeutic, the therapeutic may in fact result in a radiation burden which will manifest itself with some visible abnormality. But I have not, fortunately, seen that in my years of practice. The doses we used to use were of pharmaceuticals such as P-32-containing pharmaceuticals.

More recently, of course, we are now into other forms of therapeutics, and there is a

theoretical possibility that we will see some untoward effect from an infiltration of a therapeutic dose. However, I cannot personally speak to that experience. Perhaps Dr. Eggli may.

MEMBER EGGLI: This is Doug Eggli. I share Leon's good fortune of never having had an intravenous therapy dose infiltrate. Just as a practice, I think our concern here is beta emitters being extravasated in the soft tissue as opposed to -- or alpha emitters as opposed to gamma emitters. But we really take a whole different level of care in establishing our IV lines on therapeutic data emitters than you do typically on routine diagnostic studies.

And I would think that you will find that the incidence of infiltration of therapeutic beta emitters or other -- or alpha emitters, when they become used, is going to be -- that I think is going to be fairly uncommon because of the quality of the IV that we establish to do that.

When you inject a diagnostic radiopharmaceutical, they are often simply done with a straight stick of a needle. And you can perforate the far side of a vein or partially perforate the far side of the vein. If you get a good IV running and you run in 4- or 500 ccs of fluid prior to the administration

of your therapeutic dose, I think the chances that you have a malfunctioning IV are likely to be detected before you administer a therapy dose.

And we typically put in a fairly large volume of non-radioactive fluid through an IV where we plan to give a therapy, just to make sure that it really is where we -- a good IV, and that we are not putting anything into the tissues.

You can put 10 or 20 ccs of fluid into the tissue and not notice it. It is much harder to put 4- or 500 ccs into the tissue and not notice it.

MEMBER NAG: This is Dr. Nag. I agree with you, Dr. Eggli. However, the question would be: if someone is not very conversant with the technique, and is going to be doing an infusion and puts in only 20 or 30 ccs, and it is running well, and then start infusing a therapeutic dose, it is possible that it will not extravasate.

In that situation, what would the NRC do? I think that's the question that was being asked, or possibly that's a question that would be asked.

MEMBER EGGLI: This is Doug Eggli again. Again, I think the incidence of that would be uncommon. And, again, with the therapeutic data emitter, I think it might rise to the level of a

medical event.

VICE CHAIRMAN VETTER: This is Dick Vetter. I just wanted to point out a subtle difference in the way diagnostic radiopharmaceuticals are administered versus therapeutic. In diagnostic, they are injected. In therapy, they are infused. And that's a huge difference.

As Dr. Eggli mentioned, during infusion it is very carefully -- the IVs are very carefully administered, and then a considerable amount of saline is used to make sure you have a patent IV. And some medical centers, even during the administration of the therapeutic radiopharmaceutical, will periodically interrupt the administration and administer some saline to make sure that the line continues to remain free.

So it is really two different -- totally different types of injection or administration.

MEMBER SULEIMAN: Yes. This is Orhan. Are we in fact discussing the therapeutic? I thought the question was really limited to the diagnostic. I have no trouble discussing the therapeutic, but does the NRC want it answered? And have we digressed?

CHAIRMAN MALMUD: Orhan, this is Malmud again. You are correct. The motion referred to the

diagnostic. And if you wish to -- if there is an interest in discussing the therapeutic, I think that we can, but it might be best to first achieve closure on the diagnostic.

Are there any other comments regarding the diagnostic?

(No response.)

If not, may we move the motion forward? All in favor of the motion?

(Chorus of ayes.)

Are there any opposed to the motion?

(No response.)

Are there any abstentions?

(No response.)

Thank you. Therefore, the motion is approved unanimously regarding the infiltration of diagnostic radiopharmaceuticals.

We are getting static again. Could some -- those who are not talking -- thank you. Thank you.

The discussion regarding therapeutic radiopharmaceuticals I think was well summarized in the comments made by several of you. It is the practice in administering therapeutic radiopharmaceuticals to first establish an intravenous line, and to make certain of its patency.

And that differs from the injection of a diagnostic radiopharmaceutical, which is, as correctly described, an intravenous injection without the prior establishment -- most often without the prior establishment of an intravenous line.

Now, therefore, a question arises, and that is this is a -- first, a statement. It is a common practice for us medically to establish an intravenous line or therapeutic doses that are given IV. Should this be a matter of written requirement that -- and, quite frankly, I am not certain if it already is or is not. Is anyone familiar with the regulations regarding the administration of therapeutic radiopharmaceuticals? Do we require an intravenous line?

MEMBER LIETO: The regulations do not.

CHAIRMAN MALMUD: Should they?

MEMBER LIETO: This is Ralph Lieto. I don't think we should enter into the practice, since things might change regarding that. I think the less we have in the regulations the better.

CHAIRMAN MALMUD: Thank you.

MEMBER SULEIMAN: This is Orhan. I would agree with Ralph. I mean, the route of administration may vary depending on the pathology, and so limiting

it to one way of administering is going to cause problems.

CHAIRMAN MALMUD: Thank you. Are there any other opinions regarding that issue?

VICE CHAIRMAN VETTER: This is Dick Vetter. I agree with that as well. And, in fact, I am sure that the method of administration was worked out during development of the protocol. So it is probably already in the FDA literature on how the material should be administered.

CHAIRMAN MALMUD: Thank you. So with those opinions, we will lay the issue of the therapeutic radiopharmaceuticals to rest at the moment, and move on with the rest of our agenda, if that is agreeable with the participants in today's discussion.

MEMBER NAG: Yes, that is agreeable.

CHAIRMAN MALMUD: Thank you.

MS. FLANNERY: Dr. Malmud, this is Cindy Flannery.

CHAIRMAN MALMUD: Yes, Cindy.

MS. FLANNERY: I think we are also trying to get some input or feedback on how this applies to therapeutics. And I do want to just add one thing, a comment that Dr. Vetter made, that, you know, your

therapeutic administrations are infused. And in this particular case, this F-18 was handled the same way. It was described at a 10 mL flush, and a 100 mL infusion was done prior to the injection.

So I understand that even when you have a line set up like that, to prevent it from happening, realize that it is incredibly rare, but as in this case there is that potential. So we would like to get some input on how this would apply to therapeutic administrations.

CHAIRMAN MALMUD: Thank you. May we have some opinions regarding how this should be ideally worded?

MEMBER EGGLI: This is Doug Eggli. Even though it was given through an IV line, and we give all of our PET doses through an IV line, there are IV lines and there are IV lines, and there are levels of care taken in establishment of the IV line that I, again, think are really quite different in therapeutic and diagnostic.

The quality of the needle catheter used, a butterfly versus an angiocath or some other form of internal catheter makes a great deal of difference in the quality of the line and the likelihood of an infiltration. So, again, I think that the likelihood

in a therapeutic infusion is really very small.

However, we are infusing currently often beta emitters, and I am less concerned with gamma emitters than I am with the local radiation with beta emitters. And if we infuse and infiltrate a beta emitter in large quantities, it is conceivable we could see tissue damage.

I am not as -- I am not opposed to making a therapeutic infiltration of medical event, but I think it probably requires some more discussion about things I am probably not thinking about. But, again, I think it will be uncommon. And, again, let me say that not all IV lines are the same.

MEMBER NAG: This is Dr. Nag. The problem is that, how will you define -- for example, in other areas we say if it is more than 20 percent, you know, we have a number like 20 percent dose, how can you say that -- you know, how much infiltration? Like if one is infiltrated, obviously, that is not going to be a medical event. If the whole dose is infiltrated, I mean, that obviously would be a medical event. So how would you say how much of it infiltrated in terms of quantity? And that may be a difficult thing. It may need a separate discussion.

MEMBER EGGLI: This is Doug Eggli. I

agree with you on that, Subir. But I think, again, the flag would probably be a function of local tissue exposure, and is there enough local radiation deposited that acute tissue injury is likely to occur.

MEMBER NAG: Again, that would be very hard to quantitate.

CHAIRMAN MALMUD: Gentlemen, may I ask if it would be an issue which we should bring to the ACMUI and discuss with regard to which type of material should be used for infusions of beta-emitting therapeutic pharmaceuticals, radiopharmaceuticals, so that we can discuss it at length.

