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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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FALL 2015 MEETING

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OPEN SESSION

+ + + + +

THURSDAY,

OCTOBER 8, 2015

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The meeting was convened in room T-2B3 of Two White Flint North, 11545 Rockville Pike, Rockville, Maryland, at 8:30 a.m., Bruce Thomadsen, Ph.D., ACMUI Chairman, presiding.

MEMBERS PRESENT:

BRUCE R. THOMADSEN, Ph.D., Chairman

PHILIP O. ALDERSON, M.D., Vice Chairman

FRANCIS M. COSTELLO, Agreement State Representative

VASKEN DILSIZIAN, M.D., Nuclear Cardiologist

RONALD D. ENNIS, M.D., Radiation Oncologist

STEVEN R. MATTMULLER, Nuclear Pharmacist

MICHAEL O'HARA, Ph.D., FDA Representative

CHRISTOPHER J. PALESTRO, M.D., Nuclear Medicine Physician

JOHN J. SUH, M.D., Radiation Oncologist

LAURA M. WEIL, Patients' Rights Advocate

PAT B. ZANZONICO, Ph.D., Nuclear Medicine Physicist

Non-Voting: DARLENE F. METTER, M.D.

Member-Elect: ZOUBIR OUHIB

NRC STAFF PRESENT:

JOSEPHINE PICCONE, Ph.D., Director, Division of Material Safety, State, Tribal and Rulemaking Programs

DOUGLAS BOLLOCK, Designated Federal Officer

SOPHIE HOLIDAY, Alternate Designated Federal Officer, ACMUI Coordinator

MARYANN ABOGUNDE, NMSS/MSTR/MSEB

JACKIE COOK, R-IV/DNMS/NMSB-B

SAID DAIBES, Ph.D., NMSS/MSTR/MSEB

ANTHONY DELAMOTTE, NMSS/MSTR/MSEB

CASSANDRA FRAZIER, R-III/DNMS/MLB

MICHAEL FULLER, NMSS/MSTR/MSEB

TOMAS E. HERRERA, NMSS/MSTR/MSLB

ELIZA HILTON, NMSS/DSFM/IOB

VINCENT HOLAHAN, Ph.D., NMSS/MSTR

ESTHER HOUSEMAN, OGC/GCLR/RMR

JAN NGUYEN, R-I/DNMS/MB

KEVIN NULL, R-III/DNMS/MLB

DIANE RENDER, Ph.D., NRR/DORL/LPL1-1

NILDA RIVERA, NSIR/DPR/CB

GRETCHEN RIVERA-CAPELLA, NMSS/MSTR/MSEB

ALEX SAPOUNTZIS, NSIR/DSP/FCTSB

JULIAN SESSOMS, NMSS/MSTR/ASPB

JOANN SIMPSON, CFO/DPB/BOB2

ZAHID SULAIMAN, R-III/DNMS/MIB

TORRE TAYLOR, NMSS/MSTR/RPMB

CHARLES TEAL, NSIR/FCTSB

MEMBERS OF THE PUBLIC PRESENT:

BETTE BLANKENSHIP, American Association of Physicists in Medicine

BRIAN CAREY, Spectrum Pharmaceuticals

BONNIE CLARKE, Society of Nuclear Medicine and Molecular Imaging

JENNIFER CULTRERA, Spectrum Pharmaceuticals

KAREN FLANIGAN, New Jersey Department of Environmental Protection

CAITLIN KUBLER, Society of Nuclear Medicine and Molecular Imaging

YUNGMI KIM, Spectrum Pharmaceuticals

KAREN LANGLEY, University of Utah

RICHARD MARTIN, American Association of Physicists in Medicine

CANDI McDOWELL, University of Pennsylvania

GENE MENENDEZ, Spectrum Pharmaceuticals

CLARINE NARDI RIDDLE, Spectrum Pharmaceuticals

RICHARD PEROS, New Jersey of Department of Environmental Protection

MICHAEL PETERS, American College of Radiology

ANGELIQUE ROWLEY, Spectrum Pharmaceuticals

MICHAEL SHEETZ, University of Pittsburgh

KAREN SHEEHAN, Fox Chase Cancer Center

ED TRUSKOWSKI, New Jersey Department of Environmental Protection

CINDY TOMLINSON, American Society of Radiation Oncology

ALLEN YANG, Spectrum Pharmaceuticals

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(8:30 a.m.)

CHAIRMAN THOMADSEN: Thank you, everybody for being here and being here on time. We have a busy agenda to go through today. So, I will right away turn the floor over to our staff.

MR. BOLLOCK: Thank you, Dr. Thomadsen. As the Designated Federal Officer for this meeting I am pleased to welcome you to the public meeting of the Advisory Committee on the Medical Uses of Isotopes. My name is Doug Bollock. I'm the branch chief of the Medical Safety Event Assessment Branch and I've 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 Sophie Holiday, who is also the ACMUI coordinator.

This announced meeting of the Committee is being held in accordance with the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission. This meeting is being transcribed by the NRC and may also be transcribed and recorded by others.

The meeting was announced on the August 18th, 2015 edition of the *Federal Register* on pages 50049 through 50050.

The function of the Committee is to advise

the staff on issues and questions that arise with the medical use of byproduct material. The Committee provides counsel for 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 value their opinions.

I request that whenever possible we try to reach a consensus on the procedural issue that we discuss today. We also recognize there may be minority or dissenting opinions. If you have such opinions, please allow them to be read into the record.

At this point I'd like to perform a roll call of the ACMUI members at this meeting today.

Bruce Thomadsen, therapy medical physicist, Chair?

CHAIRMAN THOMADSEN: Present.

MR. BOLLOCK: Thank you. Dr. Philip Alderson, health care administrator, Vice Chair?

VICE CHAIR ALDERSON: Here.

MR. BOLLOCK: Thank you. Mr. Frank Costello, our Agreement State representative?

MEMBER COSTELLO: Here.

MR. BOLLOCK: Thank you. Dr. Vasken Dilsizian, nuclear cardiologist?

MEMBER DILSIZIAN: Present.

MR. BOLLOCK: Thank you. Dr. Ron Ennis, radiation oncologist?

MEMBER ENNIS: Here.

MR. BOLLOCK: Dr. Sue Langhorst, radiation safety officer? We realize she's not -- unfortunately unable to attend with us today. She's not here.

MR. BROWN: Excuse me. The room has changed. You all can control the mics. When the green light's on, that means the mic's alive. When the green light's off, the mics are dead. We got to cut down on the people that are rattling the paper.

MR. BOLLOCK: Continuing on, Mr. Steve Mattmuller, nuclear pharmacist?

MEMBER MATTMULLER: Here.

MR. BOLLOCK: Thank you. Dr. Michael O'Hara, FDA representative?

MEMBER O'HARA: Here.

MR. BOLLOCK: Thank you. Dr. Christopher Palestro, nuclear medicine physician?

MEMBER PALESTRO: Here.

MR. BOLLOCK: Thank you. Dr. John Suh, radiation oncologist?

MEMBER SUH: Here.

MR. BOLLOCK: Thank you. Ms. Laura Weil, our patients' rights advocate?

MEMBER WEIL: Here.

MR. BOLLOCK: Thank you. And Dr. Pat Zanzonico, our nuclear medicine physicist?

MEMBER ZANZONICO: Here.

MR. BOLLOCK: Thank you. I affirm that we have at least six members and a quorum.

Also at the table is Dr. Darlene Metter. Dr. Metter has been selected as our ACMUI diagnostic radiologist. She is pending security clearance, but may participate in the meeting, however, she does not have voting rights at this time.

I'd also like to recognize Mr. Zoubir Ouhib in the back. He's been selected as the next ACMUI therapy medical physicist, but cannot be seated at the table as the current medical physicist as it's currently occupied by our Chairman, Dr. Bruce Thomadsen.

I'd like to also add that this meeting is being webcast, so other individuals may be watching online.

We have a bridge line available and that phone number is (888) 864-0940. The pass code to access the bridge line is 88468 followed by the pound sign.

Individuals who would like to ask a question or make a comment regarding a specific issue the Committee has discussed should request permission

to be recognized by the ACMUI Chairperson, Dr. Bruce Thomadsen. Dr. Thomadsen, at his option, may entertain comments or questions from members of the public who are participating with us today. Comments and questions are usually addressed by the Committee near the end of the meeting after the Committee has fully discussed the topic. We ask that one person speak at a time as this meeting is close-captioned. I'd also like to add that the handouts and the agenda for this meeting are available on NRC's public web site.

At this time I'd ask everyone on the call who is not speaking to place their phones on mute. If you do not have the capability to mute your phone, please press star, six to utilize the conference line mute and un-mute functions. I would ask everyone to exercise extreme care to ensure that background noise is kept to a minimum as any stray background sounds can be very disruptive on conference calls this large. At this point I'd like to turn it over the meeting to Dr. Josie Piccone, Director of the Division of Material Safety, State, Tribal and Rulemaking Programs for some opening remarks.

DR. PICCONE: Thank you, Doug, very much. It's a pleasure to be here this morning and to see you all face-to-face. I hear your voices on the conference

calls and several of you I have known for years and years in one capacity or another, so it's very good to see you again face-to-face.

This is a bittersweet welcoming for me because I've known Dr. Bruce Thomadsen for a long time, outside of this Committee as well. This is Dr. Thomadsen's last face-to-face meeting at NRC headquarters and his last meeting as the ACMUI Chair. I'd like to thank him for his eight years of service to the staff and the Committee. Tomorrow we will hear a special presentation from the Chairman to Dr. Thomadsen, as well as farewell remarks.

With his departure, we have appointed Dr. Philip Alderson as the ACMUI Chair with Dr. Zanzonico as the Vice Chairman. This will be effective October 15th.

Since the March ACMUI meeting, we've welcomed two new members, as Doug has mentioned, Dr. Darlene Metter. Again, welcome. And, Mr. Ouhib, we welcome you as well.

And I think I want to start with just a few organizational changes that have occurred at NRC in the last couple of weeks. So they are fairly new. We have a new Executive Director for Operations. Mr. Mark Satorius announced his retirement at the end of this

year, and our new EDO is Mr. Victor McCree. And I think Dr. Thomadsen had the opportunity to meet him yesterday.

Mr. Michael Weber, who all of you know, is going to be leaving his position as the deputy executive director and he is moving to Research as the Director of that office. And the individual who will be replacing him in the EDO office is Mr. Glenn Tracy, who is coming to that position from our Office of New Reactors.

Catherine Haney, who is the Director of the Office of Nuclear Material Safety and Safeguards - I think all of you know her as well or have seen her at some of your meetings. She is leaving NRC Headquarters and going to be the new Regional Administrator for Region II. Her replacement has been announced, Mr. Marc Dapas. He is currently the Regional Administrator in Region IV. He does come to this position with significant background in the materials area, so he was the Director of the materials area in Region III. And again, he's the current RA in Region IV. So he is familiar with materials applications and issues including medical applications.

So turning now to the business of the Committee. You do have a very full two days. ACMUI held a teleconference on June 16th to discuss the

Subcommittee report for revisions to the Radioactive Seed Localization Guidance. That Subcommittee has revised their report as a result of that discussion and will present the revisions later on today.

Also, during that same teleconference, we heard a presentation from Spectrum Pharmaceuticals regarding the training and experience requirements for authorized users of alpha and beta emitters. An ACMUI subcommittee was formed to evaluate the current training and experience requirements, and we will hear an update from that subcommittee later on today as well.

ACMUI then had a teleconference this past August to discuss the draft report on the decommissioning funding plan requirements for the medical use of germanium-68/gallium-68 generators. Our staff will give a presentation later this afternoon to discuss our efforts in response to this report.

An NRC/OAS working group was formed to review ACMUI's recommendations for changes to the Medical Event Reporting Criteria for yttrium-90 microsphere events. The working group provided the ACMUI with proposed guidance in this area. Later on today we will hear ACMUI's comments on the staff's proposed rewrite.

Tomorrow there will be a discussion of the

Committee's comments on the proposed revisions to NUREG-1556, Volume 9, which is consolidated guidance about materials licenses, as well as the Committee's comments on the proposed revisions to NRC's Abnormal Occurrence Criteria Policy Statement. And I'm sure Dr. Thomadsen will report out on his interactions yesterday in this regard with the Commission.

We'll also hear tomorrow a presentation from Dr. Donna-Beth Howe regarding the Patient Release Project.

I've just touched on a few of the issues you're going to be handling today and tomorrow, so just by looking at the agenda you can see you have full days ahead of you.

So with that, I will turn it to Sophie, who is next on the agenda, and will cover old business and past ACMUI recommendations and NRC responses.

MS. HOLIDAY: Thank you, Josie.

Good morning, everyone. So this brings us to our old business presentation. Of course this is the presentation that we give at every meeting where we recount all of the recommendations and actions that were put forth by either Committee members or NRC staff and provide you a status update as to whether action has been taken or actions are still pending. A lot of this will

be a repeat from what you heard in March of this year, as it has been for a couple of years.

So to begin, on the screen and in your handout, you will see there are about 16 pages. I will just tell you that for calendar 2007 all of these listed on here are included in the current Part 35 rulemaking, so no changes for that. Are there any questions for 2007?

(No audible response.)

MS. HOLIDAY: Seeing none, we will move on to calendar 2008. Again, for 2008 the majority of these items are also included in the current Part 35 rulemaking with the exception of items 5, 19 and 20. You will note -- oh, and items 26 and 27. These items are listed as delayed, meaning that they are not included in this current Part 35 rulemaking, but will be considered for future rulemaking.

So then we can move on to -- oh, were there any questions for 2008?

(No audible response.)

MS. HOLIDAY: Seeing none, we can move on to 2009. Only two items listed on here. Again, these are all included in the current Part 35 rulemaking.

Next we go to 2011. You will note that 2010 is not included in this as it was not in the March meeting

because we closed all of those action items for 2010.

2011, just like 2009, all of these are included in the Part 35 rulemaking. Are there any questions for 2011?

(No audible response.)

MS. HOLIDAY: All right. Seeing none, we move on to 2012. There's only one item that's left on here, and this item will be carried forward indefinitely, and that was that ACMUI requested an annual report of the reporting structure to deliberate on whether or not they're satisfied with the current reporting structure. Are there any questions or comments on this?

(No audible response.)

MS. HOLIDAY: Seeing none, we can move to 2013. As many of you will recall, 2013 was when we provided the Committee with the proposed Part 35 rulemaking, and the ACMUI held two public teleconferences in March to provide their comments. So all of the items in 2013 pertain to the Part 35 rulemaking with the exception of items 21 and 25. Twenty-one has to deal with the germanium/gallium-68 generator discussion that was of course discussed in August, and as Dr. Piccone stated, staff will give a presentation on that at the end of today.

Item 25 has to deal with the ACMUI recommendation to reestablish the Rulemaking Subcommittee. You will also hear an update about Part 35 rulemaking tomorrow, so I won't delve into that, but that subcommittee has been reconvened.

We can move on to 2014. I'm sorry. Were there any questions for 2013?

(No audible response.)

MS. HOLIDAY: Seeing none, we will move to 2014. Items 6, 10, 11 and 12, these have to deal with the germanium/gallium-68, which I just mentioned, and also the yttrium-90 microspheres brachytherapy licensing guidance. You will hear items 6, 10, 11 and 12 later on today.

Item 17 has to deal with a task group that was formed between Dr. Susan Langhorst and Mr. Francis Costello to provide logistics about a Medical Regulatory Information Conference. You will hear that presentation from Mr. Costello tomorrow. Are there any questions for 2014?

(No audible response.)

MS. HOLIDAY: Seeing none, I will move to 2015. Again, item 1 has to deal with this Medical Regulatory Information Conference. As I just stated, Mr. Costello will give that presentation tomorrow.

Item 2 and item 3, you will hear both of these presentations today. As a result of the Yttrium-90 Microsphere Brachytherapy Subcommittee report in 2014, Dr. Thomadsen created a Subcommittee to review and evaluate the interpretation or the phrase "patient intervention." So you will hear a presentation from that subcommittee today.

For item 3, as Dr. Piccone stated, the ACMUI had a subcommittee that provided their comments on proposed revisions to the Radioactive Seed Localization Guidance. They gave that presentation in June of this year and they took back their actions, revising that report as a result of that teleconference. And you will also hear that presentation today.

Item 5 again has to deal with the germanium/gallium-68. Again, you'll hear that later on today.

Item 6. I have this listed as open, but I'm proposing to change this to closed because as you will remember in March Dr. Thomadsen said that he would send a letter to the Commission addressing the mis-wording of the intention of the Committee's recommendation for the medical event compatibility category. That letter was provided to the Commission back in April. And again, this has to deal with the Part 35 rulemaking,

which will be discussed tomorrow.

Item 7 also has --

CHAIRMAN THOMADSEN: I would say --

MS. HOLIDAY: I'm sorry.

CHAIRMAN THOMADSEN: -- that item in itself, regardless of what happens with rulemaking, has been closed because it's just dealing with sending the letter, and the letter went.

MS. HOLIDAY: Absolutely. Thank you.

Okay. Item 7, this has to deal with the ACMUI's recommendation that events reported under 10 CFR 35.3045 that do not result in harm to the embryo, fetus or the nursing child should not be captured as abnormal occurrences that are reported to Congress. As Dr. Piccone stated, we will hear the Committee's comments on the proposed revisions to the Abnormal Occurrence Criteria Policy Statement tomorrow.

CHAIRMAN THOMADSEN: Just for the transcript, when Dr. Alderson's reading it, it says 35.3047 and you just said 35.3045.