I think the point that was made about a butterfly versus an intravascular catheter is relevant, because butterflies can infiltrate easily, particularly when there is arm movement by the patient. And whereas intra-cats, once established, of one type or another, generally are less likely to perforate the vessel.

So that this is an issue which may be worth discussing at the -- as an agenda item at the next ACMUI. Therefore, I am making a recommendation that it be discussed at the next ACMUI rather than attempting to resolve it on a conference call without having a chance to have thought it through with all of

its ramifications. Is that acceptable to the committee?

MEMBER NAG: I would agree -- I would support that wholeheartedly.

MEMBER EGGLI: This is Doug Eggli. I agree.

CHAIRMAN MALMUD: Is there anyone that doesn't agree?

MEMBER SULEIMAN: This is Orhan. I would agree, but I think it's a much more complicated issue, and I am even hesitant to bring it up without more preparation, because somebody mentioned beta emitters versus gamma. I think you have to look and see that at some point you may see alpha emitters being approved in the U.S. And we are not talking about diagnostic here, we are talking about therapeutic and the optimum administration.

So it is very, very fuzzy to me, you know, where the -- where the practice of medicine and specific protocols come into play, and where the radiation dose excesses or events would come into play. So I think we should discuss it, but I am nervous about bringing it up without adequate preparation. Otherwise, the discussions could be in a very circuitous, neverending kind of mode.

CHAIRMAN MALMUD: Orhan, I think you are right, but it points out once again the complexity of the issue, and, therefore, the fact that this important subject brought up by Cindy is better dealt with in a meeting of the ACMUI than on a conference call such as this.

MEMBER SULEIMAN: I agree.

CHAIRMAN MALMUD: Is there anyone who was opposed to delaying this to the next meeting of the ACMUI?

MEMBER GILLEY: This is Debbie. I am not opposed. I just wanted you to know I am on the call.

CHAIRMAN MALMUD: Thank you, Debbie. We are glad that you are on the call.

Therefore, recognizing that it is a potentially important issue, we will ask that it be included on the agenda for the next ACMUI. The result of the next ACMUI meeting may be that we will establish a subcommittee to look at it, because of its complexity. On the other hand, given the fact that it is brought to our attention today, it seems to me that we should bring it to the next ACMUI, so that we keep it on the agenda and deal with it as promptly as possible.

If that is acceptable with the committee,

we will do that. If not, we will do whatever the committee recommends instead. Is it acceptable to the committee members?

(Several members respond in the affirmative.)

Thank you. Then, Debbie and Cindy, do we have any other items to discuss on today's agenda?

MS. FLANNERY: Yes, we have one more agenda item.

CHAIRMAN MALMUD: And Dr. Vetter? Dr. Vetter? Dick? Dr. Vetter? Is Dr. Vetter with us?

VICE CHAIRMAN VETTER: Am I with you now? I guess my mute was on.

CHAIRMAN MALMUD: Dick, I have to give a therapeutic dose right now. I am going to run out for five minutes and come back, so --

VICE CHAIRMAN VETTER: Okay.

CHAIRMAN MALMUD: -- could you take over for me?

VICE CHAIRMAN VETTER: As long as you make sure that that line is well administered, yes.

CHAIRMAN MALMUD: It's an oral dose, and --

VICE CHAIRMAN VETTER: Oh, it's an oral. Okay.

CHAIRMAN MALMUD: -- the practice of my

department is that I do it personally. So just give me five minutes and I will be back.

VICE CHAIRMAN VETTER: Okay. I will be happy to chair the meeting while you are gone.

CHAIRMAN MALMUD: Thank you.

VICE CHAIRMAN VETTER: So did he try to give the floor back to Cindy for the next item on the agenda?

MS. FLANNERY: Yes. I can open up that one as well. Okay. The next topic is on the NeoVista's device. We discussed it at the October meeting. And just to kind of give a little bit of background information, the current licensing guidance for the use of NeoVista's EpiRad ophthalmic device requires an authorized user to meet the T&E requirements in either 35.490 or 10 CFR 35.690, which essentially means that an AU must be a radiation oncologist.

Now, at the October ACMUI meeting, a recommendation was made to revise the licensing guidance to allow for the training and experience requirement in 10 CFR 35.491, accompanied by appropriate device-specific training to be adequate for an AU for the EpiRad device.

Now, 10 CFR 35.491 allows physicians to be

an AU with only 24 hours of classroom and laboratory training applicable to the medical use of Strontium-90 for ophthalmic radiotherapy, along with supervised case experience of five clinical treatments.

While this may be adequate for the standard treatments of 24 Gray of a single lesion for the treatment of age-related macular degeneration, as used in the clinical trials, NRC staff's concern is whether this would be adequate for off-label use. Now, once the device is FDA approved, it is perfectly legal to use the device using protocols different than the protocol followed under the clinical trials.

And it is also worth noting that just last week FDA granted a waiver to treat a patient who did not meet the criteria for inclusion in the current investigational treatment protocol. So what we would like today is just to get some input from ACMUI on whether their previous recommendation from October's meeting should apply to both the use in the clinical studies as well as to the off-label use once this device gets FDA approved. If not, NRC staff hopes to receive ACMUI's recommendation on what would be adequate training and experience for off-label use.

And I guess another consideration is whether we should have two different categories of

qualifications for authorized use in the licensing guidance. For example, having one for the standard use of 24 Gray for the treatment of AMD, as used in the clinical trials, and maybe another set of qualifications for off-label use.

So that is all I really had for opening up this discussion.

Thank you.

MEMBER NAG: Hi. This is --

VICE CHAIRMAN VETTER: Thank you, Cindy. the floor is open.

DR. HEIER: I would like to acknowledge that -- my name is Jeff Heier, and I spoke at the previous meeting. And I am on as a clinical investigator with the EpiRad 90 device.

MEMBER EGGLI: Okay. Dick, this is Doug Eggli.

VICE CHAIRMAN VETTER: Go ahead, Doug.

MEMBER EGGLI: I think I made the motion, so let me speak to my intent for that motion, which was to specify the training and experience only for the standard therapy as described in the protocol, not for any more extended therapy where dosimetric considerations may become very important.

So I think the motion, as we passed it,

was intended only for the standard treatment and not for anything beyond that.

VICE CHAIRMAN VETTER: Thank you. Dr Nag?

MEMBER NAG: Yes, this is Dr. Nag. I have quite strong feelings on this. Firstly, I think at the last meeting one of the other radiation oncologists, Jim Welsh, was not there. I mean, he had to leave. He had very strong feelings, and I believe he has sent an e-mail to all of the ACMUI and NRC, you know, on this yesterday. So I think those views have to be taken into account.

The fact that neither Jim Welsh was there, nor the Chairman of the ACMUI was there at the meeting at the time of the voting, would have to be taken into account, and I think we should revisit this.

The major concerns that we have are: a) although this is right now being used as a learning tool, once it is FDA approved it can be used for off-label and any other uses. For those things, you do need a radiation oncologist to be on the Planning Committee. The major objection that was made was that, you know, it makes it difficult to have a radiation oncologist onsite.

However, we are not saying that there is the physical presence of the radiation oncologist

needed. We are saying that the radiation oncology and the radiation physicist has to be part of the team, not necessarily to be onsite. So, therefore, to get the program going, this can be gotten going as a team, and it will not delay any treatment, because the radiation oncologist is not onsite.

Secondly, when NeoVista presented this to the CMS for approval, they said that the procedure will be done with the ophthalmologist in conjunction with the radiation oncologist and radiation physicist. And, therefore, the code for the procedure was made with this complex situation in mind, and, therefore, it reimbursed at the higher rate.

If you now bypass this, then basically you are doing a Medicare fraud, because you are now going to charge the higher level for doing something at the much lower level. So these are all considerations that need to be discussed very carefully before we have a vote.

And I would very much like the people who have the most knowledge about this, which is the two radiation oncologists on the panel, plus the radiation medical physicist, the medical -- the radiation oncology medical physicist to be on when any vote is taken, because they have the most expertise on what

are the negative and what are the problems associated with radiation at the high dose in a localized area.

VICE CHAIRMAN VETTER: Dr. Thomadsen, did you want to make any comments on this issue?