MS. HOLIDAY: Oh, I'm sorry. That's correct. If I misspoke, I apologize. Thank you.

Item 8 is where the Committee recommended to hold its fall meeting October 8th and 9th. Since we're all here, I move to close this item.

(Laughter.)

MS. HOLIDAY: Are there any objections to closing this item?

(No audible response.)

MS. HOLIDAY: Okay. Item 9, again as Dr. Piccone stated, we had a teleconference in June of this year where Spectrum Pharmaceuticals provided a presentation to discuss the training and experience requirements for authorized users of alpha and beta emitters. As a result of that presentation Dr. Thomadsen created a subcommittee to evaluate the training and experience requirements. That Subcommittee will give their presentation later on today.

Again, in June of this year the Radioactive Seed Localization subcommittee provided their report and they will revise it today.

Okay. We move on to the next item. And the last item is that we had a teleconference August 12th to of course discuss the Germanium/Gallium-68 Decommissioning Funding Plan Subcommittee report with addendum. This report has been posted on the ACMUI web site and is available for everyone's view. Dr. Said Daibes will give a presentation, again, of course, on this topic later on today to inform you of what staff's

efforts have been towards addressing the Committee's recommendations.

Are there any questions for 2015?

(No audible response.)

CHAIRMAN THOMADSEN: I don't see any. Thank you very much.

MS. HOLIDAY: Thank you.

CHAIRMAN THOMADSEN: And I would like to officially on the part of the Committee welcome Dr. Metter to the Committee.

MEMBER METTER: Thank you.

CHAIRMAN THOMADSEN: We look forward to your participation and I hope you enjoy your time with us.

And I also will welcome in the future Mr. Ouhib, who I can't say I'll enjoy working with you on the Committee since we'll be changing places. But I hope you also will enjoy your time on the Committee.

Since it is fairly public, I will mention that Dr. Langhorst was hit by a car. She's in the hospital. Should be leaving soon. Broke her hand, on which she's had some surgeries, and the femur. And we would like to express our wishes for a speedy recovery. I will pass a card around you can sign. We'll send it to her. That's sort of the less official work that I

have to do today.

And jumping into this, our first item is an open forum where all of you get a chance to give us ideas as to where we should be going, what should we do in the future, what sort of issues are out there that you would like us to address. You can think about that and make suggestions now. You can also think about it during the meeting and we will have another sessions at the end to give you a second chance. But right now I'll open the floor to Committee members. Who would like to say something?

(No audible response.)

CHAIRMAN THOMADSEN: And again, you have another chance later. If you don't have anything that you've formulated enough that you want to speak right now, that's fine. In that case -- yes, Ms. Weil?

MEMBER WEIL: I propose at this particular moment -- on the agenda, I would like to suggest just as an administrative matter that the open session agendas be less specific with time slots so that we're able to move on more efficiently so that the members of the public who are listening and participating in the meeting will know that perhaps items will not exist at exactly the time that they're listed on the schedule, but approximately so that we could perhaps be moving

forward.

CHAIRMAN THOMADSEN: Good point. Well noted. I think within the time periods between breaks we can probably go ahead at that point. Is that correct? We can move on to item No. 5 as soon as we are done with item No. 4.

MEMBER WEIL: That's correct.

CHAIRMAN THOMADSEN: Very good. I think maybe you have a point as far as the open forum. We would like to keep this open, fluid, and maybe there are better ways to do that. I think that the Committee and the staff would be open to suggestions for how that might be best to do. Possibly moving just before a break might be better.

With that, I will as Dr. Dilsizian to talk about the Patient Intervention Subcommittee report.

MEMBER DILSIZIAN: Well, thank you very much, Dr. Thomadsen, and colleagues.

We were charged to clarify the meaning of "patient intervention." And this was brought up by Mr. Costello, and because he wasn't -- he was concerned that there may be some disparity between the way the NRC interprets the term "patient intervention" and how the Advisory Committee members interpret it. And he wanted to make sure that we have a discussion and have an

alignment in the interpretation of the term and listed our Subcommittee members: Dr. Alderson, of course Mr. Costello, Dr. Ennis, Dr. Suh and Ms. Weil.

So just a brief review, which you're all familiar with. I'm just going to kind of set-up the discussion. Patient intervention obviously means actions by patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely termination of the administration. And so the question is, "what are the implications of such misadministration reporting requirements as it comes to the NRC?" And the 2002 final ruling of 10 CFR 35.3045(a) specifically says that the licensee shall report any event in the Section (a) except for an event that results from a patient intervention in which the administration of byproduct material or radiation from byproducts may result in, for example, differing the dose from the prescribed dose by 20 percent or more or would have resulted in a greater than 5 rem effective dose equivalence such as administering the wrong radioactive drug to the wrong patient.

Now, in Section (b) it addresses the issue about licensee reporting any event resulting from intervention of a patient or human subject in which the

administration of byproduct or radiation from the byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system as determined by a physician. And so, this is where the discussion comes in.

And so the 2014 proposed ruling made no changes in the 2002 final ruling. And again, the question that we are addressing today is what about unintentional treatment due to anatomic or physiologic anomaly rather than intentional or unintentional action, which are the terms that were used in the ruling. And does that constitute patient intervention, albeit passive rather than active?

So what we're talking about is an anatomic anomaly that the patient may have or physiologic anomaly, and that may result in a different dose that the patient would get from the intended prescribed dose. And so, how would we address that?

So, I just summarize here our recommendations as issue 1 and issue 2. Issue 1 there wasn't a lot of discussion, which is consistent with the final ruling; that is, the unintentional or intentional patient action would represent a reportable medical event if it results or would result in unintended permanent functional damage to an organ or a

physiological system as determined by the 2002 final ruling. Of course the real goal would be to prevent or mitigate patient actions that may impact treatment. This is consistent and we didn't really do much revisions.

Now the issue 2 is where we had a lot of discussion, and I want to thank my Committee members. And I will expand on this. So issue 2, unintentional treatment outcome due to anatomic or physiologic anomaly and/or imaging uncertainty falls into the category of the art of medical practice provided that standards of medical practice are met. And I'm going to expand on these.

First, let me take the words "the art of medical practice," and how do we come to that? Well, when we prescribe medications; for example, antihypertensive medications, 25 milligrams of a specific dose, we understand in the art of medical practice that there's wide variability of the absorption rate of that 25 milligrams in different patients depending on their renal function, liver metabolism. So the 25 milligrams not exactly 25 milligrams. And that variation is consistent with what we're talking about, physiological variation among patients such that the treatment effect will vary from

patient to patient. And so, the intended dose, prescribed dose, may vary from what the patient actually receives. So that's what we mean by the art of medical practice.

The second part, the standards of medical practice are met; this is where we had a lot of discussion. In essence, we wanted to make sure that, just like we discussed with the issue No. 1, we actually have thought about preventing, even if it's passive, potential therapeutic unintentional outcome. And that would mean appropriate non-invasive studies, shall we say, to determine whether there are any anatomical variations in that particular patient compared to the others.

Now, we had a lot of discussions here, and the reason we kind of came to this conclusion of standards of medical practice on that -- it's a clever work I think because the standards, as you know, vary -- standards of practice do vary at different parts of the country, but the standard of medical practice would hold, would be carried out as a non-invasive study, whatever that may be, whether it's an ultrasound or a CT.

We didn't want to prescribe or specify what that would be. And we also thought that we walk this

tightrope of NRC not really managing medical care. We'd like to be advisory board, but not really guide exactly how and what that therapy should be.

So, the two terms there for "the art of medical practice" and the "standard of medical practice" are met is how we came to that conclusion. It may sound vague to you, but I think that we're trying to be not necessarily controlling the medical therapy of how patients are managed, yet guide the physicians that they should be doing the right therapy.

So, the second bullet point is very important, because if we require these type of unpredictable and unavoidable -- that are patient-specific medical events to be reported and you say, well, why are we reporting these if nothing can be learned from that? Because in essence this is unique for a specific patient, for a specific anomaly. And so, by reporting it, if it can help in the future to prevent such events, I think it will be very important. But if it doesn't really help to prevent such events in the future and cannot be regulated, we felt that that should not be required. So, now I'll now open it up for discussion.

CHAIRMAN THOMADSEN: Thank you.

Mr. Costello?

MEMBER COSTELLO: Well, as I'm the one who sort of raised this issue, I'd like to thank Dr. Dilsizian, and other members of the Committee, Subcommittee, because this is exactly what I was looking for. I think it makes a clear definition of what we mean by patient intervention. And as a member of the subcommittee, I'm happy with the definition that we came up with.

My overriding goal here was that we have to mean the same things by terms, that if the Committee at some future event were to say, well, we don't believe that this is a medical event with a patient intervention, we want the NRC to hear what we mean. And I'm just saying from my previous life with the NRC, I think this goes beyond historically the way we interpret patient intervention, but I think I'm very comfortable with this interpretation of patient intervention, and I hope the other members of the Committee will feel the same way and ultimately I hope the NRC and its general counsels will feel the same way. Thank you.

CHAIRMAN THOMADSEN: Thank you, Mr. Costello. Ms. Weil?

MEMBER WEIL: I came at this as a member of the subcommittee from a slightly different perspective and while I could accept this language, I felt we should

be a little bit more suggestive in what we talked about with the standards of medical practice. I think from a regulatory point of view it's difficult for those who are inspecting to assess the standards of medical practice, and I didn't think there was any harm in suggesting that we include language that talked about all appropriate pre-treatment planning and post-treatment follow up instead of the language "the standards of medical practice." I just felt that that was more helpful to both sides of the equation.

CHAIRMAN THOMADSEN: Thank you for that comment.

Other comments?

MEMBER ENNIS: Maybe you should -- well --

CHAIRMAN THOMADSEN: Dr. Zanzonico?

MEMBER ENNIS: So, first, may I speak?

CHAIRMAN THOMADSEN: Yes. Please, Dr. Ennis.

MEMBER ENNIS: I think Frank was really perceptive in picking up on this disconnect in the phrase, and it really was a good topic for us to deal with. And it really brings a lot of the salient issues of NRC regulating something that is medical right to the head. And it's tricky. We really had a very vigorous discussion. And I think this -- I very much like the

language that we have come to. I do think it protects patients and the public from inappropriate delivery of radioactive materials while still being aware of the realities that patients are very different and there's a lot of uncertainty and a lot of judgment in medicine and not wanting to discourage that type of care, the use of radioactive materials in the service of the public.

I feel like it strikes a good balance to proscribe or prescribe -- prescribe specific interventions or tests for things that are needed. Fits a particular scenario, but won't fit all scenarios. And things will evolve over time. And I think one of the skills of regulatory is to find language that will be flexible enough to cover the next decade or whatever so we don't have to revisit it. If we say imaging, well, what about blood tests? And if we say blood tests, what about genetic tests? And if we say genetic tests, what about urinalysis? And it's going to really vary depending on the thing. So, I think standard medical practice is the best kind of phrase that we can come up with that will say you're supposed to practice medicine properly and the NRC won't regulate that as long as -- and of course there could be some tension of what that is, but nevertheless I think it's the best we could do with language and without proscribing things

that fit yttrium-90, but might not fit tomorrow's yttrium-90, whatever that might be.

So, while I do want to make sure the regulations are protecting the public and not just allowing physicians to do anything and say, oh, it's standard medical practice, I think this language accomplishes that.

CHAIRMAN THOMADSEN: Thank you, Dr. Ennis. Dr. Zanzonico?

MEMBER ZANZONICO: Yes, I want to congratulate the subcommittee. I think they captured the spirit of what was intended in terms of reportable events, namely identifying and hopefully lessen the probability of dangerous or potentially dangerous mistakes.

I would actually go one step further and maybe qualify the term "art of medical practice" with the local art of medical practice, because as Dr. Ennis alluded to, different institutions, different practitioners in good faith perform different procedures differently, and a regulator could potentially say, well, Institution X does this procedure in this way, which is, quote/unquote, "correct," while Institution Y does it different, which is, quote/unquote, "incorrect."

So, I think as long as a practitioner or an institution is complying with their standard of practice and thereby avoiding overt mistakes, I think that's not a reportable event regardless of the consequences or regardless of what ensued. So, like I said, I would just suggest qualifying this statement to acknowledge that fact that there are good faith differences among institutions and practitioners and different procedures and maybe qualify it, as I said, as the local art of medical practice, or some such term as that.

CHAIRMAN THOMADSEN: Thank you, Dr. Zanzonico.

Other comments? Dr. Ennis?

MEMBER ENNIS: I don't disagree with the spirit of the comment, but I don't think it's really necessary. I don't think the art of medical practice without that phrase really is limiting. I would say that even -- in fact adding the local phrase might be more problematic, for example, if you're at Sloan Kettering or Mount Sinai perhaps and you happen to disagree with a large proportion of your department does, but have a good reason for wanting to do it some way, I wouldn't want a regulator to say, well, you didn't follow the local practice. So I think that's

maybe not necessarily helpful.

In addition, medicine is moving more and more towards uniform standards rather than local standards anyway for a lot of good reasons. So I think that local differentiation over time is going to be lessening anyway.

CHAIRMAN THOMADSEN: Thank you, Dr. Ennis.

Dr. Dilsizian?

MEMBER DILSIZIAN: Yes, we thought about that obviously and discussed it and I pointed it out. So the terminology "standards of medical practice," from a medical legal perspective, as you know, the standard is always local. So, we thought that instead of local art of practice of medicine the words "standards of medical practice" embodies the local differences between States and practices. So I hope that will be acceptable to you.

CHAIRMAN THOMADSEN: Thank you for that comment.

MEMBER DILSIZIAN: Sure.

CHAIRMAN THOMADSEN: Other comments from the Committee? Yes, Mr. Costello?

MEMBER COSTELLO: The thing at least for the NRC to consider is what do they do with our recommendation? Okay? We were not, and are not I

don't believe, recommending rulemaking. I mean, the last thing we want to do is recommend rulemaking. This is --

(Laughter.)

MEMBER COSTELLO: Because I don't have many years left on the Committee.

However, I think particularly since we're parsing the words pretty carefully, we worked very hard on the language, I thought. The language may look simple, but we didn't arrive at it simply. And I don't even know where this would go. The language that we're interpreting is language in the rule. It's in Part 35 and I think is unmodified in the proposed Part 35. Would this be something that the NRC would -- I don't know what they would do. Okay? But I think they should adopt the language in some way and say that they agree with the language and publish it in some way so that everybody knows what this is so that we on the ACMUI and the staff of the NRC are speaking the same language, but I don't know the best way for them to do it.

I think it should be done publicly. I think that the medical community should know this when they're thinking of whether to report particularly a particular event, but I certainly would not recommend doing it in a rulemaking. But I don't really have a

particular recommendation on how to do it.

CHAIRMAN THOMADSEN: Thank you, Mr. Costello.

So what would be the recommendation of the staff?

DR. PICCONE: Well, I have a number of questions that's on what was the recommendation on implementation. So just reading the two recommendations, it's, okay, what are you asking? And I think Frank tried to get to that, but on what are you requesting NRC to consider?

But also, we had a question on what do you mean by "imaging uncertainty?" That is very qualitative.

MEMBER DILSIZIAN: Well, I can answer that. As imagers any imaging modality that we do is never 100 percent sensitive or 100 percent specific. There are uncertainties in -- even at your best technique of acquiring images, the resolution of the camera may be such that you won't detect specific anomalies that are beyond the resolution of the camera. So that every imaging modality has its strength and limitations and it can relate on soft tissue attenuation, patient's body size, patient's anatomic variations, that the technique that you use may not

necessarily be 100 percent.

So that's what we mean by that. It's no technique will be absolute and there are going to be variations. And that would be again part of the art of medical practice. We do the best we can with blood testing. We do the best we can with physical examinations, imaging. Ultimately, it's a conglomerate of information that we put together and we decide practicing or treating patients accordingly. So that's where the uncertainty comes in.

CHAIRMAN THOMADSEN: Dr. Alderson?

VICE CHAIR ALDERSON: Yes, so I would suggest given what you just said that imaging uncertainty actually is part of the art of medical practice. And in terms of the language you could just leave it out and leave the "art of medical practice." It would be covered.

CHAIRMAN THOMADSEN: Mr. Costello?

MEMBER COSTELLO: We want the NRC to adopt this language. We want them to adopt this language publicly. Okay? Well, the methods for it, I mean, you could issue a RIS, I would imagine. They still do information notices? I guess you could do an information notice. It would be some way of the NRC endorsing this definition so the practitioners, the

people in the field will say, well, is this a medical event? Well, we think it's patient intervention. Well, does it meet these criteria? And if they say, well, it does meet these criteria, then we don't have to report it. If it doesn't meet these criteria, then we might need to report it if it meets the other definitions, medical event.

I think the important thing is that the NRC endorse a definition of "patient intervention" and in a public way that is available to the licensee community.

CHAIRMAN THOMADSEN: Thank you, Mr. Costello. Yes?

DR. PICCONE: I actually can come up with a scenario for this passive, if you will, intervention, which is what you want to add, where reporting could be beneficial and could be helpful to the medical community. Let's say they're doing a study and they currently use ultrasound to define the organ. And we have a scenario that happened very recently, and I won't go into detail on that, but they used ultrasound to define the organ. Okay? They thought they had the organ using ultrasound. They used another imaging modality post-treatment, okay, and realized that what they were seeing on ultrasound was some mass that was

not the organ, was not expected, but they were able to clearly differentiate on MRI. So in that case, that might be valuable information and give someone pause on what modality to use.