MEMBER THOMADSEN: I would second everything that Subir just said. I am very concerned that this type of therapy would be going on without the input of somebody who has grown up in radiation oncology and understands the radiation. And while the results of the trial may be positive, may show very good results at the dose level selected, once people start looking at that they very likely are going to try to find other dose levels.

Once authorization has been given to the retinal surgeons to be authorized users, they will be in charge of that. They won't be using the radiation oncologists as resources during that procedure of dose investigation. And that is probably not good for patients.

VICE CHAIRMAN VETTER: Dr. Heier, did I hear you request to --

DR. HEIER: Yes, I did, if I could make a comment. I certainly understand those concerns. They are -- I think it's very important to understand that, at least as a retina specialist, and a busy retina

specialist who treats this disease, probably to the tune of 20 to 30 patients a day, the intention of the way this study was designed, and absolutely the intention of how we intend to use this, is if this -- if the Phase 3 study or the pivotal studies replicate the results we have seen in the Phase 2 studies, this will be administered as a single dose in a dose that was determined in collaboration with radiation oncology and with the radiation physicist.

If it turns out that this treatment, as described this way, cannot be delivered in that manner, I completely agree that this is a whole different process and should be looked at completely differently, and, quite frankly, probably is not going to be applicable to the treatment for most people with this disease, because the numbers we see with this, our approach to it, and the frequency we have to treat it, it is not going to make that type of approach practical.

And so as it has been explained here, and as I use it in the clinical trials, and as everybody else does, we are looking at it in a very planned, finite approach. And if the studies don't demonstrate that that approach is practical, then it needs to be completely reevaluated.

And whether or not, in collaboration with radiation oncology, that can be determined in a way that is appropriate is a whole other saying. And I know personally that is not an approach that I would be -- I would be applying to my patients, just on the sheer numbers and the complexity of what we have to do already.

As it is right now, all of the determinants in the process are determinations that are made, the type of neovascularization, the size of it, and the surgical approach how the probe is laid, and these are similar approaches that we do in determining our laser therapies, in determining our surgical approaches to patients.

The input is entirely done from a retina specialist standard. If all of that has to be modified, I completely agree this has to be reevaluated. But it is going to completely change how this therapy may or can be delivered.

MEMBER NAG: Hi. This is Dr. Nag. We have inquired within the radiation oncology community. There are not that many places that are doing NeoVista, but the places that are doing NeoVista do have the collaboration of the radiation oncologists. That does not mean that the patients held up until the

radiation oncologist can get to the OR.

No. That -- the whole planning team is part of the planning team. So this -- having a radiation oncologist be part of the team does not hold up any patient. You could be doing 20 patients per day; that doesn't mean that the radiation oncologist is going to be there during -- for all the 20 patients. It means that the program, the radiation safety program, is under the supervision umbrella of a radiation oncologist.

So this -- I would like to emphasize having a radiation oncologist on the team only helps in the safety. It does not hamper the access to any patient, because you don't have to wait for a radiation oncologist to say yes before you go ahead with one single procedure.

DR. HEIER: So, Doctor, I guess I'm a little confused then, because this is -- I have done other radiation trials as well for AMD, and, in fact, they were impractical. The way this study works, there is -- the input from the radiation oncologist has already been determined. So the input from the radiation oncologist has already been determined, and the approach doesn't change from the radiation standpoint for any of the patients.

So right now I guess I am not sure we have a radiation safety officer involved for the handling of the radiation and the storage of the radiation. So I see there are two arguments. One, the argument at the committee meeting was we are probably not treating patients in the best available manner if some of them would not benefit from alterations of either the amount or the approach of the radiation delivered. And that may or may not be the case, but, if that is the case, that is the type of scenario that becomes very impractical.

If the way it is right now, where at the other sites if there is no delay, then I think that is because right now there is no input. All of the approach has already been determined, so any of the different factors per patient are solely determined by the retina specialist.

VICE CHAIRMAN VETTER: Do any other members of the committee with to speak to this issue?

MEMBER FISHER: Dr. Vetter, this is Darrell Fisher. A question for Dr. Nag. In an active clinical setting, where the ophthalmologist is treating 20 to 30 patients a day, what is the contribution of the radiation oncologist?

MEMBER NAG: The contribution of the

radiation oncologist would be --

MEMBER FISHER: But to the individual patient --

MEMBER NAG: Not to the individual patient, to the overall program. It is to make sure that the program is set properly, that the dose levels, and so forth, are set properly. And if individual patients do come in that require modification as the program goes on, there will be someone to monitor, so that the modification, if needed, will be required.

So you don't need to call in that radiation oncologist for every patient, but to set up the program itself.

MEMBER FISHER: What is the modification that would require intervention by a radiation oncologist in a procedure for wet AMD?

MEMBER NAG: Okay. The problem is unless you go into the -- you know, in almost any treatment you always have to modify things as they go on, depending on the response you are seeing. Do we need to change the dose? Do we need to change, instead of a single-point application, maybe a two-point application? Do we need to change the direction?

So those kinds of modifications are

possible. And if you set this that it can only be done one way, you are not going to be addressing it and possibly making things better if need be. You are now -- your hands are tied, because you can only do it one way.

MEMBER FISHER: But doesn't the retinal ophthalmologist performing this procedure have more knowledge and experience than your radiation oncologist?

MEMBER NAG: The retinal specialist has more knowledge and experience on eye. They do not have knowledge and experience on radiation dosimetry and radiation microdosimetry. How do radiation may -- millimeters, how do radiation doses change depending on the angulation? Those minute things are what sometimes makes a huge difference.

I can give you an analogy on cardiac brachytherapy, which is in the domain of the cardiac surgeon or the cardiologist, because they know most about the heart, they know most about the cardiac vessels. When they did their experiment initially without much input from radiation oncologists, they were seeing a large number of failures at the end.

And when the radiation oncologist went into detail, they found this is due to the impact,

and, you know, you have to prolong the length and you have to modify the dose distribution. So unless you have those inputs, you are not going to advance this.

And, basically, you are sort of -- you are preventing this from going further, and, you know, you are now at the standpoint that you can only do 24 Gray. At that point, you cannot do any improvements to that. And, you know, are you getting the -- let's say you get a 70 percent success rate. Would you get 80 or 90 percent success rate if you changed some of the parameters, some of the angles?

Those are questions that will be unanswered if you tie yourself with only one dose, one parameter. You know, I would have liked my colleague, Jim Welsh, to have given his input, but I have talked with him and basically he has very similar concerns. I don't know if Dr. Thomadsen has, you know, any concerns along these lines.

MEMBER SULEIMAN: Well, I have already expressed that I do, indeed. I think it is a very bad idea to try to take the radiation oncologist out of the loop. We have already said that the radiation oncologist does not have to be there when the procedure is being done, so coordination becomes simpler from the retinal surgeon's point of view.

Certainly, in the procedure room, the medical physicist or radiation safety officer should be there to handle any radiation emergency that could happen. And that coordination still would have to be done, no matter what was going on here.

But I think the -- having the radiation oncologist involved is essential, whether or not you need to have each patient seen by the radiation oncologist. If the patient is just on a clinical trial, I think that is questionable. Any patients off the clinical trial start presenting big problems.

VICE CHAIRMAN VETTER: This is Dick Vetter. If I could just ask Cindy Flannery to get us back to square one here and clarify what the committee approved in October. I believe it was to apply the training specified in 35.491 to the 24 Gray standard procedure, standard treatment. And that was the only thing it applied to.

From the discussion here, it sounds like the committee would have a problem expanding the procedure to off-label use or which I guess it was a two-point treatment. But just to be clear, the only -- I think -- if Ms. Flannery could confirm for us -- the only thing we approved was the application of 35.491 to the standard procedure.

MS. FLANNERY: I don't think that's correct. I think the recommendation that was made is that the training and experience requirements in 491 would be adequate to be an authorized user for this new device. It didn't limit it to just the use in the clinical trial, so that --

VICE CHAIRMAN VETTER: Okay. That --

MS. FLANNERY: -- is a question to you is, you know, this recommendation that ACMUI made, is that applicable to off-label use as well? Because that -- you know, it wasn't specified in the recommendations.

MEMBER NAG: This is Dr. Nag.

MEMBER EGGLI: This is Doug Eggli again. I made that motion. And I know what the intent of the motion was, and the intent was to the simple 24 Gray procedure, on-label use only.