CHAIRMAN THOMADSEN: And following up on that, can I ask advice from Mr. Mattmuller? In the drug communication, medication community in reporting interesting events with drugs, do they not differentiate between something like adverse drug reactions and drug medication events or something like that? They have different classes of events that might be reportable?

MEMBER MATTMULLER: You're referring to normal pharmaceuticals and I'm a bit removed from those.

CHAIRMAN THOMADSEN: Oh, okay. I apologize.

MEMBER MATTMULLER: So, I'm sorry. But to your question, yes, they do have -- it's just not yes/no. There are subcategories as to define the adverse effect, yes.

CHAIRMAN THOMADSEN: Yes, where an adverse effect is [for] you the drug to do one thing, but in a particular patient it doesn't. It does something quite different. And that's not an event, but it's a drug reaction, which as you point out, Dr. Piccone, that

things like that might be good to capture and let the community know about, and particularly as we move into targeted radionuclide therapy, it may be that the reactions that we see in patients may be more variable and less predictable than things like brachytherapy or external beam. So I think the point is well taken. I'm not sure we would want to group these as events and that they have a different nature to them. Unfortunately, the NRC does not have another classification that we could put those into.

Yes, Dilsizian?

MEMBER DILSIZIAN: Thank you. I just want to address Dr. Piccone's comment. So that ultrasound case that you brought up is a nice one, but you could also understand that some patients will have limitations of not having MRI study. They may have some metallic objects where MR may not be the right study. So you bring up the right example of why we can't prescribe particular imaging modality. Depending on the patient's needs and limitations the proper technique -- so for example, one could argue that the ultrasound was misread by the individual, which is also part of the art of medicine and that someone else could have actually identified that that's actually a mass, that's not the organ. So again, we don't want to

prescribe to detail, I think. NRC should I think stay out of that.

So, Dr. Alderson, just to your comment about the uncertainty, imaging uncertainty, remember that we actually -- if you look at the way we worded this, due to anatomic or physiologic anomaly and/or imaging uncertainty, that falls into the category of art of medical practice, which is what we did.

VICE CHAIR ALDERSON: It does, right.

MEMBER DILSIZIAN: So we don't have to change it, right? We just defined it as the subject.

VICE CHAIR ALDERSON: All right.

CHAIRMAN THOMADSEN: Dr. Ennis?

MEMBER ENNIS: Just responding to Dr. Piccone's -- so, let's keep in mind of course that there are other spaces in society to deal with all kinds of errors. So there's the legal space where malpractice -- which may be what you kind of describe, someone not understanding how to interpret an image properly. Is it really something the NRC needs or wants to regulate or report in the tele-medical community, oh, there's someone out there who didn't know how to read an ultrasound, if the ultrasound is the imaging that you're talking about, but rather that's a hospital or regulator, whether the practitioner is appropriately

trained.

So, it seems to me that the kind of scenario you describe, while in some ways could be a considerable event, is really more about malpractice, hospital regulations on practitioners, and/or the clinical research space. So, let's not also forget that the doctors are trying to figure out how to do things better by and large and aren't always reporting things. And there's always studies. Oh, if you do this imaging, it's going to be better. I mean, so much of our medical literature now is about how imaging improves things and showing, you know, we had three adverse events with ult[rasound] and we got rid of those with this new imaging. So those spaces I think really kind of deal better with the kind of scenarios you raised.

CHAIRMAN THOMADSEN: Ms. Weil?

MEMBER WEIL: At the root the subtext to everything we're saying here is that we think reporting medical events is somehow bad or detrimental, that it dings the practitioner or the institution who is the subject of the medical event or the generator of the medical event. But I think we need to think of these things as opportunities for information sharing that can enhance patient safety. And as such, I think over-reporting is perhaps better than under-reporting.

And there are public things to be learned from even reporting patient -- passive patient intervention.

CHAIRMAN THOMADSEN: Thank you very much. Mr. Costello?

MEMBER COSTELLO: And correct me if I'm wrong, I don't think Dr. Piccone was talking about misreading the MRI. I believe that she was talking about that that modality was not able to see this. It was a properly done MRI. It was just a modality that wouldn't identify the mass. I think, and one reason I brought this issue up, it comes to the -- as Ms. Weil was saying, the underlying reason of why we have medical events, reportable medical events. And I think that the Subcommittee and the Committee basically feels that if the authorized user and the medical team did everything right, did everything according to the standards of medical practice -- and for another reason, the normal imaging modality, one that's normally used just didn't happen to identify it in this case, or the patient's anatomy or whatever, okay -- if they did everything right, if something that they had no way of knowing about caused the treatment to have an unintended outcome, that that should not be reportable because the team did everything they could possibly do. I think that's the underlying belief for the Committee.

I do not believe, in my previous life, that that was the NRC's underlying understanding, that it wasn't about whether the authorized user and the team did everything right. It was about the outcome. Okay? And that's just a very big difference.

When I brought this up, I didn't bring up what I think is very good language because I didn't have a solution. I thought I could identify what I thought it was a problem, but I didn't really have a solution. I just -- and now I'm comfortable with the language that we've come up with, but I could understand why reasonable people can differ on this. That's why it's very important I think that the Committee and the NRC come into alignment on what we mean by this term.

But going back to what I said before, I don't think she was talking about doing the MRI wrong. It's just that after doing it right it's still having a problem.

CHAIRMAN THOMADSEN: Dr. Alderson?

VICE CHAIR ALDERSON: So to go back to our previous discussions in relation to these things that were just said about imaging uncertainty, I think that the other two terms are not being debated, the art of medical practice and standards of medical practice. People aren't debating that. But the words "imaging

uncertainty" have created this whole last 15 minutes' worth of discussion.

Therefore, it suggests to me again that the ability to implement something here that will be meaningful, that will go out and have a meaningful impact in the public and with patients and patient care -- that that phrase is going to continue to trip us up. And imaging is going to continue to change, but the standards of medical practice will be changing with it as it does. So I still think in terms of the interest of clarity and the ability to be able to implement this properly that we ought to consider dropping "imaging uncertainty."

CHAIRMAN THOMADSEN: Thank you, Dr. Alderson.

Dr. Palestro?

MEMBER PALESTRO: Yes, thank you, Bruce. In going through this I agree with Phil's comments about removing "imaging uncertainty," and I do think that it is in fact covered by the phrase or included in the phrase "standards of medical practice."

CHAIRMAN THOMADSEN: Thank you, Dr. Palestro.

Dr. Zanzonico?

MEMBER ZANZONICO: I basically just wanted

to echo Dr. Ennis' comments. I don't think anyone disagrees with publicizing suboptimal practice where we can be identified. And to me that's a big purpose of the medical literature, the scientific literature. And I really think it's outside the scope of responsibility of regulators to identify and by extension help define optimum medical practice. To me reportable medical events is to identify and hopefully prevent harmful or potentially harmful mistakes, overt mistakes, not suboptimal practice, so forth and so on. That really is the purview, as I say, of the scientific literature, the peer reviewed literature where independent referees vet the validity of what's being reported and so forth.

So while there is value to publicizing suboptimal practices and so forth and so on, I don't think that's the scope of responsibility of regulators. And I think what the Subcommittee has recommended with or without the term "imaging uncertainty" really captures what should be the intention of reportable medical events.

CHAIRMAN THOMADSEN: Thank you, Dr. Zanzonico.

Before Dr. Ennis speaks, I would not particularly disagree with what you said. It would in

a world that actually was supposed to be, but has not gotten into legislation yet, that practices would be required to report events to patient safety organizations where this information could be gleaned and could be presented to the community where it could be useful. And that is where this type of work should belong as opposed to a regulation space. Unfortunately, we don't have that. And the question becomes, well, what is useful to society given the reality on the ground at the moment.

Dr. Ennis?

MEMBER ENNIS: Really, almost mirroring what you were going to say is that, regarding Ms. Weil's comments, they're incredibly important, that these kind of -- other kinds of things that don't quite reach the level of medical event get reported and get analyzed. And patient safety organizations have been developed to do just that across the whole house of medicine. I assume many specialties are doing it. Radiation oncology actually have a very large patient safety organization and reporting mechanism. So, and I guess I would feel that that's the space for these. things.

Medical events, the reality is they are as you described them. They are as bad for the practitioners and the people involved. Whether that

was the original intention or not, that's the current reality. It percolates up to the highest levels of a hospital and the States, and it's a big deal. So unless there's some other way, a patient safety organization seems to me to be the way of doing what is a very important part of figuring out quality.

CHAIRMAN THOMADSEN: Mr. Bollock?

MR. BOLLOCK: Thank you. Just to address Ms. Weil's comment. And I know Dr. Zanzonico has kind of touched on with the -- in talking about medical event. We have received a lot of feedback where it comes to medical events, and basically the purpose behind it just to identify issues that have happened and correct them, and then by disseminating information prevent it from happening again. And so we are working to kind of get that -- to help get that out there to our purpose in the public forum. So, we are working to do that. That may help some clarification, but we do realize, as Dr. Zanzonico said, there is a difference between there was a mistake and kind of like a best practice thing. So, we understand that and we appreciate the feedback from the subcommittee when it comes to this area.

CHAIRMAN THOMADSEN: Are there other comments from the Subcommittee? Yes, Mr. Mattmuller?

MEMBER MATTMULLER: Yes, in reading

through this I couldn't help but think of a recent abnormal occurrence that was in the 2014 report about a licensee in Ohio that was doing a Y-90 microsphere study. And they did everything right, but unfortunately from the time they evaluated the patient with technetium MAA for shunting to the time that the patient was actually treated collateral vessels developed, which would be analogous to extra valves appearing in a nuclear power plant spontaneously.

(Laughter.)

MEMBER MATTMULLER: And so there was this unexpected unusual shunting of the microspheres going to the gut. So it seems to me this would almost be like the poster child for exactly what you're talking about. I mean, they did everything right, but you're dealing with a human, and they don't always cooperate. So I'm assuming your subcommittee is saying that type of event should not be considered a medical event.

MR. BOLLOCK: I don't know if that's on the Subcommittee -- on the yttrium-90 guidance, the update. I think that's one of the things that was covered by --

CHAIRMAN THOMADSEN: Mr. Costello?

MEMBER COSTELLO: Yes, I'm on the subcommittee, and our recommendation basically was if the medical team did everything right and they put the

spheres in the right location and then -- then that would not be a medical event. So I think that that involves changing the guidance that's in 35.1000. And I think that would solve that.

MEMBER MATTMULLER: Right, I think that's going to be like in the report later.

MEMBER COSTELLO: And I think we're in process. I think we're going to get there.

MEMBER MATTMULLER: Okay.

MEMBER COSTELLO: However, I think the approach that we took there, the philosophy and the approach that we took there is reflected in here. Okay? It's the philosophy that comes up and is there, but it was the same philosophy that we used, I believe, in coming up with the recommendation for the Y-90 microspheres.

CHAIRMAN THOMADSEN: Dr. Dilsizian?

MEMBER DILSIZIAN: No, I just wanted to concur with Mr. Bollock's recommendation. I think that there were three words he used: report, correct, prevent. If the reportable event cannot be corrected or preventable, then it should be regulated. Is that fair?

CHAIRMAN THOMADSEN: I think I would have to diagram that.

(Laughter.)

CHAIRMAN THOMADSEN: But thank you. Thank you for that.

Ms. Weil, did you have your --

MEMBER WEIL: No, I'm just grimacing.

(Laughter.)

MEMBER WEIL: I have a little trouble with that, because I think that you report in the hopes that you will generate enough information that might prevent similar occurrences. And correction might be the change of medical practice. Maybe that's the correction. As new information becomes available the ultrasound won't be used. The MRI will be used, when it can, granted. I'm having a lot of trouble with the big black hole in this language. The more we talk about it, the more I have trouble with it. It strikes me that it's just too qualitative and interpretation is too wide.

CHAIRMAN THOMADSEN: Thank you, Ms. Weil.

Mr. Bollock?

MR. BOLLOCK: And, thank you, to address just -- so we do recognize that and to go what is -- determine what is a mistake and what's not, that's why we rely on this Advisory Committee. So, yes, we recognize that. We understand your point. We also

understand -- we see it's --

MEMBER WEIL: A fine line.

MR. BOLLOCK: -- a fine line. So what is the right -- what is basically the stage that needs to be reported? And then correct and prevent. And what is not necessarily a mistake, but things that can help. And there are other -- we would also like to, as much as we can, help disseminate information that would make things safer in this practice. So we do want to do both, but there is a fine line between what's deemed a reportable event and what's not. So, but we do appreciate the input from the subcommittee on this and we will -- as with everything, we'll consider this and see what can be done.

CHAIRMAN THOMADSEN: Thank you. Dr. Zanzonico?

MEMBER ZANZONICO: I think it's important to recognize that a report of a medical event, as far as I know, is not peer-reviewed. So a statement from a practitioner does not necessarily equal a fact. In other words, if a practitioner were to report an event which actually was more related to suboptimal practice as opposed to a mistake. And that sort of gets into the public sphere. Other practitioners can adopt it without it having been vetted by the profession or

without it having been peer-reviewed and actually propagate even worse mistakes potentially.

So, that's why I think it's important that reportable events in a regulatory context refers strictly to mistakes and that improvement in medical practice subject to the regular scientific peer-reviewed and so forth really is the scope of improving and publicizing medical practice, best practices and so forth. I think you can't lose sight of the importance of peer-review in these sorts of things. And unless the regulators want to take on that responsibility of peer-review of reportable events without -- and thereby hoping to avoid parsing the distinction between a mistake or it's a suboptimal practice, I think their responsibility should be restricted to mistakes, to an I-131 thyroid cancer patient being given the wrong administered activity because it wasn't properly assayed and so forth. I mean, to me that's the essence of what should be a reportable medical event, not suboptimal practice. That's the scope of the scientific literature and professional societies where these things are peer-reviewed and vetted properly.

CHAIRMAN THOMADSEN: One problem with that philosophy is that rare events are never going to be

peer-reviewed. If you have an anatomical or a physiological anomaly in a patient, which may also exist in some other patients, but few patients, that people should be aware is a possibility you are not going to have a study that gets peer-reviewed and published in the future.

Yes, Dr. Zanzonico?

MEMBER ZANZONICO: Well, isn't that the purpose of case reports for isolated incidents where -- as opposed to say a clinical trial sort of thing? So I think there is an opportunity for even individual very rare unusual events that you encounter in practice.

CHAIRMAN THOMADSEN: In much of the radiotherapy literature they no longer will publish case reports because they are not statistically significant.

Mr. Bollock?

MR. BOLLOCK: And just to address that on the regulatory side. When events are reported to us, our regional offices will do some follow up. And there are chances when we do allow those licensees, practitioners, to look into the reports. And if it turns out there was -- basically there is a chance for them to review, look at it more, and if it is not -- it turns out it shouldn't have been reported, they can

retract it. And I mean, we do understand once you get it out there, it's out there, but we also understand once it's retracted, it means it's not -- it's no -- it wasn't an event.

And we do understand things that are mistakes and not, but we also -- there are some things that are just -- there's a regulation, there's certain compliance that has to be met. If it's not met, it's reported. So that's the nature of regulation. So unfortunately in some cases that's just -- that's what's in the regulations. If it's not met, you have to report in some cases.

CHAIRMAN THOMADSEN: Thank you, Mr. Bollock.

Dr. Palestro?

MEMBER PALESTRO: Two comments. In terms of publishing case reports, certainly in the imaging literature there still are a plethora of journals that will accept case report publications.

And regarding the imaging uncertainty and the example of the ultrasound that was interpreted one way and the MRI that was interpreted another way, let's assume for the moment that the ultrasound was performed correctly and was interpreted by a competent individual and for some reason the MRI provided different

information. Does that now mean based on this single case that everyone has to start doing MRI? And I think that's the potential implication of looking at something like this.

And I think there I agree with Pat Zanzonico that that's really the purpose of peer-reviewed literature, to accumulate -- and albeit it may be a small number of cases, but before people begin to jump to conclusions and say the mistake was made with imaging modality A; we need to go to B now, you need to sit back and take a careful look at it.

CHAIRMAN THOMADSEN: Thank you, Dr. Palestro.

Mr. Costello?

MEMBER COSTELLO: That does go to the -- again, back to the underlying thought of why we have medical event reporting at all. Okay? If it's strictly based on outcomes, just outcomes, regardless of whether or not a mistake was made, then if that's what you're looking for, then it should be reported because the outcome was unintended. You discovered in the MRI that something was there that you didn't see with ultrasound. If the purpose of it is to make sure that the team -- if they do everything right, they do everything right, that probably couldn't have been

preventable, then they shouldn't be reported, then that should be the definition.

But it's whether or not we want to have a medical event reporting rule based strictly on outcomes that -- with a few exceptions that are in the rule. And if the outcomes are unintended and negative, that that needs to be reported. If that's what we want, then you have one kind of a rule. If it's to identify whether or not the medical team did everything that they could in their power in the normal practice of medicine, then that's another kind of rule.

And so one of the reasons I brought this up here is this is the perfect forum to define that. I believe that it is the sense of the Committee and that it is if the team did everything they could possibly do, then that's not the kind of event we want to have reported. But if perhaps, as a patient advocate, if the outcome is very negative for the patient, then it should be reported. These are very different points of view and I think it is well worth debating here.

CHAIRMAN THOMADSEN: Thank you, Mr. Costello.

MEMBER COSTELLO: The outcomes.

CHAIRMAN THOMADSEN: Dr. Suh?

MEMBER SUH: So, I think we've had a very

nice discussion about the definitions of patient intervention and obviously the Subcommittee worked very hard on the nuances of what issue 2 should entail.

Just listening to everyone's discussion, right now I think we're kind of at a little bit of a standstill in terms of, at least in my mind, how proactive the Committee feels we should be in terms of reporting of patient intervention versus kind of a reactive approach. So what I mean by that is I think we're going to have to find middle ground in terms of what the definition of patient intervention should entail, because obviously you can learn from every event.

But I guess the question comes is that the purview of the NRC to report every possible event, every possible imaging anomaly that occurs for every event, which I think would be beyond the scope of what it is clear the NRC could do. Or is it more of a -- you're trying to be very focused in terms of what you're trying -- and I think that it's -- right now I think we're going kind of back and forth in terms of are we taking more of a proactive stance in terms of patient intervention should entail? Is it more of a reactive approach? And I would propose that we need to be somewhere in the middle in terms of how we do this, otherwise I think

we'll go back and forth in terms of what patient intervention really entails.

But I think you can take either side. Right? You can take the patient advocacy side and say, well, every potential medical event is a learning possibility for everyone involved, and that should be some type of forum to learn from. But the other approach is to say, well, let's really focus on the standards of medical practice and making sure that the art of medical practice is being protected. So I think you can take different stances in terms of how the Subcommittee wants to proceed and how the Committee wants to proceed with this language.

CHAIRMAN THOMADSEN: Thank you.

Dr. Palestro?

MEMBER PALESTRO: Yes, I know we're going to be covering this later and I'll be presenting the subcommittee's review of the guidance for the yttrium-90 microspheres, but I would think -- or I think that we would want to have these two topics in parallel with one another and not in conflict. And I think that the way it's phrased now, including provided that standards of medical practice are met very close to the wording that's used in the suggested changes to the guidance. I think we need to be mindful of that.

CHAIRMAN THOMADSEN: Thank you for that observation.

If there's no other comments from the subcommittee, I would now ask if there's comments from the Full Committee on the report. Any recommendations we should make on the report. Dr. Alderson?

VICE CHAIR ALDERSON: Based on all the previous discussion and what I believe is the sense of the Committee, I would like to suggest a motion in the interest of clarity that we remove the phrase "and/or imaging uncertainty" from this advice, the reason being that it engendered all the uncertainty that we saw here today and it also moves well beyond the radionuclide PET area in which the NRC typically regulates. So, I would suggest that we remove it, and make that motion.

CHAIRMAN THOMADSEN: Okay. Do we have a second for that motion?

MEMBER COSTELLO: Second.

CHAIRMAN THOMADSEN: We have a second. Discussion on the motion?

(No audible response.)

CHAIRMAN THOMADSEN: We have no discussion. Call for a vote. All in favor of that motion, please say aye?

(Chorus of aye.)

CHAIRMAN THOMADSEN: Opposed, say no?

(No audible response.)

CHAIRMAN THOMADSEN: Any abstentions?

(No audible response.)

CHAIRMAN THOMADSEN: One abstention. Dr. Ennis. And would you like to explain that, or just --

MEMBER ENNIS: No.

CHAIRMAN THOMADSEN: Abstaining is fine, but if you wanted to make comments on that, that's fine, too.

(No audible response.)

CHAIRMAN THOMADSEN: Very fine. No comment. In that case, the motion passes and in the report if the next motion is that the Committee does something with the report, the phrasing on imaging uncertainty will be removed.

So, we have the report from the Subcommittee. We have some choices on what to do with that report. We can adopt the report as the report from this Committee. And then we also need to decide, as Mr. Costello very nicely pointed out, what recommendation to the staff to make from this report. So, I might first ask is there a motion on the floor to adopt the Subcommittee's report as a report from the Whole Committee?

MEMBER COSTELLO: I move we adopt it.

VICE CHAIR ALDERSON: Second.

CHAIRMAN THOMADSEN: We do, and it's seconded. Is there discussion on that motion? Dr. Zanzonico?

MEMBER ZANZONICO: My impression is that the report incorporates essentially recommendations to the Committee, so is there --

CHAIRMAN THOMADSEN: To the Committee?

MEMBER ZANZONICO: I mean, to the staff. So, are we considering some additional or different recommendations perhaps than what's already in the report?

CHAIRMAN THOMADSEN: Possibly so. And what is the recommendation in the Committee's report to the staff?

MEMBER ZANZONICO: Well, I think it's incorporated into what's on this slide.

CHAIRMAN THOMADSEN: So, I don't think it gives them the guidance that they're going to need. And if this report is adopted as the ACMUI's recommendation, I would ask the NRC staff to please come back to this Committee next meeting with recommendations for how this can be achieved. But I think we've made the recommendation to them, but not in a way that will assure

that it will actually affect users, or licensed users.

Other discussion?

MEMBER SUH: So, just for clarification --

CHAIRMAN THOMADSEN: Yes, Dr. Suh?

MEMBER SUH: -- so the verbiage would read -- just it would say "unintentional outcomes due to anatomic and physiologic anomaly," period? Is that the --

VICE CHAIR ALDERSON: No, falls into the category of. We didn't remove any of that language. We just removed "and/or" --

MEMBER SUH: Okay.

VICE CHAIR ALDERSON: -- "imaging uncertainty."

MEMBER SUH: Okay. So it's into the category? Okay.

VICE CHAIR ALDERSON: Yes.

CHAIRMAN THOMADSEN: If there's no other discussion, I will call this question. All in favor, say aye?

(Chorus of aye.)

CHAIRMAN THOMADSEN: All opposed, say no?

PARTICIPANT: No.

CHAIRMAN THOMADSEN: Abstentions?

(No audible response.)

CHAIRMAN THOMADSEN: We have adopted the Subcommittee's report as the ACMUI's. And so, I will please ask the NRC staff to come back to the Committee at the next meeting with recommendations on how this can be manifested into the NRC space most effectively.

And with that, I see that we are on break until 10:15. Please be back at that time and we can resume.

(Whereupon, the above-entitled matter went off the record at 9:53 a.m. and resumed at 10:17 p.m.)

CHAIRMAN THOMADSEN: If we can come back to order, please? Before we go on to item No. 6, training and experience, I would like to call on Mr. Costello as a follow up to our last discussion. Mr. Costello, please?

MEMBER COSTELLO: Okay. I spoke earlier that it's important that we have a recommendation very specific of what the NRC can do with what the Subcommittee came up with. And to clarify what we want the NRC to I would move that we request the NRC through -- and it leads up to then some generic communication. It could be an Information Notice or a RIS -- indicate that the second definition we had up there can be used to clarify the existing definition in the regulation. We are not recommending a change to the regular definition of a "patient intervention." The

current definition in the rule gives a couple of examples and says "such as." Okay? I don't believe that that was meant to be an all-inclusive list of things that could be patient intervention. So, I think if the NRC were to -- I'm thinking Information Notice, but I'll leave it up to them -- could indicate that that could be interpreted to be not just such as the two that are listed there, but also could include what we had in the second example that came from the subcommittee. Is that clear?

The first one's really out of the regulation, but the second is examples of what patient intervention could be, which could have included in the original such as, but I don't think you could list every possible such as. It would go on for pages. That could be interpreted to include not just the two examples given in Part 35, but also to include the examples that we have in the second part of the recommendation.

CHAIRMAN THOMADSEN: And to make clear that those are not inclusive examples.

MEMBER COSTELLO: Yes, all inclusive. You can't come up with all possible examples.

CHAIRMAN THOMADSEN: Yes.

MEMBER COSTELLO: And in some ways I almost wish the regulation didn't have examples, because it

might be interpreted as those are the only all possible examples, which I don't think that everything can be mentioned. But I move that we tell them that -- ask them, request that they have a generic communication; and I think information notice, but I'll leave that up to them, so that licensees in the medical community and state can say that the rule which defines patient intervention be interpreted to include our second definition out there as being one of the examples.

CHAIRMAN THOMADSEN: And as part of your motion can we have them fold that into the task we've asked them --

MEMBER COSTELLO: Yes, I mean, report to us back in March, I guess it is, right?

CHAIRMAN THOMADSEN: In the next meeting. Do we have a second for that motion?

VICE CHAIR ALDERSON: Second.

CHAIRMAN THOMADSEN: We have a second. Discussion?

(No audible response.)

CHAIRMAN THOMADSEN: Hearing none, all in favor, please say aye?

(Chorus of aye.)

CHAIRMAN THOMADSEN: Opposed, say no?

(No audible response.)

CHAIRMAN THOMADSEN: Abstentions?

(No audible response.)

CHAIRMAN THOMADSEN: And so it's passed and you now have an addition to your task for next time. Is that acceptable to the NRC?

MR. BOLLOCK: Yes, it is. And just to be clear, because this deals with a definition that's in the rules, we'll have to get our Office of General Counsel to first see if this -- if that, what you're requesting is possible, that we're not reinterpreting, just understanding it's a -- that this interpretation can be used in what the definition is as --

MEMBER COSTELLO: Exactly.

MR. BOLLOCK: -- it is.

MEMBER COSTELLO: The regulation gives a couple of examples. It gives two examples, I think. I don't think the rule was ever intended that that be an all-inclusive list, sort of just giving it other --

MR. BOLLOCK: Right, and we can't --

MEMBER COSTELLO: And we're not supposed to be supposed to be all-inclusive either, but there might be things we haven't thought of.

MR. BOLLOCK: Right. Right, but we can't -- I can't say -- nobody can definitely do that. We'll need our counsel to allow that. And so we will work --

CHAIRMAN THOMADSEN: I think it would be assumed that the counsel would be involved in --

MR. BOLLOCK: Yes.

MEMBER COSTELLO: I think the Subcommittee all along knew that whatever we discussed would have to go through the Office of General Counsel. We knew that from the beginning.

CHAIRMAN THOMADSEN: Very fine. Now, Dr. Palestro, I see your name tag, your name tent is up there and your slides are up. It's time for the report of the Subcommittee on Training and Experience for Authorized Users for Alpha and Beta Emitters.

MEMBER PALESTRO: All right. So, this is the report of the Subcommittee on Training and Experience for Authorized Users of Alpha and Beta Emitters. Members of the Subcommittee include Drs. Dilsizian, Ennis, Langhorst, Zanzonico and Ms. Weil.

Our charge was to determine if the current requirement of 700 hours for training and experience for authorized users of alpha and beta emitters in 10 CFR 35.396, which is Training for User of Unsealed Byproduct Material for which a written directive is required, places hardship on the patient community and to make recommendations for ACMUI action.

Just by way of a bit of background,

radiolabeled antibody treatment of lymphoma with beta emitters was approved by the U.S. Food and Drug Administration more than 12 years ago. Initially there were two agents available: yttrium-90 ibritumomab tiuexetan (Zevalin) and iodine-131 tositumomab (Bexxar). The use of both agents peak a few years after their introduction. Despite favorable clinical results, the use of these agents had decreased steadily over time, and in fact Bexxar was withdrawn from the market in 2014 when fewer than 75 patients were treated with this agent.

So what are the factors that are affecting the use? Well, certainly at one time, no longer the case, but at one time was cost. In a 2007 survey by the Society of Nuclear Medicine, now the Society of Nuclear Medicine and Molecular Imaging, Zevalin cost hospitals somewhere between 22 and $24,000 per treatment, while Medicare's planned reimbursement was only about $21,850, and even less for Bexxar. That, however, has been resolved.

There are other factors. Remember that these agents were introduced more than a decade ago and there has been the development of other effective therapies that do not use radiation that were developed after Zevalin and Bexxar. So that's certainly one

factor that potentially affects the use of these two agents.

Another factor that was raised in the telephone conference call I believe by Dr. Cultrera was a lack of familiarity with these agents; that is, that hematology oncology fellows not exposed to these agents during training. That, however, really is not a regulatory issue; that's an educational issue.

What about a shortage of authorized users? It's been suggested that a direct result of the requirement for 700 hours of training and experience to obtain authorized user status, which went into effect shortly after these agents were introduced, is the explanation for the decreasing use of these agents. And that is a complicated issue.

It's difficult to determine the impact of a lack of authorized users on these agents because even at large medical centers with an abundance of clinicians and authorized users who work closely together these radiopharmaceuticals are used and have been used infrequently. And this is just some information that I obtained from members of this Committee, the ACMUI.

You can see that Memorial Sloan Kettering Cancer Center, New York, an institution dedicated almost exclusively to care and management of patients

with malignant tumors, that between 2009 and 2014 a total of 190 therapies, radiolabeled antibody therapies were performed, or approximately 35 per year.

University of Maryland in Baltimore, over a 12-year period, a total of 25 of these therapies were performed.

My own institution, North Shore Long Island Jewish Health System, over a 10-year period approximately 50 of these therapies were performed. And we have a catchment area among all of our various satellite hospitals of somewhere between 2 and 3 million people.

And then finally, Washington University/Barnes-Jewish Hospital in St. Louis, very similar numbers over that same 10 or 11-year period, roughly 5 patients per year.

So the explanation for the infrequent and steadily decreasing use of radiopharmaceuticals for the treatment of lymphoma appears to be due and is likely due to many factors. Based on the currently available information the Subcommittee really isn't able to determine whether or not this can be attributed to a shortage of authorized users, if in fact there is one, caused by the current training and educational requirements.

And just as an aside, radium-223 dichloride, also known as Xofigo, was approved for treatment of castrate-resistant prostate carcinoma with symptomatic bone metastases and no known visceral metastases about two years ago. Now, there are no trending data yet available and the factors affecting its use cannot even be addressed at this time.

So the Committee therefore requests that we continue pursuing this charge with recommendations to be presented at the spring 2016 ACMUI meeting.

CHAIRMAN THOMADSEN: Thank you, Dr. Palestro.

Comments from the Committee? Questions?

MEMBER COSTELLO: From the Committee or Subcommittee?

CHAIRMAN THOMADSEN: We could start with the Subcommittee. Anybody on the Subcommittee wish to make comments about the report? Dr. Zanzonico?

MEMBER ZANZONICO: So, I think Dr. Palestro made a compelling case that clearly the lack of use of these lymphoma-targeting agents is not attributable to a shortage or non-availability of authorized users despite looking at the institutions that have an abundance, some may say an over-abundance of authorized users, and yet it was used infrequently.

A question I have in terms of defining the scope of the charge of the Subcommittee. It seems that an additional question is, independent of the impact of the training and experience requirements on these specific agents, are we also considering whether the 700-hour requirement in and of itself is excessive, unnecessarily excessive regardless of whether it impacts the use or non-use of certain specific agents as in this case? So can we get some guidance on that?

CHAIRMAN THOMADSEN: Yes. Do you want to address that?

MEMBER PALESTRO: My understanding based on the charge that I was given was that it focused exclusively on whether or not it affected this specific instance as opposed to whether or not the 700 hours in general should be looked at. That I looked at as a different topic.

CHAIRMAN THOMADSEN: And in answer to your question, probably after this discussion goes where it goes, I may be adding to the charge of this Subcommittee.

Ms. Weil?

MEMBER WEIL: I'd suggest a clarification to Dr. Zanzonico's statement. The training and experience requirement is not solely responsible for the lack of use of these agents.

CHAIRMAN THOMADSEN: Thank you. Anybody else on the Subcommittee?

(No audible response.)

CHAIRMAN THOMADSEN: No? Okay. Anybody on the Committee? Mr. Costello?

MEMBER COSTELLO: Yes, I feel strongly really that the charge should be focused on 700 hours. Whether or not this is holding up the use of it, I don't think we'll ever know as long as this 700 hours is there. And the NRC really, their only handle on this, their only involvement in this, I think, is the requirement for the training and experience requirement. Are people doing this? So, I mean, I would definitely recommend that the charge focus on are we at the right place for T&E for this modality? Maybe 700 hours is correct. Maybe 80 hours is correct. Maybe something in between is correct. But I think we need to get that correct. And then I believe the time in the market will determine how often this is used. Okay? So that's my recommendation, that the charge be modified to focus on what should the T&E requirements be for this modality?

CHAIRMAN THOMADSEN: Thank you, Mr. Costello.

Dr. Ennis?

MEMBER ENNIS: If we're going to approach

it more broadly, then I think we need to be thinking about these agents plus, in terms of classes of agents, rather than these specific ones. And if you think that lesser hours might be appropriate, you need to be careful about defining what class that is and then going forward so when new agents come out we're not kind of doing a case-by-case analysis of exactly how many hours. I believe that would be practical.

CHAIRMAN THOMADSEN: Thank you, Dr. Ennis.

Other comments from the Committee? Mr. Costello?

MEMBER COSTELLO: Yes, I think the only way to approach this, if we wanted to change the hours, is we could put this under 35.1000. You know, 35.300 says what it says. And I think it would be hard to -- particularly if we're talking about the targeted agent thing. I don't know why. But if we could find a way to put this in 35.1000 and pick an appropriate number of hours, whatever that may be, I think from a regulatory point of view that would fit better.

CHAIRMAN THOMADSEN: Thank you, Mr. Costello.

Ms. Weil?

MEMBER WEIL: When Bayer came to this Committee a couple years ago with radium-223

dichloride, as I recall, the Committee recommended to NRC that that particular agent be licensed -- was it under 1000?

CHAIRMAN THOMADSEN: No.

MEMBER WEIL: No?

CHAIRMAN THOMADSEN: It was under 300 just as a regular radiopharmaceutical.

MEMBER WEIL: And does that particular drug require 700 hours?

CHAIRMAN THOMADSEN: It does.