MEMBER NAG: This is Dr. Nag. I do remember that day, it was getting towards the end of the day, and end of the meeting. I felt that there was inadequate time for discussion, but the motion was called, and, therefore, voted upon. And I believe it was somewhat premature to have taken the vote, but, anyway, that was done. I believe we really need to think this a little more thoroughly.

Some of the people who are directly

involved, which would have included Dr. Welsh as one of the radiation oncologists, was not present. The Chairman of the ACMUI was not present. And I think this does require more thinking before we, you know, give a blank check.

MEMBER LIETO: Dr. Vetter?

VICE CHAIRMAN VETTER: Yes.

MEMBER LIETO: This is Ralph Lieto. First of all, a point of clarification. Dr. Welsh was there. If you look at the minutes on October 28th, he did make a number of comments, and Dr. Nag has echoed I think nearly all of those concerns that Dr. Welsh expressed at the meeting.

MEMBER NAG: Actually, Dr. Welsh was not present during the voting.

MEMBER LIETO: Excuse me. Point of order. Excuse me. The one thing that I would also like to -- I would agree with Dr. Eggli in that the presentation, and I think that the manner in which the vote was taken, was that the training and experience requirements were based on the fact of the presentation that this was a fixed dosimetry -- in other words, 24 Gray at the center, and I think it was 6 Gray, or something like that, out to a perimeter of five and a half millimeters.

The second point was that this was a fixed -- a visually identified location by the retinal specialist, so there was visual confirmation of the treatment site by the retinal specialist. And that there was -- this was a single site treatment per application.

And so I think all of those things were I think the predicate for the vote that was taken and the motion made by Dr. Eggli. At least that was my interpretation at the time.

I think, based on some of the concerns raised here, that since this is not -- this is a 1,000 -- or, actually, not a 1,000, but in terms of regulatory guidance for this, we might want to think about adding as a part of the regulatory guidance for this application that the authorized user training and experience requirements are the same regardless of off-label versus labeled use; two, that an AU with 35.400 approval is on the license.

So that you would have to have the -- that type of training and experience available, and that a person that needs to be present in addition to the -- say, the retinal specialist is the RSO or his designee.

CHAIRMAN MALMUD: This is Malmud. I've

been listening back on the committee with you again.

Mr. Lieto, is that a motion?

MEMBER LIETO: Before I make it a motion, I just would like to have it discussed as possible. Or does it have to be a motion to be discussed?

MEMBER NAG: I think we can have a discussion -- I think this does require more discussion before we can crystallize it into a motion.

DR. HEIER: I'm sorry. This is Dr. Heier again. I would also just like to point out that all of the potential changes are by no means changes that have been put forward by the users of the NeoVista device. From a retina specialist standpoint, the intention is exactly as it was proposed before. This is a single dose, single site treatment, and, in fact, if the pivotal study does not demonstrate the efficacy of this, that is an issue for the treatment overall. There are no intentions on the clinical investigator's part to modify this in any way.

MEMBER LIETO: Thank you for clarifying that, Malmud.

MEMBER NAG: This is Dr. Nag.

MEMBER THOMADSEN: This is Thomadsen.

CHAIRMAN MALMUD: Yes.

MEMBER THOMADSEN: And I think that is one

of the problems, that if there were a successful trial here, assuming that you don't cure 100 percent of the patients in that trial, the next step of course would be to investigate what you could do to improve that. That is sort of the nature of most radiotherapy regimes.

The fact that the -- that it is being said now that that would not be part of the thought, I think is either disingenuous or narrow-sighted.

DR. HEIER: That would be the focus of another study. That would then have to go through the same types of parameters and criteria that this one has. I mean, it has been my experience that if we look to modify a procedure, we then need to go through all of the steps to do that. And especially with devices such as this, there are very appropriate critical steps you have to do in order to have that go through a study.

MEMBER SULEIMAN: This is Orhan. This is Orhan Suleiman. First off, I want to clarify that once a protocol or a medical product has been cleared or approved by FDA, how it is used by the medical physician is really up to them. So you're getting under this practice of medicine issue.

They can -- if they think it is in their

professional judgment that if they change the dose they change a dose, they modify the protocol in any way that they think is medically necessary, they can't do that. The issue that I see -- and I'll ask the NRC staff to step in -- is when does the radiation safety aspect that is the responsibility of the NRC come into play in terms of they may be deviating the medical process, but, in fact, are we now introducing a very, very different radiation safety issue that needs to be addressed?

So I don't want anybody to assume that just because it has been approved in a very specific way, with a specific protocol, that that is necessarily how it is going to be practiced out there. And if it is changed, it may be because of other trials, it may be very well because of the individual's position or practice. They want to -- it is their prerogative to make some minor -- what they would perceive as minor but maybe better adjustments in the protocol.

MEMBER NAG: This is Dr. Nag. You know, the issue was raised that if this does not work, there would be a new policy made. Where would you get the input if the radiation oncologist has not made the input now? They need to get -- they need to know what

are the problems that are occurring. Maybe the wrong angle, maybe it is the positioning. So all of these little things are known only when you are in the OR.

I used to do a lot of eye plaque. We modified a lot of eye plaque based on what I saw in the OR. I am not an ophthalmologist. But when I go to the OR, I see what the ophthalmologist is doing. I learn from them, and I give feedback to them. So the feedback cycle is very, very important.

DR. HEIER: Doctor, this is a totally different procedure. You won't have a view of this. This is done through the operating microscope, and the only other person who will be there is an ophthalmology surgical trained assistant. So you won't have a view of this. If you have a view through the monitor, it doesn't give you 3-D. It won't give you any of the type of input you are talking about that would enable you to make modifications.

If this -- there is -- at least in my circles, there is no intent of redesigning the protocol if this does not work. I understand that this may not be the ideal approach from a radiation oncology standpoint, but this is a very practical approach to 200,000 new cases of wet AMD we see every year, and two million patients with this.

There is a practical component here that we have to deal with. And if that changes, there is no intent of this going further.

MEMBER NAG: This is Dr. Nag. If, for example, you get a 70 percent response, and if there was a way to get a 90 percent response, would you want to deprive your patients from going from that 70 percent to 90 percent, because you said there is only one way of doing it? This is the dose I chose at random, and this is the dose I am going to go forever. If you can improve it, why not?

DR. HEIER: I understand. But I fail to see how radiation oncology will modify that from the basis of this procedure. We've got fluorescein angiograms that take us two years of fellowship to truly appreciate and read. We have the surgery which is being done, which goes through a two-year fellowship, which you are not going to be able to look at directly.

So it is -- I am not questioning the skill of the radiation oncologist in modifying that. Some of the intricacies and difficulty of the whole process is how this is applied and the manner in which it is applied and how to interpret that. And right now the only means we have of interpreting that are with the

retinal techniques and diagnostics that we have.

And that requires -- does that mean the radiation oncologist is going to go through a two-year fellowship to enable him to interpret the angiograms and be involved in the surgical assist, so that we can eliminate the surgical assist, so he can have the view?

MEMBER NAG: We can ask the same question. Do you want to go through a four- or five-year radiation oncology training to know all of the nitty-gritty details of radiation oncology and how the microdosimetry is presented? So this is a collaborative effort, and you need the skills of both, and you are depriving your patients right now of the skills of one.

The second point is that when this was presented to the CMS, the CMS approved this and gave us codes, the complexity of which was due to the coordination that NeoVista said this would be done under collaboration with the ophthalmologists and the radiation oncologists and radiation physicists. And now, you know, they are going back on their word to the CMS.

DR. HEIER: So I would defer. I am not privy to those discussions. I wasn't involved with

them. I would defer those discussion to NeoVista.

MEMBER NAG: Okay.

CHAIRMAN MALMUD: Gentlemen, have you all had an opportunity also to read Jim Welsh's e-mail regarding this issue?

(Several members respond in the affirmative.)

Thank you. So it doesn't need to be read into the minutes?

MEMBER NAG: It could be an attachment to the minutes.

CHAIRMAN MALMUD: I will put it as an attachment, if you have all had the opportunity to read it. Yes, it will be an attachment to the minutes.

Okay. Thank you.

Now, let me get back on track. And the question on the table is training and experience requirements for the medical use of the material. And do we have any kind of a motion from a member of the committee regarding such?

MEMBER NAG: This is Dr. Nag. I would like to formulate the motion.

CHAIRMAN MALMUD: I think I heard Cindy's voice?

DR. HOWE: No, this is Dr. Howe. Just

before you make a motion, I wanted to clarify that during the last ACMUI meeting I asked for a clarification as to whether the AU had to be a retinal surgeon, and the ACMUI voted no, it is just a physician. So I want the ACMUI to remember that we have not designated the AU as someone with retinal specialty.

CHAIRMAN MALMUD: Thank you for reminding us of that.

DR. HEIER: I'm sorry, this is -- the reason that wasn't designated, it was felt that nobody would be going in to do a peritectomy who wasn't a retinal specialist.

CHAIRMAN MALMUD: Thank you.

DR. ZELAC: Dr. Malmud?

CHAIRMAN MALMUD: Yes. Who is speaking?

DR. ZELAC: This is Ron Zelac.

CHAIRMAN MALMUD: Thank you, Dr. Zelac.

DR. ZELAC: If you can indulge me, I would like to just make a brief statement.

CHAIRMAN MALMUD: Please do.

DR. ZELAC: Clearly, I think everyone understands that patient safety is an NRC concern. That is the first point. Secondly, the principal approach that is used by NRC is through assuring that

the patient gets what the physician wanted. That is as far into medical practice as we go.

But the decision on what is needed is in fact the physician's. Therefore, NRC relies on having qualified physicians, qualified on the basis of their training and experience requirements being met. Approvals are not protocol-specific, but they are use-specific. An AU is an AU, and can do what he or she wants. So modifications of the protocol are within the scope of the authorization.

Therefore, it behooves us, as regulators, to be sure that the qualifications of those who are approved as authorized for a particular purpose indeed are appropriately qualified to do the variety of things which are available once that authorization is granted.

MEMBER NAG: Could you repeat that last portion, Dr. Zelac?

DR. ZELAC: I'll try.

MEMBER NAG: Or clarify, basically.

DR. ZELAC: What I was trying to put across is the point that once an individual has met the training and experience requirements, and is designated as an authorized individual for the particular purpose, meaning this class of therapy, he

or she then has full authority under that responsibility to make whatever modifications he or she feels are appropriate to those techniques.

So if you give authorization to an individual, you are essentially saying this person is qualified to use this device in any manner in which he or she feels is appropriate. Therefore, it behooves us, as regulators or as advisors to regulators, to be sure that those persons who are authorized in fact are qualified to make those kinds of adjustments.

CHAIRMAN MALMUD: Thank you for that clarification, Dr. Zelac.

I believe Dr. Nag wanted to say something.

MEMBER NAG: Well, I wanted -- if the discussion is finished, I would like to make a motion once the discussion is finished. But I would like everyone to have the opportunity to have their discussion heard.

CHAIRMAN MALMUD: Well, the discussion can follow the motion.

MEMBER NAG: Okay. I would like to make the motion that the -- for the NeoVista device, which is under 35.1000, the training and experience requirement would be under 35.400, to be someone in the 35.400 or the user to be involved in the

treatment. However, that person does not necessarily have to be onsite or does not have to be physically present during the treatment.

CHAIRMAN MALMUD: Is there a second to the motion of Dr. Nag?

MEMBER THOMADSEN: Could you repeat the motion?

CHAIRMAN MALMUD: Dr. Nag said that --

MEMBER THOMADSEN: I got lost somewhere.

CHAIRMAN MALMUD: -- a person should be an authorized 35.400 user, to be involved in the therapy, but that that individual need not be physically present at the time of the therapy.

MEMBER NAG: And this can be modified to make the language, you know, more appropriate. But the idea is that the 35.400 -- I mean, the 35.400 person should be involved in the planning, and so forth, in the protocol but does not necessarily have to be present during the procedure. You know, we can tighten up the language.

CHAIRMAN MALMUD: That is the motion on the floor. Is there a second?

MEMBER THOMADSEN: I will second that. This is Thomadsen.

CHAIRMAN MALMUD: Yes, Dr. Thomadsen.

MEMBER THOMADSEN: I will second that.

CHAIRMAN MALMUD: The motion has been made by Dr. Nag and seconded by Dr. Thomadsen. Now it is open for discussion.

MEMBER EGGLI: This is Doug Eggli.

CHAIRMAN MALMUD: Yes, Dr. Eggli.

MEMBER EGGLI: I think sometimes perfect is the enemy of good. If, as the retinal surgeons tell us, if we make this too difficult, the procedure will be abandoned and patients will not be offered this procedure, I think we are doing a disservice to a large, large number of patients with a disease leading to blindness, which is a severe impairment in lifestyle.

I think that I can support any modification from the standard protocol requiring a full court radiation oncology involvement. But in the limited procedure, as described, which we hear from the retinal surgeons is their intent, in spite of the fact that the regulation allows you to do other than that, I think that we really limit the availability of a potentially useful therapy by making it too difficult. Again, perfect can be the enemy of good.

MEMBER NAG: This is Dr. Nag. I would like to ask Dr. Eggli, how will it limit, if the

individual patient does not need to be seen by the radiation oncologist, the radiation oncologist doesn't have to be onsite, how would that limit? You can have 100 patients per month. The radiation oncologist, they don't have wait for the radiation oncologist to be -- to see them before they can be treated.

So I do not understand how it will limit the access. Would you explain that to me, please?

MEMBER EGGLI: I will give you a roundabout explanation. Again, we are talking about a standard protocol, which has already been reviewed and has had the input of the radiation oncology community in its original design. And I see no added value to adding a radiation oncologist on top of something that is now a standard procedure, and dosimetry isn't going to change it any. And even the process of having to form a committee for this may cause some ophthalmologists in practice to be dissuaded from even pursuing it.

I think that if they follow the simple standard practice, which has been evaluated by radiation oncology and been deemed to be an appropriate treatment algorithm, that the radiation -- if they follow the standard practice, the radiation oncologist adds no additional value reviewing this

once again.

MEMBER NAG: This is Dr. Nag again.

CHAIRMAN MALMUD: This is Dr. Malmud. Dr. Eggli, are you suggesting that if the standard protocol is followed, and not varied in any fashion, that it would not require the continuing intervention -- participation of a radiation oncologist?

MEMBER EGGLI: Yes. But that any deviation from the protocol would.

MEMBER NAG: This is Dr. Nag. As Dr. Zelac reminded us a few minutes ago, when this is opened as a regulation, it is not protocol-dependent. It is dependent on the class of applicators or the class of radioactive material. And that point will apply to the NeoVista device, irrespective of how it is being used. That is point number one.

And that being the case, once this is put in the regulation, if someone wants to change it, they can. And that is a major problem.

Secondly, when you send that this protocol has already had the input from the radiation oncologist, why was that there? Because initially when this was started, it required the input of the radiation oncologist. If that requirement was not there before, it would have started without any

involvement, because obviously it takes a little effort to try to get help from anyone else.

And unless you have that help from the beginning, you are not going to --

MEMBER EGGLI: Well, the --

MEMBER NAG: So, again, having a radiation oncologist will not delay anything.

MEMBER EGGLI: This is Eggli again. I have to respectfully disagree with that. The protocol was designed with the assistance of the radiation oncology community, because that was an appropriate input. And you're right, in the practice of medicine, I can do almost anything I want. But I'm probably not going to. I'm going to follow good practice.

And in the places where people are going to vary from that, odds are they are going to do it on protocol, and those protocols are involved -- will involve a radiation oncologist to design those clinical protocols. You know, you can't regulate against the rare occurrence of something untoward, and then deprive everybody of an opportunity for a very beneficial treatment.

Essentially, I think that you are worried about edge cases. And you can't -- you can never regulate edge cases out of existence. I don't think

that if the standard protocol is followed that the continued involvement of the radiation oncologist adds any value, and all of your arguments deal with the retinal surgeon doing something different than the standard protocol, which may or may not occur.

And my inclination is to listen to what the retinal surgeon says, which is that they don't anticipate that this deviation will occur. And if it were, it would go back to the protocol stage. Do we have any reason not to believe the input we are getting from our professional colleagues in retinal surgery?

CHAIRMAN MALMUD: Thank you both for your comments. I would ask: are there any other members of the committee who wish to make comments? I think that the positions of Dr. Nag and Dr. Eggli are clear.