MEMBER WEIL: Okay. Thank you.

CHAIRMAN THOMADSEN: Dr. Alderson?

VICE CHAIR ALDERSON: As we begin to pursue this line of reasoning, which I think is a good one to pursue, a very important one to pursue, thus far we've talked about just the issue of are the number of hours correct? What I think we have to be talking about is the rigor of the training that's provided. Is the rigor of the training sufficient to provide the safety that we need to support? So that is at least as important. Then you back into the hours from that. And so, I think that's a key component of our concern.

CHAIRMAN THOMADSEN: Thank you for that observation, Dr. Alderson.

Other comments from the Committee? Dr.

Suh?

MEMBER SUH: Chris, do you have a sense of what percent of these drugs are being administered by nuclear medicine versus radiation oncology? Do you have a sense of that?

MEMBER PALESTRO: No, I don't have a breakdown as to that.

MEMBER SUH: And I know at our institution the nuclear medicine physicians are the ones injecting the Xofigo and the Zevalin, so I was interested in what the other centers are doing, like at your center.

MEMBER PALESTRO: At our own center the few Zevalin's that are administered, are administered by nuclear medicine. The radium dichloride, Xofigo, is a joint administration by radiation oncology and nuclear medicine.

CHAIRMAN THOMADSEN: Dr. Dilsizian?

MEMBER DILSIZIAN: At the University of Maryland it's all done through nuclear medicine, all three of your medicines.

MEMBER ZANZONICO: Likewise at Sloan Kettering. All of the radionuclide therapies are administered by nuclear medicine physicians.

CHAIRMAN THOMADSEN: Dr. Ennis?

MEMBER ENNIS: For whatever it's worth, at

Mount Sinai Xofigo is done by radiation oncology. The others are done by nuclear medicine.

CHAIRMAN THOMADSEN: And for what it's worth, at Wisconsin Xofigo is done the same, in radiotherapy. Zevalin is done in nuclear medicine. It can also be done in radiation oncology, but there are so few of them that get done. Mostly it's nuclear medicine. Dr. Zanzonico?

MEMBER ZANZONICO: But just to clarify, even when it's administered by radiation oncology, those are AU radiation oncologists.

CHAIRMAN THOMADSEN: I'm sorry. What's that?

MEMBER ZANZONICO: That they are AU radiation oncologists. In other words, it's not some ad hoc arrangement for the administration by radiation oncologists. They're authorized users.

CHAIRMAN THOMADSEN: Oh, absolutely.

MEMBER ZANZONICO: Yes, so I think that's an important point.

CHAIRMAN THOMADSEN: Yes, yes. Of course. Yes.

MEMBER ZANZONICO: Regardless of departmental who's administering it, I think it's an important point to make.

CHAIRMAN THOMADSEN: That is correct.

Dr. Palestro?

MEMBER PALESTRO: Pat, you raise a good point. In going through some of the letters and so forth, just to clarify, there's a bit of confusion regarding training and authorized user status. Nuclear medicine residency, radiation oncology residency and nuclear radiology fellowship individuals completing any one of those training courses are all qualified as authorized users because they have met all of the requirements both for diagnostic and therapeutic radiopharmaceuticals.

CHAIRMAN THOMADSEN: Thank you for that clarification.

Other comments from the Committee? Oh, I'm sorry. Mr. Mattmuller?

MEMBER MATTMULLER: Yes, in your examples where you listed by institution the number of total therapies, do you have a sense of this is -- given your metropolitan areas and your patient population, whether this is a lot, a small amount? Because if you were to add Kettering Medical Center in Kettering, Ohio, for about the past 10 years we've done three Bexxars and two Zevalins. So we're very frustrated that our numbers are so low. And it's not because we don't have AUs that

are ready to go.

MEMBER PALESTRO: It's the exact thing. I can speak personally for North Shore LIJ. It's a fraction of the patients who are -- and I can't give you an exact number, but a small fraction of patients who are eligible to receive this sort of therapy. And again, just like your institution, we have radiation oncology, nuclear medicine and a large group of hematologist-oncologists, and we work hand in hand. It isn't a question of being concerned over stealing patients, that sort of thing. In terms of performing these procedures, the referrals just aren't there. And never had been.

CHAIRMAN THOMADSEN: Thank you.

Ms. Weil?

MEMBER WEIL: Irrespective of -- well, there's two issues: This is a therapy that is under-utilized. I don't pretend to know the reasons why, but as you say, there are a large number of patients, or there's a substantial number of patients who are eligible for this therapy, but it seems not to be offered to them. There are many reasons why that barrier seems to exist to patient access. But that's in the large perhaps metropolitan areas or areas where there may be an authorized user. In the community I

think it would be safe to say that there are community medical settings where it's not even an option because there isn't an authorized user.

So I think we're looking at two really very different issues here in this Subcommittee. One is there a barrier to access? There seem to be several barriers to access. But the other is is that a reasonable -- is the 700 hours of training and experience a reasonable barrier, or is it not? And there's such disparate situations that I'm not sure why one Subcommittee really can address these two things.

CHAIRMAN THOMADSEN: I would hope they could. Dr. Palestro?

MEMBER PALESTRO: Yes, in terms of lack of use, you mention, I think importantly, the potential for a lack of authorized users. But then there are really two parts to that: One, is there a lack of authorized users because there's now a requirement for 700 hours of training, or is there, for whatever reason, some other reason, a lack of authorized users? There's no way to answer that question with the data that we have in front of us now, but I think one of the important things that we want to try to look at if we're going to focus on that question is how many authorized users were there before the change in regulations versus after the

change in regulations? I don't know how easy that is to come by. And then we'd want to look at a breakdown. All right?

MEMBER WEIL: Yes. Of course.

MEMBER PALESTRO: The second question I have, if you look at the public comments that are included with today's handouts and you go to the Spectrum letter, on page 8 there is a bar graph. And you'll notice that in 2006 when the new 700-hour rules and regulations were implemented, there's a decline in the use of Zevalin. And there's another decline in 2007. And if you calculate it out, each of those years there's a drop of nearly 16 percent of the number of administrations of Zevalin.

The fact that the new hours or the new rules were implemented in 2006 I think makes it very unlikely that that initial drop of almost a third over two years can be attributed to the new regulations. Things don't change that quickly. Everyone else who was -- all of the authorized users who already were AUs, their status didn't change if they didn't meet the 700 hours. So I think that raises, at least in my mind, how much of this we can attribute to a lack of AUs and how much of that can be attributed to a lack of AUs resulting from the new training requirements.

CHAIRMAN THOMADSEN: Dr. Ennis?

MEMBER ENNIS: Also, I just want to kind of reflect a little bit on just the practice of medicine in rural and urban areas. People who live in rural areas, there's a lot of great things about that, but you obviously are further away from care. And lymphoma patients, as an example, they're getting many therapies and many imaging technologies that are requiring them to travel to authorized users who can do their PET/CT scans, for example, which is crucial in lymphoma. There are other CT scans if they're getting radiation. So there, as part of rural life, you have to travel a little bit.

But those nuclear medicine physicians and radiation oncologists could be authorized users, and it's hard to imagine why they are not choosing to do that and it's hard to imagine it's because of training because they are already trained. So, if the community is being served by nuclear medicine people for their PET/CT scans and radiation oncologists for their external beam treatments, it's hard for me to understand how those same authorized users are not available for a specific therapy unless there's some other reason that they don't want to do it that we don't seem to understand but is getting in the way, but it's not the training

because they are already trained and authorized users for all kinds of radioactive materials.

CHAIRMAN THOMADSEN: Thank you, Dr. Ennis.

Other comments?

(No audible response.)

CHAIRMAN THOMADSEN: I understood that there may be members of the general public who would like to make comments. Are there? Please, step to the microphone and give your name.

DR. CULTRERA: My name is Dr. Jennifer Cultrera. I'm with Florida Cancer Specialists and Research Institute and I really appreciate the Committee allowing me to speak to you again regarding this topic.

I just want to say a few things and address a couple of points that I was hearing you discuss. I am a physician in a rural part of Florida. I'm actually probably an hour to an hour-and-a-half north of Orlando in the Villages, Florida, and Leesburg, where I have two very, very different patient populations.

And I've had access to beta emitters, both at an academic center when I worked at Moffitt for three years and then when I moved to The Villages to my community practice, and I feel very strongly that beta emitters are very effective for this incurable disease,

follicular lymphoma. And knowing that there is a treatment that can prolong a cancer patient's life and improve their quality of life at the time, and these patients are now not having access to them is very disheartening.

And I'd like to refer back to the map that Spectrum provided for you on -- I think it's page 11 where it does have a listing of all the AUs per state. In Florida we do have a large number of AUs. We have 23. And if you look at the breakdown amongst those 23, they're all surrounded around academic centers, and namely Moffitt Cancer Center where I was. And it's very difficult for my patients who oftentimes they can't even go anywhere that's not golf cart accessible because they can no longer drive. They can no longer get even 10 miles away from their home to get to these academic centers.

Luckily, I do have nuclear medicine doctors. I have one unit that does a -- there actually two places in The Villages that have a PET/CT access and one area in the Leesburg area, but neither of my nuclear medicine doctors there want to be AUs. And that's been the problem that I've been encountering.

We are lucky to have a nuclear medicine doctor through Florida Cancer Specialists that can

travel to different practices that have PET/CT capability and administer Xofigo and Zevalin, but it's very difficult to get him out there unfortunately because of how large the State is.

And I do want to make a point as to the education. Unfortunately, I completely understand that the education is not to be determined by the role of this Committee, but by limiting access out of sight is out of mind. So unfortunately, you don't have the mentors and the attendees teaching their younger fellows that this is actually a drug available. I have new doctors entering Florida Cancer Specialists, new medical oncologists and hematologists that don't even know what Zevalin is, or when I mention radiopharmaceuticals, they go what's that, which is just as disheartening to me.

I just want to close in that this is a very safe highly-effective class of agents and basically just don't take away one of the drugs that we have in our arsenal for personalized medicine. Thank you.

CHAIRMAN THOMADSEN: Thank you for your comments.

Others?

DR. YANG: Thank you. My name is Allen Yang. I'm with Spectrum Pharmaceuticals and I lead

clinical development there.

CHAIRMAN THOMADSEN: Please stay close to the microphone.

DR. YANG: Okay. Sure. So, one of the things I'd like to say is that not all authorized users have the ability to give Zevalin. They have to be proctored cases. So it's not the fact that everybody who graduates from a nuclear medicine residency is ready to give Zevalin. You may disagree, but let me finish my statement and then you can respond.

So, the one thing I'd like to say is that I'm an oncologist by training and treating follicular lymphoma, it's a very indolent disease. Unfortunately, it's not curable. So the more therapies there are patients, the better. So what happens with a patient with a low-grade follicular lymphoma is they receive one treatment, and when the relapse they receive another treatment and so on and so forth. So the more treatments that are available, the better it is for patients.

The one thing I want to say about Zevalin; and you went through the numbers, Dr. Palestro, the number of uses have declined for some reason. It's probably multifactorial, very complicated. What I will say is that Xofigo, which is used quite a bit,

probably for prostate cancer, is marketed by Bayer Pharmaceuticals. Now, Bayer is a large pharmaceutical company. Spectrum is different. Remember, Zevalin was first owned by Biogen Idec and Bayer ex-U.S. And we acquired the rights after three companies. So the annual sales of Zevalin is very small.

So my concern is as the number of patients who use it and the number of people who use it, this therapy might not be available. You already mentioned that Bexxar, which was another radioimmunotherapy, was pulled from the market not because of safety issues, but clearly because of lack of use and commercial viability. Even with that, our main competition in terms of radioimmunotherapy has been pulled. We're still struggling.

So, we would like to make this therapy available for patients. We understand that decreasing the hours is a very complicated thing. Will it lead to increased use? We don't know. But my concern is that if we don't act and act quickly, that we may lose that window to try to turn this product around.

CHAIRMAN THOMADSEN: Thank you. Any others? Dr. Palestro?

MEMBER PALESTRO: Yes. I don't want to turn this forum into a debate on resident education, but

I can tell you without a shadow of a doubt -- and if you check, because I double-checked to make sure -- the ACGME program requirements for nuclear medicine, nuclear radiology and radiation oncology -- the individuals completing those training programs and being eligible for sit for the boards in their respective specialties must have completed the appropriate training for both diagnostic and therapeutic radiopharmaceuticals including alpha and beta emitters. And I know that for nuclear medicine because I helped write those program requirements. I was Chair.

So lots of times there are these terms about who's nuclear medicine, who's this and so forth get tossed around, but I can tell you; and, Dr. Ennis, you correct me if I'm wrong for radiation oncology, Dr. Metter for nuclear radiology, all of those individuals are in fact qualified and meet the requirements to administer these radiopharmaceuticals. Whether or not they choose to, that's a different story.

DR. YANG: No, I concede your point, sir. You're an expert in nuclear medicine and the training. So, I will say that one of the complexities about access is that -- I think it was mentioned before that PET scan is part of nuclear medicine and that the physicians who

do PET scan could also do Zevalin as well. The one thing I would say is that PET scan is a little bit different and that Zevalin is a therapeutic and there is some toxicity associated with it in terms of myelosuppression, so there may be sort of a less of a tendency in the community setting in rural areas to manage both the administration and the myelosuppression associated with that.

So again, clearly I think it's an issue of access and whether there is access available to patients for this product in the entire the United States. Clearly in some central sort of metropolitan areas access may be better, but in rural areas it may be more difficult. The physician who administers a PET scan may be less like to administer a therapeutic knowing that there may be some myelosuppression if that patient has to go away, etcetera.

CHAIRMAN THOMADSEN: Thank you. Go ahead, yes.

DR. CULTRERA: Thank you so much.

CHAIRMAN THOMADSEN: State your name again, please, just so the recorder gets it.

DR. CULTRERA: Yes, this is Jennifer Cultrera. And I totally agree with you and I thank you for your comments and input, but I'm a medical

oncologist and hematologist and we're not -- ACGME does not require us to see radiopharmaceuticals. And unfortunately, the patients will come to me first and we'll be the ones that usually refer out because lymphoma is a systemic disease. So we'll refer them to the nuclear medicine doctors and to the radiation oncologists and the nuclear radiologists. And from my standpoint and those of my colleagues I know at Florida Cancer is that if I had them to refer to, they'd be there. I would be referring. As it is now that I've had some availability with my traveling one, but it's just very limited. Thank you.

CHAIRMAN THOMADSEN: Thank you. Dr. Palestro?

MEMBER PALESTRO: Just one last comment. As an aside, when the program requirements for specialty or sub-specialty are being developed, they are posted routinely for public comment. And I don't know because I didn't go through the public comments for hematology oncology, but I would certainly encourage you and all of your associates to advocate strongly that training for therapeutic radiopharmaceuticals and so forth be included in the training program.

CHAIRMAN THOMADSEN: And just as an observation, I don't think that decreasing the hours

would increase the exposure of those residents, because they're being trained at the large facilities where you do have people who are trained in this.

Yes, please?

MS. LEE-ROWLEY: So, I'm Angelique Lee-Rowley. I'm from Spectrum Pharmaceuticals.

CHAIRMAN THOMADSEN: Yes, speak right into the microphone, please.

MS. LEE-ROWLEY: I'm counsel and patient advocacy for Spectrum, and we work with the American Society of Hematology that does help make those training requirements. And what they've basically told us is if it's not something that is ever going to be an option for a hematologist or oncologist to administer, then they're not likely to put in their training requirements. So if the requirements were lowered to an amount that could be incorporated into their program, they would be open to them discussing. So, just for what's worth.

CHAIRMAN THOMADSEN: A question to you. Do they cover anything like the importance of PET scans?

MS. LEE-ROWLEY: Yes.

CHAIRMAN THOMADSEN: Even though they won't be doing them?

MS. LEE-ROWLEY: Yes, that's diagnostic

though. Yes.

CHAIRMAN THOMADSEN: Thank you.

MS. LEE-ROWLEY: That's diagnostic though. Yes.

CHAIRMAN THOMADSEN: Dr. Ennis?

MEMBER ENNIS: Okay. So, I think this was very helpful for me because I was trying to connect the dots and there was just -- I could not really quite understand what I think I do now understand more clearly. It seems, at least from what I understand, there are many, many nuclear medicine and radiation oncologists across the country, and even rural patients have reasonably good access to that care. The problem that we have here is that some of those who are authorized users choose not to offer this therapy.

In my view that's not a regulatory issue. It's an issue of politics and finances, sadly, that come into play. And why the users choose not to offer it, perhaps there are just too few cases to make it worth their while. It was suggested just a moment ago that it could be management of complications that is something authorized users are uncomfortable with. That would be disappointing to me. But even if that's true, if a hematologist-oncologist really feels the patient needs it, then they could consider a

collaborative arrangement with the nuclear medicine physician who has the expertise in the radiologic aspects, and then the hematologist could manage the hematologic aspects and together they could provide care without changing the regulatory requirements. So, anyway, that's kind of how I see or understand the situation. Now, it seems to me it's more of a political financial issue than a regulatory one.

CHAIRMAN THOMADSEN: Thank you for that comment.

I can also ask is there anybody on the telephone lines that would like to make a comment?

(No audible response.)

CHAIRMAN THOMADSEN: Hearing none, we'll go back to our microphone here.