MEMBER GILLEY: Yes, this is Debbie.

CHAIRMAN MALMUD: I'm sorry. Who is this?

MEMBER GILLEY: Debbie Gilley.

CHAIRMAN MALMUD: Thank you, Debbie Gilley.

MEMBER GILLEY: I have two, one to NRC staff. I want to make sure that these guidelines do not require adoption by the agreement states. Can I get a confirmation on that, that they are just

guidelines?

CHAIRMAN MALMUD: You are asking the question of NRC staff.

MEMBER GILLEY: Yes, I am.

CHAIRMAN MALMUD: Anyone on the NRC staff want to answer Debbie Gilley's question?

MS. FLANNERY: Yes, this is Cindy Flannery. Debbie, the answer to your question is, no, the agreement states are not required to adopt the guidance. It is under 35.1000.

MEMBER GILLEY: Thank you. And the second question I have, if you are going to have this team approach, and we have a medical event, is the radiation oncologist who now wants to be listed as part of this team going to step up and be accountable for activities that he had general overview for?

MEMBER NAG: Well, that would be part of the requirement if you have an oversight. That person would be playing an oversight role in the design and overall responsibility. I mean, we have many other instances where we have an overall responsibility of radioactive material where they are, although we don't necessarily see it every day. But we do oversight of that, you know, in --

MEMBER GILLEY: You have missed my point.

You have made it very difficult on the regulatory community in implementing this to identify who should be accountable in the event of a medical event. If you remember when we did the cardiology that I -- the intravascular brachytherapy, we didn't list the cardiologist. We list the authorized user.

They were the ones that were responsible as the medical person in the event of a medical event. Now you were looking at putting two people as being part of the team, and it concerns me in trying to write regulations and implementation to have clear guidance given to everyone as to what the responsibilities are of both of these professions.

CHAIRMAN MALMUD: Debbie, I ask you a question. Are you in support of the motion of Dr. Nag, or opposing it?

MEMBER GILLEY: I am opposed to the motion.

CHAIRMAN MALMUD: You are opposed to Dr. Nag's motion.

MEMBER GILLEY: That is correct. I voted when we met in October, and I stand by that vote.

CHAIRMAN MALMUD: Thank you for that clarification.

DR. HEIER: I apologize. This is Jeff

Heier. And I don't want to speak out of turn, but I wonder if I could just make one point and ask one question.

CHAIRMAN MALMUD: Please do.

DR. HEIER: The first point is, in any clinical trial that we design, there is input of a whole vast number of medical specialists. Every clinical trial we looked at for AMD, we speak to a cardiologist, we may speak to a pulmonologist, we may speak to a neurologist, because treatments we are going to do may have an impact in their area, and we want their expertise in the design of the study.

Once we have had their expertise, they are almost never further involved in the study. And that is very common.

The question I have is, it is not clear to me, if the proposal is to now have a radiation oncologist as part of the team on every patient, meaning they are going to have input into every patient, because that, once again, will eliminate this as a practical application for these patients. We see them too often.

It is too hard to just coordinate with their primary care physician or their families on the extent of treatment. And if we are having to

coordinate with another medical specialist, and it is a fairly -- what you are proposing in terms of the coordination is not simple now.

Now you are talking about changing dosimetry and maximizing outcomes based on lesion characteristics and lesion size. If these are things that we agonize over and speak among our colleagues, I can only imagine the type of intervention that is going to occur if we have to do it with another medical specialty. I think you eliminate it as a practical approach.

CHAIRMAN MALMUD: Thank you. Thank you for that information.

VICE CHAIRMAN VETTER: Dr. Malmud, this is Dick Vetter. I just have a question for NRC. If we approve this motion, how would they implement it?

CHAIRMAN MALMUD: Excuse me. Dr. Vetter? Dr. Vetter?

VICE CHAIRMAN VETTER: Yes.

CHAIRMAN MALMUD: I am also going to ask you to take it for another five minutes. I have another patient to treat, and ask NRC to answer your question.

VICE CHAIRMAN VETTER: Okay.

CHAIRMAN MALMUD: Thank you.

DR. ZELAC: Dr. Malmud, this is Ron Zelac. I think that the motion that Dr. Nag has put forth is in fact consistent with respect to the requirements for the authorized user for this device with our current guidance. So, in effect, it would be an endorsement of the current guidance and puts to the side the motion that was made at the October meeting concerning modified, substantially reduced training and experience requirements for the authorized user for this purpose.

So that is the answer to the question. If you will indulge, I have something else I can add I think.

VICE CHAIRMAN VETTER: Please do.

DR. ZELAC: It appears that there are really two things going on here. One is concern to be sure that patients who could benefit from this treatment have an opportunity to receive it, meaning specifically the protocol that is in place right now. And the second is concern about the possibility that authorized individuals could go on, using medical judgment, and make modifications to the usage of this device for select patients.

The suggestion I would have and throw out for consideration is whether the Advisory Committee

would be supportive of essentially letting your previous recommendation stand with respect to the training requirements, but limit those who are authorized under those limited training requirements to only be authorized to use this under the existing protocol. That could be accomplished through a license condition for anyone who was authorized for 491 use for this particular purpose.

In that way, you know, the persons who are interested and wish to be participants in this protocol could have access to the device for that specific purpose, but yet not have the full range of authority that would be associated with an open, untethered authorization.

MEMBER NAG: This is Dr. Nag. Dr. Zelac, I really liked your suggestion. And what I can do is to reword my motion to basically say that for patients being treated under the existing protocol, the 491 user would be sufficient. However, for the overall use of the device under any other -- under any other condition, it will require a 35.400 level user.

DR. HOWE: Dr. Nag, this is Dr. Howe. I guess I have an underlying question. That is that we know that there was a recent humanitarian compassionate --

MEMBER NAG: Exemption.

DR. HOWE: -- exemption, and we don't know how that patient differed. Maybe the patient wasn't qualified to be in the test. Maybe there was something else. Now, you don't necessarily want to be in a position where for the compassionate choices you now have to go to a higher level. I mean, we are already seeing some variation, and I don't know how to address that. But I just want to bring it back to the discussion.

MEMBER NAG: But, basically, I think what we are trying to do is to make a fast track for the large number of patients who will be treated by one single means and have back on the fast track, so that they could be seen by the ophthalmologist as an authorized user. And any modification, therefore, thereof, whether it is a humanitarian exemption, whether it is someone trying a different dose, etcetera, would have to be done under the supervision of a 35.400.

I think this -- there would be only a limited number of them, and I think it will provide a good balance between excess and the overall safety. And I think that is why I kind of support Dr. Zelac's recommendation.

MEMBER EGGLI: This is Eggli. I can support this as well. And in response to Dr. Howe's statement, even though it is compassionate use, it is a different use that would benefit from the input of a radiation oncologist, and probably should have it. And, you know, compassionate use doesn't necessarily always mean emergency use.

But I think that a formal dosimetry planning would be very appropriate where you vary from the protocol. So that -- I think that is perfectly compatible with what we agreed to before. As long as the practitioner agrees to practice the limited protocol, then we can give a limited authorization. If it is anything different, it requires a Part 400 authorization.

So that is perfectly compatible with what I believe we agreed to in the last meeting.

MEMBER THOMADSEN: Dr. Vetter? This is --

VICE CHAIRMAN VETTER: There is -- I'm sorry. If everyone could quiet down for a moment, there is someone in the background trying to get our attention, and the volume is very low. Go ahead, please.

MEMBER THOMADSEN: Dr. Vetter?

VICE CHAIRMAN VETTER: Yes.

MEMBER THOMADSEN: This is Bruce Thomadsen.

VICE CHAIRMAN VETTER: Bruce.

MEMBER THOMADSEN: And the question for the proposal is -- assume that the current trial will close relatively soon, and a new trial will probably open. Are we stating that we would be limiting people to the -- limiting the retinal surgeons to what is in the current trial, without regard to the next trial? And if it turns out the next trial is doing better, do we come back and revisit this each time there is a trial and a change?

DR. HEIER: If I could -- I don't -- this is Dr. Heier again. I don't know for certain that the -- what the compassionate use was. But I know I almost had a compassionate use, and the disease was exactly the same. It was choroidal neovascularization. But the patient didn't meet the exact criteria of the study guidelines, which was a visual acuity change.

And yet the disease -- the underlying disease was exactly the same. And what I have seen in compassionate use for diseases like this is the compassionate use is usually for the same process -- choroidal neovascularization -- which by far the large

majority are age-related macular degeneration. But there are some other causes, like hymyopia and histoplasmosis.

And those occasionally are what get the compassionate use and not -- so it is the same underlying problem, a growth of new blood vessels from -- growing in a similar manner, but it is usually patients who don't fit the exact criteria from the study. It is not a change in the study application at all. It is not a change in how it is delivered. It is simply they didn't meet one of the criteria.

CHAIRMAN MALMUD: This is Malmud again. Was that the question that you were asking, Dr. Thomadsen?

MEMBER THOMADSEN: No, not at all. It was -- I was not discussing the compassionate use, but with the changes in a protocol, that a new protocol would probably open once the old protocol changes.

CHAIRMAN MALMUD: Thank you. That's what I thought you meant, Dr. Thomadsen. I think your question might be best addressed to a member of the NRC staff who was with us on this conversation. Would a -- is this applicable only to the existing protocol?

DR. ZELAC: My thought personally, and this is strictly only personally, would be that the

license condition would limit the authorization of the individual named to follow -- to be -- to use the device in approved protocols, you know, FDA-approved protocols for example.

CHAIRMAN MALMUD: Thank you, Dr. Zelac, but --

DR. ZELAC: So if you went off of that, then you'd be in another sphere entirely.

CHAIRMAN MALMUD: But you used the -- this is Malmud again. Dr. Zelac, could you clarify this for us? You used the plural "protocols." Does that mean that it is beyond this single protocol?

DR. ZELAC: To me it does, because Dr. Heier was speaking of this going from Phase 2 to Phase 3, which I presume would be a different protocol.

DR. HEIER: No.

DR. ZELAC: No? Same protocol?

DR. HEIER: It is in the pivotal phase already.

CHAIRMAN MALMUD: Thank you, Dr. Zelac.

Dr. Thomadsen, Dr. Zelac says this is applicable to protocols, with a plural.

MEMBER THOMADSEN: My question to Mr. Zelac, then, is: when the protocol closes, does that

mean that the practitioners would have no recourse to treat their patients?

DR. ZELAC: My answer is yes, it would have to come back to have the license condition removed.

MEMBER THOMADSEN: So if I may clarify, what we are saying is we are giving approval to retinal surgeons to treat patients according to the protocol on the protocol only. Is that their authorization that we are approving?

CHAIRMAN MALMUD: This is Malmud. That is my understanding of it. Dr. Zelac, is that your understanding of it?

DR. ZELAC: Yes, it is.

CHAIRMAN MALMUD: Thank you. Now, with that understanding, is there any change in concerns regarding the approval?

MEMBER SULEIMAN: This is Orhan Suleiman.

CHAIRMAN MALMUD: Yes, Dr. Suleiman.

MEMBER SULEIMAN: Yes. Let me explain something in terms of if the manufacturer decides that they want to expand their indication or their -- or if a user is trying to do experimentation of a significant deviation, at some point it is not -- there is a questionable area, just like everything

else, of when it is the practice of medicine and when it is human research.

And so if it is practice of medicine to treat a patient, and the changes that they are advocating are within the overall scope of practice of medicine, it is okay. But if they are really doing experimentation and trying to test new protocols and whatever, that is human research. It has got to come under, you know, FDA umbrella, and the whole nine yards again.

So I think the -- it is never an easy answer. But I want to make clear that you've got these different little areas that are actually distinct, but they are not -- the borders are not very, very sharp and clearly defined.

But there is following the protocol that has already been approved in a very specific manner, there is deviating from that under the practice of medicine, which could be minor differences, you know, which will have a significant, you know, change in the patient safety and whatever, but how much you start to deviate is a different issue.

If the physician is deviating in a very terrible way, you know, then you get into litigation and liability issues. If you are doing

experimentation to come up with something very different, very dramatic, and you are doing it in a much more formal manner, then you are back into a clinical trial environment. Those are very, very different areas, and one size doesn't fit all, so I think we -- I am just trying to remind the committee members that we do have those differences.

So I think what Dr. Zelac is proposing sounds like it has enough flexibility, but at the same time assures enough safety -- radiation safety in terms of patient protection.

CHAIRMAN MALMUD: This is Malmud again. I'm going to -- as chair, I am just going to ask you to clarify something, Orhan. Are you suggesting that you are in favor of approval of this if it adheres to the current protocol, and that it is limited to the current protocol?

MEMBER SULEIMAN: Again, I am a little confused in terms of how -- what are the radiation safety or radiation dosimetry assurances. Does the protocol in fact address that? Or what I'm hearing also is that, if it is under practice of medicine, is it possible you may deviate enough that you may change the dosimetry characteristics, that you may cause a safety issue?

CHAIRMAN MALMUD: For the dosimetry issue, may we refer either to a radiation oncologist or to a radiation physicist?

MEMBER SULEIMAN: Well, somebody who knows what they are doing.

CHAIRMAN MALMUD: That is why I chose those.

MEMBER SULEIMAN: Yes.

MEMBER THOMADSEN: Well, certainly, depending what the changes you want to make are, if it is the criteria for accepting a patient, no. If it is going to be sizes of lesions, yes. So, I mean, that depends.

MEMBER NAG: Again, I think that is where -- the way I had framed my motion was that, if it is exactly opposing the current protocol, then that is fine. But anything that is already in the dose, whether it be notifying the patient, and so forth, or number of areas that are irradiated, then it does require a 400 user to be involved.

MEMBER THOMADSEN: And the patient has --

CHAIRMAN MALMUD: I'm sorry. Who is speaking now?

MEMBER THOMADSEN: I'm sorry. This is Thomadsen again.

CHAIRMAN MALMUD: Thank you.

MEMBER THOMADSEN: And in some of the patient selection criteria, such as diabetes, for example, it would definitely affect how the patient responds to radiation. So there are -- while some things would change the dosimetry, some things would change the effects of the dosimetry.

DR. HEIER: This is Jeff Heier again. I certainly agree with that, and those are there for a reason. But there are certain things that are there just because it is a study. And, for instance, any AMD study that treats wet macular degeneration has visual acuity guidelines. And usually it is vision of 20/40 or worse.

Yet when the treatment is approved, those are automatically wiped out. Every single AMD study that has had approval in the last 10 years has had those same criteria. And once the drug is approved, then the visual acuity criteria is wiped out. And those are usually there solely so you can demonstrate certain degrees of improvement.

If a patient starts with 20/20 vision, they are not going to be able to gain three lines of vision. So they keep those patients out of the study intentionally.

MEMBER THOMADSEN: And is the proposal that if once -- let's say this meets approval, the study is successful, and there are those guidelines. Is the proposal that when patients meet those guidelines, that disease with that criteria, you can treat them in a medical setting? It is not that the patient has to be in a study protocol to be treated.

VICE CHAIRMAN VETTER: Yes. This is Dick Vetter. My understanding of this is that what we are approving are the training and experience requirements for medical use, for routine clinical use once this protocol is completed. Is that correct? Maybe Cindy Flannery can clarify that.

MEMBER THOMADSEN: Can Dr. Zelac address that? Because that was my question before, and the answer was it was just for this protocol.

DR. HEIER: Right. Which makes no sense to train people, have them do it all, and then say, "Okay. You've done it, you've been successful, now we have to retrain you differently."

DR. ZELAC: This is Zelac. I understood from Dr. Heier and the discussion at the last meeting that we are talking about a specific -- in terms of inclusion for the patient, a specific limited size lesion, one treatment with a particular given

angulation of the device, and that's it. Correct?

DR. HEIER: Correct. That is correct.

DR. ZELAC: Now, my intent was essentially to, in appropriate fashion with wording, limit the authorizations of individuals as authorized users to that, to that particular use, and not to offer -- open it up to variations in any one of those characteristics, be it, for example, dose painting as being within the realm of the authorization.

MEMBER NAG: This is Dr. Nag. This is what I was afraid of, that we will be going to a slippery slope. Once we allow a limited application, then the next thing will be, well, we have this limited application. This is somewhat similar, so that point will extend to that. And, you know, you change a few other things, very much similar, so, therefore, it doesn't require any further approval, and so on.