DR. CULTRERA: This is Jennifer Cultrera. Just to kind of answer your point, one of the issues of course is that in the rural community we don't have the just basis where everybody's in the same place, in the same building. I'm kind of lucky. We are getting to that point in the not-too-distant future, but in several areas across Florida we don't have that. So that's basically politically and just physically unable to do so to have those collaborations. And I have asked. I have asked my nuclear med docs in the hospitals and

they're fairly adamant. They just don't see the need or want to have to deal with patients, unfortunately, after -- with therapeutics versus diagnostics.

And I just also wanted to bring up that I have a colleague at Florida Cancer Specialists, Dr. Mace, who's a hematologist and medical oncologist who was grandfathered in on an 80-hour training. And he's actually administered both Zevalin and Xofigo for 10 years now with no safety incidences. And he's been able to provide that access. He's in the Tampa area where there are several AUs. And that's what we would like to do. And I'm not expecting all medical oncologists to go for this training. It's still 70, 80 hours or whatever the panel decides, but I think there will be a significant few that will be able to just fill in the holes within the country.

CHAIRMAN THOMADSEN: One question. Your colleague that performs these, it's a he?

DR. CULTRERA: Yes.

CHAIRMAN THOMADSEN: Is he at a facility with a medical physicist that assists with that?

DR. CULTRERA: I believe so, because he's in our Tampa Bay Cancer Center. So they have full access, both to radiation oncology and nuclear medicine. They have an in-house PET/CT scanner.

CHAIRMAN THOMADSEN: Thank you very much.

Dr. Zanzonico?

MEMBER ZANZONICO: Can I ask Dr. Cultrera a question?

DR. CULTRERA: Yes.

MEMBER ZANZONICO: So given the current lack of availability of these radionuclide therapies in your area in your practice, what do you do as an alternative for these patients?

DR. CULTRERA: Generally if they're unable to travel, I will find an alternative. It depends on the patient's population. I will either have to find them another type of care. So if it's a follicular lymphoma that's front line, I will do rituximab maintenance. I'm hesitant to do that for some patients who haven't achieved a partial response. I don't want to get into all the medicine just because there is stronger data for the radiopharmaceutical Zevalin to be used in those patients. It gets them into a CR and helps them have larger progression for survival.

For my patients who are in the relapse setting, I usually have to put them on medications long term. So it would either be an IV medication where they have to come in every few weeks or I have to put them on a pill, which has significant toxicity despite being

a targeted therapy. And this is going to be life-long for them, both costly and diminishing in time and effort and quality of life. With Zevalin it's fairly easy for me because it's a one and done. Basically they come in, they do their rituximab and the next week later their treatment dose. After that it's really just follow-up visits. And once they get out of that dangerous period for their blood counts and that we have to follow them closely, they're really coming to see me every two or three months if they go up.

CHAIRMAN THOMADSEN: A follow-up question. Do you see breast cancer patients?

DR. CULTRERA: Yes.

CHAIRMAN THOMADSEN: What do you do for their radiotherapy?

DR. CULTRERA: I send them over to a radiation oncologist. We do have a radiation oncologist in -- we have two in The Villages, and none in Leesburg. So I usually have to send them to surrounding areas.

CHAIRMAN THOMADSEN: Thank you.

DR. CULTRERA: Yes.

CHAIRMAN THOMADSEN: More questions or comments? Mr. Mattmuller?

MEMBER MATTMULLER: Yes, this will be a

question to our Committee members who do have experience with this. As the AU administering either one of these, who does the follow-up with the patient as far as who's monitoring their blood work to see -- is it you or is it the medical oncologist who referred?

CHAIRMAN THOMADSEN: Dr. Palestro?

MEMBER PALESTRO: North Shore LIJ Health System is -- the patients are followed by the medical oncologists --

MEMBER MATTMULLER: Okay.

MEMBER PALESTRO: -- nuclear medicine physicians and radiation oncologists for Xofigo, a joint project. We manage the patients from the administration of the radioactive material, but they then are taken care of, followed up by their hematologist-oncologist.

CHAIRMAN THOMADSEN: Thank you. Dr. Dilsizian?

MEMBER DILSIZIAN: Just to echo, which makes it even simpler. As you pointed out, it's a single dose administration from the AUs perspective. Everything else is followed by the oncologist. So yet another point why you could easily be gone to an AU community hospital where the administration is given one, but the follow-up is with the oncologist.

CHAIRMAN THOMADSEN: Thank you. Dr. Zanzonico?

MEMBER ZANZONICO: This is more of a comment or observation, but in this whole issue I'm still having a hard time reconciling the historical lack of use of these radionuclide therapies at academic centers like my own, like Sloan Kettering where nuclear medicine some might say is very aggressive in radionuclide therapies and has an excellent collaborative arrangement and so forth with hem-onc, with the clinical departments in radionuclide-based therapies, yet even under those ideal circumstances it simply hasn't been used.

And my inference is that the reason is there are better therapies. There are better alternatives clinically. And the clinicians who care for these patients have made that judgment and therefore have an equal access to both types of therapies, radionuclide versus conventional, that the new and existing therapies are in fact better. So the implication is that it's not lack of AUs, it's not lack of willing and even enthusiastic AUs to offer this therapy, but rather it's driven by clinical issues. So that's just an observation.

I mean, I appreciate the convenience and so

forth, but again it seems like the lack of use is driven again more by other clinical issues than lack of AUs. And at Sloan Kettering, which is on the Upper East Side of Manhattan, we have the opposite issue in that it's probably almost as inaccessible --

(Laughter.)

MEMBER ZANZONICO: -- to many of our users as patients in rural areas. Many of our patients come from New Jersey, Long Island, Westchester and it's a real hike for them to come in. It's a real effort for them to come in to Manhattan. Yet despite the convenience of the single administration of radionuclide therapies the clinicians caring for them have opted for conventional therapies.

CHAIRMAN THOMADSEN: Thank you. About how long does it take to get from Nassau to Memorial Sloan Kettering?

MEMBER ZANZONICO: Well, it could take up to four hours depending upon the day and who is in town, the Pope or the President.

(Laughter.)

CHAIRMAN THOMADSEN: Thank you very much. Dr. Palestro?

MEMBER PALESTRO: Yes, if you go back; and I don't have a graph in front of me, it seems back about

20, 22 years ago with the introduction of strontium-89 (Metastron), samarium-153 (Quadramet) for pain relief, so-called palliative therapy of painful bone metastases, there was an immediate upsurge in the use over about a year or two. Then as time went on you would probably find a graph very similar to what we're seeing here for Zevalin, decreasing use of those radiopharmaceuticals. And I think there the explanation -- and that was before the 700-hour training regulation went into effect. I think there the explanation was it's simply better, more effective methods of pain relief evolved over time. And here again you've got what, 12, 13 years of evolution of new agents for treatment of lymphomas. But I think somewhere in there that factors in.

CHAIRMAN THOMADSEN: Other comments?

DR. YANG: There's a comment in the back.

CHAIRMAN THOMADSEN: Oh, I'm sorry.

DR. YANG: A couple of comments.

CHAIRMAN THOMADSEN: Your name again, sir.

DR. YANG: Oh, Allen Yang from Spectrum Pharmaceuticals. So addressing the use in sort of major medical centers, one of the things that I'd say -- and we don't have statistics around this, but at major medical centers you're encouraged to patients on

protocols and put them on experimental therapies. And there have been, as you stated, a number of different agents being approved or examined in low-grade lymphoma: PI3-kinase inhibitors, Bruton's tyrosine kinase inhibitors, et cetera.

The one thing that I would say is if you look at the NCCN guidelines; this is what a lot of medical oncologists, most medical oncologists use as guidelines, for follicular lymphoma, the single agent therapies that are there, Zevalin has the highest overall response rate compared to Rituxan. The other agents that are looked at of course are bendamustine lenalidomide, which is not approved, and Rituxan as a single agent. And then those recommendations, the one that is only compared into a randomized study was Zevalin versus Rituxan early on, and that was one of the registration studies for Zevalin. Zevalin was superior.

So, I think it really is a matter of access and I think it has to do with the physicians who treat the patients who initially get the patients, who have seen them for their follicular lymphoma, gave them their induction chemotherapy and how they're managing them. I'm not sure that oncologists are going to jump up and say I would like an additional 70 hours of training, but

they definitely don't want to say that I want to do another 700 hours of training. And again, it may be okay in academic centers, major metropolitan centers with a nuclear medicine or radiation oncologist and the oncologists or hematologists have a practice in the same building, they work within the same medical school, etcetera, but in the United States where there's a lot of practicing hematologists-oncologists in the community setting, in rural settings, clearly there's an access issue.

One thing that I can bring up from our experience at Spectrum Pharmaceuticals, if you look at a country like Japan where hematology and oncology are separate specialties, the hematologists are sort of separate. They're usually hospital-based with the nuclear medicine or radiation therapy physicians. And there in Japan, Zevalin use is actually fairly high. And we think that it has to do with access, the fact that the hematologist, nuclear medicine physician are working together.

And so, clearly will dropping the training hours from 700 to 70 hours solve all the problems with Zevalin? Probably not. There are other issues with Zevalin in terms of logistics, but we think that we'll leave it to you the experts about the training hours that

are required, but we think that dropping those training hours could be helpful especially in rural areas where the access is limited.

CHAIRMAN THOMADSEN: Thank you.

DR. YANG: Sure.

CHAIRMAN THOMADSEN: Mr. Costello?

MEMBER COSTELLO: Yes, I don't think that whether or not training dropped from 700 to 80 hours would make more authorized users is really the right question. I think the question is what's the appropriate training experience for people providing therapy? Okay. Because I don't think it's our business to have more people using Zevalin or fewer people using Zevalin. It's to make sure that the people who are providing this therapy have the appropriate training and experience.

And I think that would be a perfect charge for our Subcommittee because I don't think it's something that you can just calculate on the back of a piece of paper and say, well, it should be the root mean square between 100 and 700. It's something that requires thought from the type of people doing the Subcommittee. So, I don't think we should be doing it to create more authorized users. I think we should be doing it to get the training and experience requirements

right.

CHAIRMAN THOMADSEN: Thank you, Mr. Costello.

Dr. Alderson?

VICE CHAIR ALDERSON: I'll yield to Mr. Mattmuller and then I'd like to speak.

MEMBER MATTMULLER: Okay. I just want to second what Frank said, because that's exactly what I was going to say, is what are the appropriate hours for this therapy?

CHAIRMAN THOMADSEN: Thank you.

VICE CHAIR ALDERSON: Okay. So, yes, I was driving at the same thing with my earlier comment, and I appreciate that comment. And so, in thinking about this, I'm not going to give you all the details, but I started thinking about this. Well, what would that require? Could a Subcommittee of this group do that? And what would that require and how would you document it and so on?

And then I ask yet another question, which is the one I'd like the NRC to entertain, is, well, is this the NRC's space? Is this where the NRC should be in recommending educational requirements, or should this be graduate medical education organizations and specialty societies and other people who document these

things? I don't know.

But I share your concern. If there were a really rigorous training program that was less in time -- I have no particular thing about 700 hours, but I don't think it's been demonstrated that the shorter courses really achieve that goal. And then again, the question is, so, whose business is that? Should we even set up a Subcommittee if that's not the NRC's business to do? I don't know.

CHAIRMAN THOMADSEN: Mr. Bollock?

MR. BOLLOCK: Well, yes, the -- it is -- because it is in our regulation. So, but we would have to reach out to medical community and you. So we wouldn't come up with that to make that determination. We would rely upon, as I said, the medical community and the ACMUI to advise us to make those changes. But it is in our regulation, so it is in our purview.

VICE CHAIR ALDERSON: So let me say then, so the NRC would welcome advice on that issue if it were to come from this Committee?

MR. BOLLOCK: Yes.

VICE CHAIR ALDERSON: Okay. Thank you.

CHAIRMAN THOMADSEN: Yes, just yesterday as I was talking with the Commissioners, they welcomed input into that. That's definitely something that we

are the people that should making such a recommendation.

VICE CHAIR ALDERSON: Good. I support that recommendation of a Subcommittee.

CHAIRMAN THOMADSEN: Yes. Michael, do you have your hand up?

MEMBER O'HARA: No, I was going to ask a question. Who came up with the 700 hours?

(Laughter.)

MR. BOLLOCK: I don't know if I can defer to many of my staff that recalls where that came from.

CHAIRMAN THOMADSEN: Yes, Mr. Ouhib?

MR. OUHIB: Yes, Zoubir Ouhib, medical physicist. I think I'd like echo several people here. Actually your comments were right on the money Dr. Palestro, Frank, and so on.

I think these are two different issues, and the first one is you focus on the training. And I like your comment, because that was on my mind, who came up with the 700? But I also like your original comment that says, well, let's start first with what is needed? Let's work into is that 73.5 hours, or is that 89 hours, and so on and so forth.

Now, to go back to what Dr. Palestro said, we experience the same thing. Bexxar came and Bexxar went out, or took a nap. Zevalin came and Zevalin took

the back seat. Here is Xofigo here, and it's taken off. But I foresee the same scenario what happened. We saw a decline using these. We use more Xofigo now, but I don't really foresee this being a hot commodity probably in 5 to 10 years from now. Who knows? We'll probably see the same track.

So, I think we need to separate perhaps these two and then resolve the first one, which is the training issue and identify what exactly is needed and can it be done efficiently, in a reasonable time perhaps, but people have to meet those requirements basically.

And then, as far as this training here, I'm not really sure if there is a lack of users per se. I mean, I've heard some clinicians saying that there's toxicity they're seeing using certain radiopharmaceuticals and they simply don't feel like using it anymore. And so, those are all my comments.

CHAIRMAN THOMADSEN: Thank you for that.

Other comments? Mr. Costello, you've had your hand up.

MEMBER COSTELLO: I did. We don't know why it's not being used more. We don't. There are many, many nuclear medicine physicians out there. I don't know if they're all even seeing these patients.

I mean, I don't think they naturally see these patients in the course of their treatment. They're mostly seeing their oncology physician, medical oncology physicians. And it's not our problem to figure out why they're not seeing these patients.

If medical oncologists want to be the ones actually providing this treatment, if they're the ones normally dealing with these patients, that's the people with Hodgkin's lymphoma, the non-Hodgkin's lymphoma see, then what's the proper amount of training for someone who has that specialty? I don't know. It may well be more than 80 hours that you expect with cardiologists, because this is a therapy as opposed to a diagnostic treatment, but I don't think that's our -- I think we should do what the NRC does, is decide what's the training so this could be done safely.

And this Committee I think is the best place for the NRC to get that recommendation, although they also get recommendations from the public. I'm sure the NRC, if they get information from the various societies and such, that you'll review those recommendations and take that into account as well. But I think that's the only way we're going to come up with the proper T&E requirements is from this Committee and recommendations from the various societies.

CHAIRMAN THOMADSEN: Thank you. Mr. Bollock?

MR. BOLLOCK: Yes, this was the rulemaking that came out in 2005 I think that established this, so the whole process, going the ACMUI, going to public comment, that's -- I don't know where, but it was determined back in that space, the 700 hours, is where it came from. So we didn't just -- it didn't just drop from the sky.

So, but for something like this to change it, we want what's best. What's the appropriate training? So it would have to go through that process. And I think the Subcommittee and what you would recommend to us would be a great start for that, but it would have to go through that public comment, go out to the entire medical community, have everybody have their say. And unfortunately, that is through -- this is in the rules, so this would be rulemaking. And because this issue isn't just straightforward, change it from 700 to 80, it's going to take a determination of what is correct. And so, it is a little bit more complex than just changing it. We realize this and we would rely upon you and the medical community to inform that.

CHAIRMAN THOMADSEN: Yes.

MEMBER COSTELLO: I was hoping, if we were

to change it, we could avoid rulemaking, okay, because of obvious things. Is there a way to do something under the auspices of 35.1000 where it's then in guidance space and you don't have to go through the process of rulemaking?

CHAIRMAN THOMADSEN: Actually, right now I think I would like to defer the question --

MEMBER COSTELLO: Okay.

CHAIRMAN THOMADSEN: -- of how any changes --

MEMBER COSTELLO: Sure.

CHAIRMAN THOMADSEN: -- should be implemented until we know if there --

MEMBER COSTELLO: Whether?

CHAIRMAN THOMADSEN: -- whether we would want to recommend --

MEMBER COSTELLO: Fair enough.

CHAIRMAN THOMADSEN: -- if there are changes.

And I think we -- oh.

DR. YANG: Sorry.

CHAIRMAN THOMADSEN: Yes?

DR. YANG: Sorry. I'll just make a comment about other therapies. So, one of the things that was mentioned is that there other therapies

available and oncologists are choosing other therapies. The other agent is Dilsilibs Idilic which was recently approved for a very similar indication or the same indication. So the one thing that I would say is that it may be not toxicity. You mentioned that Zevalin has toxicity and the toxicity profile is driving decisions. I would say that it is actually access.

So as an oncologist who's treating someone with follicular lymphoma, Zydelig is just a prescription. Now, remember that patient has to stay on that medication daily and it's associated with toxicity. A third of the patients will develop diarrhea. Whereas Zevalin does have mild suppression, but it's transient and it's one sort of therapy and then done. And so if I was looking at the toxicity profile, I don't know if that would be driving my decision or the fact that if I'm in a rural area it's hard for me to find an authorized user that will allow the patient to get access to that therapy.

So, in terms of training hours, again I'm not an expert on this, but the 700 hours versus the 80 hours, the one thing that I would say about Zevalin is that is a beta emitter. It comes as a single ready-to-deliver dose where it can be injected by the physician. In comparison, if you look at other

radionuclides that are treated by other physicians, iodine-131 I believe only requires 80 hours of training. And that's a gamma emitter delivered by an endocrinologist for thyroid disease.