So, you know, that leads to a slippery slope. And, therefore, I had only -- in my motion I had only said in this particular protocol, and then, if there is some other new protocol coming in, we can reexamine that, see whether that makes sense, before we give approval for that protocol.

CHAIRMAN MALMUD: So the -- my

understanding -- this is Malmud. My understanding is that we are approving a use-specific approval. Is that correct, Dr. Zelac and Dr. Nag?

MEMBER NAG: Well, that was my intention, that this -- that the 491 user, authorized user, would be for this particular protocol. And if anything else changes, it goes under the 400 user until, you know, they bring back anything else on the table and we examine it and see whether that would be something that can go back to a 491 user.

CHAIRMAN MALMUD: Thank you. Dr. Zelac, was that your understanding also?

MS. FLANNERY: He just stepped out. This is Cindy Flannery.

CHAIRMAN MALMUD: Cindy, is that your understanding?

MS. FLANNERY: Well, I just want to clarify that when the recommendation was made at the October meeting, it was not clear or specific to -- you know, when the recommendation was made for 491 to be adequate for the T&E, it didn't really specify whether it would be just for the clinical trial protocol or for any use.

MEMBER EGGLI: This is Eggli. If you look at statements of consideration, I think in the

discussion, again, the intent of the motion was that it was for this protocol as applied to clinical patients, once the FDA approves this protocol. So what we are talking about is not per se a research protocol, but a clinical treatment protocol. It was the intent of my motion to limit the authorization to that treatment protocol.

MS. FLANNERY: And I not sure that everybody understood it that way. And the reason why I say that is because one person on ACMUI, you know, abstained, and with the reason being that when this device gets approved it could be used off label. And, you know, the T&E that was being suggested in the motion might not be adequate, and it was too early to tell. So I -- I'm not certain that everybody in the ACMUI understood it that way.

CHAIRMAN MALMUD: Thank you. Dr. Vetter, you chaired that session of ACMUI. Do you recall what the feeling was? I know what the minutes said, but do you recall what the spirit of the committee was?

VICE CHAIRMAN VETTER: This is Dick Vetter. I can only say what my understanding was, and it was exactly as Dr. Eggli outlined. It was limited to once the clinical trial was complete, and the procedure is approved by FDA, that it would be limited

to this 24 Gray standard procedure.

CHAIRMAN MALMUD: Thank you. Thank you for clarifying that again.

So that was the spirit and the decision of the committee in the October meeting on day 2. And now, the motion on the floor -- before us today, Dr. Nag's motion, reaffirms that. Is that correct, Dr. Nag?

MEMBER NAG: Yes. Except that I added that for any other uses it has to be under 35.400. So I basically clarified the previous one, because the previous was slightly ambiguous because it didn't state, you know, what happens if it is not on that particular protocol.

CHAIRMAN MALMUD: But in a brief statement, your motion simply says that if there are any changes it has got to go under 35.400. Is that it?

MEMBER NAG: Yes. That if it is done under the current protocol, 35.491 authorized user is sufficient. However, if there are any deviations or alterations, it has -- there has to be a 35.400 authorized user involved.

CHAIRMAN MALMUD: And that is your motion with us today.

MEMBER NAG: Yes.

CHAIRMAN MALMUD: May we move the motion, it being five after three? Or does anyone else have something they wish to say?

MEMBER LIETO: This is Ralph Lieto. I -- just for clarification, to be sure I understand, when you say "involved," you mean that he would be -- that they would have to have an AU on the license --

MEMBER NAG: Yes.

MEMBER LIETO: -- for this use. That's what you mean by "involved," correct?

MEMBER NAG: So what I had said in my previous one was that a 35.400 authorized user would have to be involved, but does not have to be physically present during the procedure.

CHAIRMAN MALMUD: So by "involved," do you mean it has to have an authorized user who does not need to be physically present?

MEMBER NAG: Yes.

CHAIRMAN MALMUD: Thank you. May we move the motion?

MEMBER MATTMULLER: This is Mattmuller, Dr. Malmud.

CHAIRMAN MALMUD: Yes.

MEMBER MATTMULLER: First of all, I want

to come out and say that I am in full support of Dr. Eggli's position on a number of the points he made. My concern with Dr. Nag's amendment is that, does this -- with the way it is worded, would this preclude, if yet another protocol was verified through a clinical trial, that the individual couldn't use this device under 491, it would have to then go to 490?

MEMBER NAG: Well, basically, my intention is that this protocol has been approved. We have noted that, and, therefore, it is approved for this protocol. If there is a new protocol that is made, it is very easy to bring it back and say, "This is a new protocol. Is this acceptable?" And if we find it equally acceptable, we'll say yes. If we find that, you know, that new protocol is for some reason not acceptable or not safe, we do have the right to say that.

CHAIRMAN MALMUD: Does that answer your question, Dr. Mattmuller?

MEMBER MATTMULLER: Yes, it does. Thank you.

CHAIRMAN MALMUD: Thank you. Call the motion? All in favor, aye?

MEMBER THOMADSEN: Excuse me. Can you please read the motion back, so we are quite clear on

exactly what we are voting on?

CHAIRMAN MALMUD: Thank you. Who was speaking?

MEMBER THOMADSEN: That is Thomadsen again. Sorry.

CHAIRMAN MALMUD: Thank you, Dr. Thomadsen. Dr. --

MEMBER NAG: Nag?

CHAIRMAN MALMUD: -- Nag?

MEMBER NAG: Okay. I make the motion that for this NeoVista device, under the present protocol, a 35.491 use -- authorized user will be acceptable. If there are any deviations or changes from the protocol, it will require the involvement of a 35.400 authorized user who does not necessarily have to be present during the procedure.

CHAIRMAN MALMUD: Thank you. Does that clarify your question, Dr. Thomadsen?

MEMBER THOMADSEN: Yes. Thank you.

CHAIRMAN MALMUD: Thank you. If we may, we will call the question. All in favor of Dr. Nag's notion?

(Chorus of ayes.)

All opposed to Dr. Nag's motion?

(No response.)

All --

MEMBER GILLEY: Aye.

CHAIRMAN MALMUD: So there is one opposition.

MEMBER GILLEY: Yes.

CHAIRMAN MALMUD: Is that you, Debbie?

MEMBER GILLEY: Yes, that's me.

CHAIRMAN MALMUD: Thank you.

MEMBER GILLEY: Thank you.

CHAIRMAN MALMUD: Any abstentions?

(No response.)

So the motion moves forward with all in favor except for one.

MEMBER NAG: How many ayes were there?

CHAIRMAN MALMUD: How many ayes were there? Shall we -- let's count the ayes. Please identify yourselves by your vote.

MEMBER NAG: Dr. Nag, yes.

CHAIRMAN MALMUD: Nag, yes.

VICE CHAIRMAN VETTER: Vetter, yes.

CHAIRMAN MALMUD: Vetter, yes. Lieto?

MEMBER LIETO: Yes.

CHAIRMAN MALMUD: Yes.

MEMBER SULEIMAN: Suleiman, yes.

CHAIRMAN MALMUD: Mattmuller?

MEMBER MATTMULLER: Yes.

MEMBER EGGLI: Eggli, yes.

CHAIRMAN MALMUD: Thank you.

MEMBER THOMADSEN: Thomadsen, yes.

MEMBER FISHER: Fisher, yes.

CHAIRMAN MALMUD: Thank you. Other members of the committee? Malmud is a yes, if you want my vote.

MEMBER NAG: Thank you.

CHAIRMAN MALMUD: Thank you. Does that answer your question, Dr. Nag?

MEMBER NAG: Yes.

CHAIRMAN MALMUD: And does that meet the requirements of an approval?

MS. FLANNERY: Yes, it does. This is Cindy Flannery.

CHAIRMAN MALMUD: Thank you, Cindy.

That I believe covers the items on the agenda for today. Are there any other informational items or comments from the public that we would entertain?

(No response.)

If not, I want to thank all of the participants, both the members of the committee, the NRC staff, and the public, for their participation,

and wish you all a very happy holiday season and a healthy new year. And we look forward to our next committee meeting.

Thank you.

(Whereupon, at 3:10 p.m., the proceedings in the foregoing matter were adjourned.)