And so, the question here is I just don't see Zevalin being 10 times riskier that iodine-131.

CHAIRMAN THOMADSEN: Thank you. I think -- oh, last comment maybe.

MEMBER MATTMULLER: I've got a comment and a question. And am I allowed to --

CHAIRMAN THOMADSEN: Oh, in that case, maybe it won't be the last --

(Laughter.)

MEMBER MATTMULLER: Am I allowed to ask a member of the public a question? I have a question for Dr. Cultrera.

CHAIRMAN THOMADSEN: You may.

MEMBER MATTMULLER: Your colleague Dr. Mace, does he work with a nuclear medicine technologist in handing the radioactive material before it's administered to a patient, or is he working just by himself?

DR. CULTRERA: I believe that he works by himself because it comes in a prepackaged syringe. I don't have all of the data on that. I know we have a

nuclear physicist in that group where he is in that practice because we have the PET/CT scanner there and they aid in administration of the nuclear diagnostics with that. But I believe because it comes in that prepackaged syringe he's able to administer it based on how his training was.

MEMBER MATTMULLER: Okay. Well, I know there are some on this Committee whose bias is towards medical physicists be present for his therapy, but it's really in my opinion the technologist who would perform a much bigger role in the safe use of these radiopharmaceuticals.

CHAIRMAN THOMADSEN: Thank you for your potentially biased comment.

(Laughter.)

CHAIRMAN THOMADSEN: With that, I think we'll draw the discussion to a close, and I would like to thank the Subcommittee for their report. And I think one thing that the report has brought out and this discussion has amplified is that we really cannot say and will not be able to say why the use of this radionuclide has decreased, whether it is lack of authorized users or other factors.

I did look at the question of how many places could be doing this in Florida, and rather than

the 15 on the map, I do count 20 nuclear medicine departments that employ medical physicists. I'm sorry I did not check how many employed technologists. And 45 radiotherapy facilities that employ medical physicists giving 65 potential places throughout the State that could deliver this therapy if they chose. And it's not available they are choosing not to for reasons we do not understand.

But I will task the Subcommittee further with the question of establishing recommendations for beta and alpha emitters as far as training and experience that would be necessary to provide the therapy safely and effectively, understanding that training is one thing and experience is another, and both are separate and necessary for the safe and effective use of anything. And just the lack of opportunity does not necessarily translate into the need to reduce the necessary training and experience. We certainly would not, if they did not have neurosurgeons locally, recommend that general practitioners with a few weeks of training should start doing brain surgery.

If the Subcommittee will accept the expansion or redirection of their charge, we'll ask them to study this and report back at the next meeting. Is

that compatible? Yes, Dr. Palestro?

MEMBER PALESTRO: For clarification --

CHAIRMAN THOMADSEN: Please.

MEMBER PALESTRO: -- the charge is being changed, and I correct?

CHAIRMAN THOMADSEN: That is correct.

MEMBER PALESTRO: Okay.

CHAIRMAN THOMADSEN: It seems that you have done as much as you possibly can to come up with the answer to the question that you were sent to look at last time, but you raised -- or at least the issue has raised the question of what is appropriate training and experience for the use of these materials, recognizing that you're not -- because it's going into regulation possibly or something similar to regulation. We're looking at a class of materials of which those that are in use now are just examples and we do not know what's coming up. They may be different and they may be the same, but we would want to make sure that anything that would fall in that category would be appropriately addressed by the training and experience recommended. Does that make sense?

Yes, Ms. Weil?

MEMBER WEIL: One more clarification.

CHAIRMAN THOMADSEN: Yes.

MEMBER WEIL: So this is in rulemaking space now?

CHAIRMAN THOMADSEN: No, not necessarily?

MEMBER WEIL: Not yet? So we're going to make a recommendation that might impact rulemaking space? Is that where we're going with this?

CHAIRMAN THOMADSEN: Perhaps.

MEMBER WEIL: Okay. So the rulemaking period ends soon?

CHAIRMAN THOMADSEN: Never.

MEMBER WEIL: Well, there's --

(Simultaneous speaking.)

CHAIRMAN THOMADSEN: It goes on longer than we --

(Simultaneous speaking.)

MR. BOLLOCK: Okay. There's a current rule that's actually back with the ACMUI Subcommittee for the Proposed Final Rule, and there's a public meeting I believe what, January 6th. It was just publicly announced. So January 6th will be the next ACMUI public teleconference to address that. And then after that we will have a final proposed rule that will go to the Commission and at which time, early 2016, the rule will be going out.

MEMBER WEIL: So this issue does not fit

into that bunch?

MR. BOLLOCK: Right, because it's -- we would have to go -- if we're talking about what is in the rule right now with the training and experience, the 700 hours versus 80 hours -- and it is more complex. Like I said, it's not a simple we can just say, yes, this is right, this is wrong. We would need advice from your Committee to even get to any kind of change. Yes, it would be a complex change. And if we put that into the rule, it would then delay --

MEMBER WEIL: The whole thing?

MR. BOLLOCK: -- because it has to be vetted through you all, the entire public, medical community, everyone and go back through public comment, go back through resolution because of the complexity of it. And it would delay the final rule, the proposed rule we have now that you all -- that the Subcommittee was -- or that was just sent at least a year-and-a-half, which would then delay any relief that the current proposed rule gives to the medical community.

CHAIRMAN THOMADSEN: How long has the current proposed rule been in the making?

MR. BOLLOCK: 2011, I believe. Is that right? Yes, 2011.

CHAIRMAN THOMADSEN: That would be the

starting -- when this one is finished is when you're talking about starting the process again?

MEMBER WEIL: So, it's several years out that one could envision any potential changes?

MR. BOLLOCK: I mean, if this -- yes, it's dependent upon the complexity of the issue, how many different sides there are, the different views on what the proposed changes are. That all goes into the length of --

CHAIRMAN THOMADSEN: And my guess is this is a complex issue.

Mr. Costello?

MEMBER COSTELLO: Yes, just a comment on the rulemaking aspect of it. Rulemaking is normally done in a batch process. Particularly a complex rule like Part 35 that a bunch of things are changed at once. I believe the impetus for the current rulemaking goes back to a 2005 recommendation from the Commission to switch from a dose-based rule for prostate implants to -- and now it will probably become final in 2016, which is 11 years. So just to put that in context.

The other thing I would note, when you look at on the ACMUI recommendations and actions, that there are some that are delayed, I mean, some that are open but delayed, that will be captured in the next

rulemaking. And some of those recommendations go back to 2008. Okay? So, I really hope -- and really, this is a how rather than a whether, I understand that, Dr. Thomadsen, but I really hope we can manage to handle this in a way that doesn't require rulemaking.

CHAIRMAN THOMADSEN: Thank you. Yes?

MS. LEE-ROWLEY: If I could just echo what --

CHAIRMAN THOMADSEN: Your name, please.

MS. LEE-ROWLEY: Angelique Lee-Rowley from Spectrum Pharmaceutical.

CHAIRMAN THOMADSEN: The transcriptionist has to identify --

MS. LEE-ROWLEY: If I could echo what Mr. Costello just said. Spectrum had been waiting patiently for an open rulemaking period to try to address this issue, so my issue is two-fold. One, Zevalin in particular will not make it to another rulemaking period if it continues on the trajectory it's on. And secondly, there are other companies and institutions, academic institutions currently developing new radiotherapeutics that are watching very closely what transpires here and as to whether they -- and how robustly they continue that research into additional alpha and beta emitting

radiopharmaceuticals. And it would be a shame to see those never come to fruition as options for patients because of the training and experience.

CHAIRMAN THOMADSEN: Thank you for your comment. Mr. Bollock?

MR. BOLLOCK: And as far as new radiopharmaceuticals in development that come out, if they fit into our current regulations, as I believe Zevalin, then it goes to what's in the regulations. If it does not fit, it may fall into 35.1000 space, which Mr. Costello has touched on a few times today, and which because it's new, it's outside of what's already in the regulations, we could develop guidance and everything at an accelerated rate. So it doesn't
-- but unfortunately my understanding right now is that with Zevalin it does fall into our regulation as it is, so that's why it falls under the 700 hours.

CHAIRMAN THOMADSEN: Thank you. And thank you, Dr. Palestro. I think -- yes?

MEMBER PALESTRO: I'm going to ask for one more point of clarification.

CHAIRMAN THOMADSEN: Yes.

MEMBER PALESTRO: In terms of our charge --

CHAIRMAN THOMADSEN: Yes.

MEMBER PALESTRO: -- does this encompass only therapeutic radiopharmaceuticals, number one? And number two, if so, is our charge limited to intravenous administration of these therapeutic agents, or does it include, for example, oral administration of I-131? Are we being asked to revisit that?

CHAIRMAN THOMADSEN: I think at the -- you don't have enough to do?

(Laughter.)

MEMBER PALESTRO: I just want to know my assignment.

(Laughter.)

CHAIRMAN THOMADSEN: I think at the moment it would be enough to look at the use of the alpha and beta emitting radionuclides and their appropriate training. I don't know that it would be limited to intravenous and that that would not be the case with the regulation. I think I would leave iodine to follow if you find that there should be any change here. Then that would be for another round of discussions to take that up.

MEMBER PALESTRO: Thank you.

CHAIRMAN THOMADSEN: That's fine?

MEMBER PALESTRO: Yes.

CHAIRMAN THOMADSEN: Yes. Okay. Right now we're supposed to be breaking for lunch. We're running behind. It's been a very useful discussion and a very important one. I think we've had to say everything that has been said. But let's go on and try to finish up if we can relatively quickly with the Radioactive Seed Localization Subcommittee report.

MEMBER ENNIS: Good morning, everyone. I hope you're not crashing from sugar and caffeine depravation and we can have a discussion about radioactive seed localization. I want to first thank my fabulous Committee members: Drs. Alderson, Zanzonico and Mr. Costello. We've really I think had a great time working together on this issue and a lot of good discussion has come out.

In terms of background, most are aware, but some may not, so we will briefly review. A procedure of placing radioactive sources into tissue to guide procedures such as biopsies has been developed in the early 2000s. Started off being used for breast cancers. NRC had its first guidance issued in 2006 and requests from users stimulated a review. The ACMUI formed a Subcommittee which presented in a June 16th meeting its findings. After further discussion among the larger Committee and the users, the Subcommittee

went back to make revisions. And I'm here to kind of prevent -- not prevent --

(Laughter.)

MEMBER ENNIS: -- excuse me, to present the whole presentation again with a focus on the changes that we have made since June.

Nicely RSL has increased. Interestingly, its uses are reportedly expanding to other sites beyond breasts, at least to the axilla, which is the same type of interests that are involved in that, but there's reasons to think in some case reports of it being used elsewhere in the body. And certainly we can envision that happening. It's usually used with radioactive seeds that are the same type that are used for brachytherapy procedures, although with slightly lower activities. And the dose to the surrounding tissues is very low, particularly if they're removed by the procedure, the biopsy or the surgery shortly after placement.

One of the main issues that was brought and that has been discussed at length, and probably will be again, is the authorized user. What are the requirements for an authorized user? The complexity involves the fact that physicians who are expert at placing needles into breast tissues, as an example, but

could apply to other tissues, to put wires and clips for all kinds of procedures and could potentially be used to put radioactive materials into these tissues to guide the procedures are generally radiologists, some of whom, but not all, have the training to be an authorized user. And that presents a conundrum for those who do not because they really only have the training for half of what they kind of need to do, at least by the current regulations.

Acquiring that training for someone who is in practice as a radiologist would be almost impossible. Very, very difficult. And hence, a question has been raised whether the authorized user rules could be modified. On the other hand, there is an understanding on the Subcommittee that there's a reason for those needs in training and the interaction between radioactivity and tissues in the body, particularly radioactive materials that have a high dose close to them, particularly if things don't go smoothly and things are not removed in a timely manner or don't end up in the right place and how one deals with that in a safe way, requires a high level of expertise and understanding.

There are some other specific things that are slightly more minor than that conceptual one that

the Subcommittee has modified, and they include the following: That the training requirements be modified such that someone who would be an authorized user no longer would need to be supervised for cases by a 35.490 user; i.e., the radiation oncologist, but could also be a -- by a 290 user who is already him or herself an authorized user for this procedure. That seemed quite logical and appropriate.

Some again more minor changes about work experience requirements. So for example, the authorized user is only putting in the sources, so his or her training about removing the sources is not necessary, although it had been stipulated as such in the first guidance. Similarly, the surgeon doesn't have to worry about the placement of the sources since it's being done by the radiologist and therefore training around that is unnecessary. So that should be removed in our opinion.

The second big topic is the written directive and the need or not for such. There was a suggestion that perhaps it was unnecessary. The Subcommittee does not agree with that. The Subcommittee feels fairly strongly that a written directive is required. It should be tailored to the specific procedure and the requirements modeled after

others would be, as in one and two, that before the procedure there be a written directive that says where in the body -- the site; that is, where in the body that it will be implanted: left breast, right breast, kidney, etcetera, what isotope is going to be used and the activity that isotope. And then afterwards really what isotope was used, where it was placed, how many sources, the total activity implanted and the planned time until the source is removed.

These would then inform a medical event. Medical event requirements here are fairly standard for these types of things. So if you put in the wrong radioactive material, you put it inside the wrong person, you -- wrong part of the body. And again, it's 20 percent more activity than you intended or 20 percent longer than you activated, or a leaking sealed source. And any intervention which leads to serious unintended permanent functional damage would also need to be considered a medical event.

Regarding safety, there are some recommendations that we've come back with, modifications based on the June meeting that we thought were reasonable. One is that we no longer recommend a requirement that the radioactive source's measurement be done by the user, but would allow the manufacturer's

reported activity to be used as the activity for the user. That's number one.

The second issue was somewhat discussed at length, I believe, last meeting and that had to do with whether radioactive survey is required at the removal or whether an X-ray, which would see the seed, would be adequate. And the Subcommittee feels that a radiation survey is necessary to verify seed removal. Other clips could potentially confound or confuse an X-ray and the risks are too high to take that chance in our opinion, and we do feel that a radiation survey is required. However, we do not feel the need to be so precise in definition of what type of radiation survey meter is used and how its calibrated, which had been in the prior requirements, and we would recommend that that be removed and just state simply that you have to use a portable properly calibrated survey instrument capable of detecting the type of radioactivity that the source emits.

In terms of safety, we feel that issues regarding ruptured sources that are in the guidance ought to remain, although it's a rare and has already been reported event and therefore warrants maintaining them.

We do recommend some wording regarding

breastfeeding specifically that be included in the new guidance and say that first that a patient be advised not to breastfeed from the breast in which the source is implanted until it has been surgically removed. And then number two, if it's not going to be removed for some reason or it ruptures, then patients ought not breastfeed from that breast for 10 half-lives. And we also recommended written policies be developed for these scenarios as have been discussed previously.

Kind of more minor are wordsmithing issues just to make the guidance consistent with the realities of time. Any words about therapy or brachytherapy ought to be removed since it is not that. Dose be removed because we're not trying to deliver dose. It's an activity and the medical events are determined by the activity, whether you did what your written directive said.

And a final thing that is also of importance though is that we clarify that seeds being returned to the supplier be allowable. And also that is a change and seems a wise one.

Again a relatively minor thing, but the prior guidance said that the staff had to be trained about how to take care of patients including types of patients who are not going to be discharged from the

hospital, but that would never really happen with this procedure, so that kind of training is not necessary and ought to be removed from the guidance. We suggest language that is not specific only to breast, can use breast as an example, but make it clear. And in our thinking about this our Subcommittee was trying to be clear, anticipating wider use in other places in the body.

And lastly, and again a reminder, since it's now approved by FDA for use, as that was not the case in 2006, there should be changes to the guidance in the Change of Physical Conditions of Use section.

I believe that concludes my presentation, but I would be very happy to discuss any aspects.

CHAIRMAN THOMADSEN: Thank you very much, Dr. Ennis.

Questions or comments? Ms. Weil?

MEMBER WEIL: On slide No. 8, "a licensee shall report any event except for an event that results from patient interventions" --

MEMBER ENNIS: Yes.

MEMBER WEIL: -- this is interesting to me because it goes back to the other Subcommittee's definition of patient intervention. On the recent NMED database there were several instances cited of patients

who failed to return for removal of implanted seeds. And there were corrective actions alluded to, which I assume; it's an assumption, implied that there was insufficient education to the patient about the need for returning for the removal of the implanted seed.

And it strikes me that here we have an example of patient intervention, patient didn't come back, but it does need to be reported because it falls into the art of medical practice, whereas I think this is important. I think it's important to note that the patients were not appropriately motivated to return in a timely way to have the seed removed. And if there's anything that could be done on the physician side to appropriately motivate them to come back, I think it should be reported as a medical event. It's not patient intervention.

MEMBER ENNIS: It's an interesting point. It gets to the root of our prior conversation. If one is looking at a medical event from the perspective of the authorized user did something inappropriate and --

MEMBER WEIL: Or failed to do something appropriate.

MEMBER ENNIS: Fair enough. Then people would not want to view that as a medical event. If it leads to corrective action, I see there's a potential

gain to be said by that.

CHAIRMAN THOMADSEN: Dr. Dilsizian?

MEMBER DILSIZIAN: Yes, I agree, Laura. That's a great comment. And I guess I see this two ways: One is education to the patient; one is compliance. And I think education is a must. It should be part of your directives. And the non-compliance received also in medical practice recommends that the prescriptions. They may not take it. They may not follow up with medical therapy. You ask them not to eat salty meals. They may come back with heart failure. So that's a problem.

So given, however, the implications of this, I would be for having a follow-up with a patient of access by phone call or something to document that the patient was followed up over the next 48 hours or so if the patient did not return. I think that would be an important part of the directives, just like you do bioassays and make sure to follow up with I-131 therapy. I would be in favor of that because -- to kind of complete the circle.

CHAIRMAN THOMADSEN: Thank you. Other comments? Yes, Mr. Mattmuller?

MEMBER MATTMULLER: I have questions and comments for you. And one may be my institution would

be a test case because we've not yet to do these, but we're looking at them.

So people are asking who assays the seed and who retrieves the seed? And are the current seed manufacturers very generous, or they have an easy seed return program so disposal is a little bit easier rather than holding it for decay?

MEMBER ENNIS: So in terms of specifics of how the programs work, you may want to talk to users who have the programs. Mr. Sheetz who has been here before might be a great resource for you. My institution does not do this. My understanding is that some of the manufacturers do do the assays for you and do have -- allow -- welcome returns.

CHAIRMAN THOMADSEN: All the seed manufacturers assay the seed before they send it.

MEMBER MATTMULLER: Okay. So most sites then just rely on label calibration? And so there's not --

CHAIRMAN THOMADSEN: That is what this report is recommending --

MEMBER MATTMULLER: Okay. Yes.

CHAIRMAN THOMADSEN: -- since the goal is not to give a dose -- the precision and the accuracy of the calibration of the seed is not of paramount

importance.

MEMBER MATTMULLER: Okay. I agree.

CHAIRMAN THOMADSEN: Dr. Zanzonico?

MEMBER ZANZONICO: Could I point out that the way the seeds are packaged really is not compatible with a reliable independent assay. They're provided in a sterile catheter sort of thing, and so it's really not the geometry that's compatible and reliable anyway. So you really want to rely on the manufacturer's assay in any case.

CHAIRMAN THOMADSEN: And that is a problem that also occurs in prostate brachytherapy with seeds that are in sterile needles.

Mr. Mattmuller?

MEMBER MATTMULLER: I'm glad you made that statement in regards to the actual calibration isn't that important, because that was my concern with the one medical event criteria, that the activity must be within 20 percent. That seems rather arbitrary because as I understand it you could have a planned procedure where it's the properly calibrated seed for up to seven days, and to me that wouldn't make much of a difference if you had a seed that was over 20 percent but only in for one day. I mean, the procedure itself would still be completed properly.

MEMBER ENNIS: Yes, I mean, this is a tricky area. The 20 percent is something we've inherited essentially that's out there as a definition for medical events in similar settings. And we were not able to come up with a better definition that would still create a space of what would be reasonable to do and what is not safe.

CHAIRMAN THOMADSEN: Any other comments? Yes?

MEMBER MATTMULLER: Again, are we limited by what's -- I mean, do we have to use that 20 percent --

CHAIRMAN THOMADSEN: No.

MEMBER MATTMULLER: -- for all?

CHAIRMAN THOMADSEN: If you have something else to propose now -- I mean, you would not want it to be 100 times what you propose, I mean, what you've prescribed.

MEMBER MATTMULLER: Well, I mean, because there's another in the medical events as far as 20 percent longer than planned. And it seems like one of the great advantages of this procedure is that once it's implanted it can be there for a day, it can in there for seven days. So if the original plan was for a day but for whatever reason it goes to two days, which would be

more than 20 percent than the original plan, 24 hours, again that seems rather arbitrary to say, oops, that's now a medical event. And it almost seems like it limits one of the advantages of this very useful procedure.

CHAIRMAN THOMADSEN: Dr. Alderson?

VICE CHAIR ALDERSON: Yes, I was a member of the Subcommittee and I'm sort of remembering some of the debates we had. I don't think this Committee or any committee can regulate the kind of things you just talked about, Steve. I mean, the local group has to make its own decision, make its plans appropriately. I think the reason that we're more rigorous here than we might have been in our earlier discussions is because in this case a radioactive source which is being used just for localization is being put into a patient and it's going to stay there. And if you don't follow up on these things this way, what if that patient, a woman, later develops another breast cancer and you didn't ever worry. She just -- she's, well, I never came back. They didn't tell me it was a problem.

And so, now the liability -- there's a health issue and a liability issue. So we're being more rigorous here. So I think the Committee thought we had to be more rigorous and I think that's why this is that way and why it's somewhat perhaps you might feel

inconsistent with our earlier discussions. It's a special case.

CHAIRMAN THOMADSEN: Mr. Costello?

MEMBER COSTELLO: I think we're trying to get away from dose, when you say we're taking dose out of here. And so, putting the activity and the time is somewhat the surrogate for those. Right? And I'm okay with that. I would imagine that when they have the written directive they can take that into account, maybe when they put it down. And maybe with the time they could be a little generous in how long it could be. But that's how we got there. It's a surrogate for dose.

CHAIRMAN THOMADSEN: Yes, my guess is most practitioners will be very generous on the time that they --

MEMBER COSTELLO: I assume that they will, yes.

CHAIRMAN THOMADSEN: Other comments?

(No audible response.)

CHAIRMAN THOMADSEN: Do we have a comment from the -- yes?

MR. SHEETZ: Yes. Hi, Mike Sheetz, radiation safety officer at University of Pittsburgh. We have a very active RSO program. We do about 100 -- or a 1,000 cases per year. I want to thank the

Subcommittee for reviewing the RSL guidance document. They have a lot of good recommendations. However, I have three comments on some issues that I think warrant some further consideration.

One is with respect to you've outlined the pathway for an authorized user. That's good. You've identified what training should and should not be included for the surgeon removing the lesion and for the pathologist or pathology assistant extracting the seed from the specimen, but you haven't addressed training and experience requirements for the radiologist who doesn't meet the AU requirements as you've identified, but should be able to implant seeds under the supervision of an authorized user as permitted in 35.27 and as is done in lots of other diagnostic procedures in nuclear medicine.

The other one is in the written directive as we discussed here, the requirement of the seed being left in 20 percent longer. That becomes problematic in that if the surgery is scheduled that day, say five hours later. If the surgery goes six hours later, it becomes a medical event. So there has to be -- and then 5 hours for a 24-hour survey. So there has to be some other criteria there.

I know you wanted to eliminate dose, but

maybe you want to go back to dose to the tissue and a conversion provides -- you get those tables and you take one centimeter for the seed for the activity and should that dose exceed say 50 rads or a current tissue dose threshold for a medical event, then it would be appropriate to report as a medical event. But just leaving it 20 percent longer than the plan will be problematic because surgeries are changed all the time.

The other is there was a question on the 20 percent of the activity prescribed. Typically, we prescribe a dose range. So you may want to add outside of the dose range. And our dose range is 50 microcuries to 250 microcuries.

CHAIRMAN THOMADSEN: When you say "dose," you mean activity?

MR. SHEETZ: Activity. I'm sorry. Thank you very much.

(Laughter.)

MR. SHEETZ: We prescribe an activity of 50 microcuries to 250. And most institutions will do that. The seeds are supplied, you know prepacked, sterilized in a needle. They come with a shelf life of 90 days due to their sterility from the company and from FDA approval. And someone will basically keep that for the full 90 days so not to endure that cost. And so

they'll have a range of activities that's appropriate. And anywhere between the 300 and 50 is appropriate for doing this study.

CHAIRMAN THOMADSEN: Why would you not just use the activity on that day when you implant it?

MR. SHEETZ: We do state that in the record, but as far as a prescribed activity we have a protocol in the prescription just like we would do for lung scans. Lots of our nuclear medicine studies we prescribe a dose range, not a dose activity due to the short half-life of the nuclear medicine.

MEMBER ENNIS: But again, if you have the isotope and you survey it the day you're doing the procedure, then your written directive would reflect the activity of that day. I don't know why that would be a problem.

MR. SHEETZ: Yes, that's okay. I mean, I guess that's workable.

CHAIRMAN THOMADSEN: Lung scans don't need a prescription. They're following a protocol. That's all. But this doesn't --

MR. SHEETZ: This has a written directive, so you'd --

CHAIRMAN THOMADSEN: A written directive, so that wouldn't --

(Simultaneous speaking.)

MR. SHEETZ: So, right. I mean, everybody uses a spreadsheet to evaluate the current activity of seeds so that does not become problematic.

And then the other was with the survey post-excision of the seed and that you identified using any instrument that you want because there's the Geiger counter, the sodium iodide probe and the gamma probe used for the survey. But most of these procedures are performed in conjunction with technetium-99 and sulfur colloid for sentinel node biopsy, and therefore that would preclude the Geiger counter or sodium iodide probe from being used because they cannot discriminate between the two isotopes.

And so, really the only instrument that would be able to be used for a survey post-explant would be the gamma probe where the surgeon would identify the seed in the specimen and what we do is identify -- you don't get a reading in the cavity where the specimen has been removed, but you still do get some signal from the gamma probe, even from technetium because it does scatter down into that window. So you'll never really be able to see small amounts of activity.

So then I go back to the radiograph. It gives you 100 percent confirmation that there is the

seed, the seed is intact and it's going to be much more reliable than a radiation survey. And radiologists are very trained to identify clips from seeds. That's what they do for a living.

And then in response to Mr. Mattmuller's question on disposal, there are two companies now with FDA approval for the prepackaged seeds and needles. One does accept the seeds back; the other one does not. So those -- using the one company will store them for decay.

CHAIRMAN THOMADSEN: I would take issue with anything giving you 100 percent confidence.

MR. SHEETZ: As was discussed earlier, the practice of medicine is an art. No, nothing is 100 percent.

CHAIRMAN THOMADSEN: Right. Dr. Alderson?

VICE CHAIR ALDERSON: I think when we had discussed this particular it; and Dr. Metter may wish to comment, I think that the interpretation of mammograms is an art, and it's very difficult, especially in patients who have a lot of fibrosis in their breast. And people also do post-op radiographs to find foreign bodies left in after surgery, and despite the fact that radiologists are very well trained

to do that, once in a while the conditions that are present in the body cause them to miss those things. So I just don't think that what you just said is correct at all. I disagree.

Dr. Metter, do you want to comment?

MEMBER METTER: There was an article recently in the *Journal of the ACR* that talked about radiographs of like surgeons that have instrument miscounts. And there's a 10 percent -- that's a fairly notable percentage that they miss them because they can't see them. Usually they're small needles that are about a centimeter or less. And so, you're looking at that sort of item.

And so, other institutions have instituted policy where they actually take a radiograph of a lost item and compare it with that. But that still hasn't been as effective. It's 100 percent.

CHAIRMAN THOMADSEN: Dr. Zanzonico?

MEMBER ZANZONICO: I also take some issue with the assertion that even in the presence of a post-sentinel node biopsy that a survey would not reliably find seeds. We're talking about a minimum of a 200-microcurie focal source. So you can take a background measurement or an initial measurement and you'll get some very significant count rate or exposure

rate and then verify that the exposure rate has gone down subsequent to removal of the seed. So I think there is some value certainly to doing a survey measurement to test for the removal and accounting for the all the seeds even in the presence of some significant background activity from a sentinel node procedure.

CHAIRMAN THOMADSEN: Dr. Ennis?

MEMBER ENNIS: No, I think we should open up. As Mr. Sheetz perceptively noted, we actually were not clear about what our recommendation was vis-á-vis the authorized user issue. And that is because the Subcommittee actually did not come to consensus. And there were two opinions. So one was that it ought to remain as is and that the use of a radioactive source and its interaction with human tissue requires a high level of training. And certainly for many cases where it goes smoothly and simply and everything goes properly, even for a lesser-trained individual such as a radiologist that doesn't have that full training would be fine, but part of regulation space is to really protect from those cases where things don't go so smoothly and that at least happen with some regularity and that that requires a higher level of training as is currently in the guidance.

However, others on the Subcommittee felt

that perhaps just supervision of an authorized user, even if the individual actually placing the seed was not one, would be sufficient. And I think the Committee as a whole ought to discuss it.

CHAIRMAN THOMADSEN: Yes, let's start -- well to follow the process, I assume that the Subcommittee is making a motion to adopt its report. We'll get that on the floor.

MEMBER ENNIS: Yes.

CHAIRMAN THOMADSEN: It doesn't need a second because it's coming from the Subcommittee. And now I think what we need is to have a particular motion that we can discuss as far as the authorized user supervision situation. What would you like to propose?

MEMBER ENNIS: I would propose a motion that we discuss the specific --

CHAIRMAN THOMADSEN: No.

MEMBER ENNIS: No? Sorry.

CHAIRMAN THOMADSEN: We don't need that.

MEMBER ENNIS: Oh, sorry. Okay. I would propose that the guidance remain intact and that the authorized user be -- the person who places the seeds be an authorized user.

CHAIRMAN THOMADSEN: Okay. Do we have a second to that motion?

(No audible response.)

CHAIRMAN THOMADSEN: We have no second for that motion. Would somebody like to make a counter-motion?

MEMBER COSTELLO: Oh, for the sake of discussion, I'll second the motion.

CHAIRMAN THOMADSEN: Okay.

(Laughter.)

CHAIRMAN THOMADSEN: Thank you. We have a motion, we have a second. Discussion, please? Those of you who didn't second the motion may want to tell why. Yes, Dr. Zanzonico?

MEMBER ZANZONICO: I mean, I think there's going to be a significant number of radiologists who are not going to be AUs, and those are the folks that are most experienced in placing these sorts of devices. One is not the dealing with high-activity sources where there's a real time pressure for corrective action if a source were lost or even misplaced or whatever. And given those considerations, mainly the logistical consideration that the folks most expert at placing these sources will most likely be radiologists and non-AUs and the fact that an emergent situation regarding the sources could be safely dealt with over a period of time I think is such that the person placing

the source does not need to be an AU.

What we do at Memorial is virtually none of our radiologists, who are the people who place these, are AUs. And what we have is have them proctor three cases where they're trained on radiation safety issues and -- they're proctored three cases where they go over radiation safety issues, so forth and so on. And then the department will authorize them or certify them as users. We haven't had any issues. And I think in general people would expect that it's going to be a very low frequency of issues in any case. But I just think the circumstances of this procedure are such that there's really not a compelling need to have the individuals who place the sources actually be AUs, but rather to work under the supervision of an AU.

CHAIRMAN THOMADSEN: And that is what we do at Wisconsin, likewise.

Dr. Alderson?

VICE CHAIR ALDERSON: Yes, I'd like to support that particular position. And I think that -- I was the Chairman of an large academic radiology department for 20 years and worked with a lot of great breast imagers, and I would want the patient to have the ability for those experts who do this sort of thing all the time to put that source exactly where it needs to

be. And I feel it's quite adequate for them to be working under the supervision of an AU.

MEMBER ZANZONICO: And I think it's important to point out as well those individuals do have a great deal of relevant training even though they're not AUs. It's not as if it's an internist or some person such as that with little to no training and experience in working with radiation generally.

CHAIRMAN THOMADSEN: Yes?

MR. BOLLOCK: Sorry. I apologize for interrupting this great discussion, but I just want to make you aware we're 35 minutes over.

CHAIRMAN THOMADSEN: Understood. Believe me, I've been watching that clock very carefully.

MR. BOLLOCK: Yes, and we should have some time the next presentation following lunch with that half hour for that. We don't believe it will take the full half hour. So I'm just making you aware we should have time in the afternoon to continue discussions if, at your discretion, you'd like to break.

CHAIRMAN THOMADSEN: Well, we should take care of this motion before we adjourn, although believe me, there are other pressing matters that I would like to take care of also.

Dr. Ennis?

MEMBER ENNIS: Yes, I just do want to at least, make the case. So, first, I would not certainly advocate that someone who is not good at placing needles do that just because he or she is an authorized user. I think what I'm looking for is people doing this who have both levels of expertise that are required.

And for example, under the guidance now if a surgeon wants to do this in a part of the body and he or she has absolutely radioactive training, but he's an expert at sticking needles into that part of the body, is that going to be okay? And I envision a lot of scenarios particularly outside the body where the source is going to be placed somewhere near a vessel, or might be, and not having a good understanding of how radioactivity interacts with these body tissues can lead to significant medical events. So, that's my source. When it goes smoothly in a breast, it's easy and it's fine, but I foresee potential medical events because of a lack of understanding of that aspect of it.

CHAIRMAN THOMADSEN: Other comments?

(No audible response.)

CHAIRMAN THOMADSEN: Hearing none, we'll vote on the motion, which is -- can you restate the motion?

MEMBER ENNIS: Oh, the motion that was accepted was --

CHAIRMAN THOMADSEN: Yes. Right. Exactly. Which was that the person placing the sources --

MEMBER ENNIS: That places the source be allowed to do that under the supervision of an authorized user.

CHAIRMAN THOMADSEN: Oh, I thought it was exactly the --

(Simultaneous speaking.)

MEMBER ENNIS: No, my motion was not seconded.

CHAIRMAN THOMADSEN: I think the --

MEMBER COSTELLO: I seconded it.

MEMBER ENNIS: Oh, you did second it? Okay. So, my motion was that an authorized user must be the one placing the sources.

CHAIRMAN THOMADSEN: Correct. And that's as I remember it. All in favor, say aye?

MEMBER ENNIS: Aye.

CHAIRMAN THOMADSEN: All opposed, say no?

(Chorus of no.)

CHAIRMAN THOMADSEN: Abstentions for that?

PARTICIPANT: I abstain.

CHAIRMAN THOMADSEN: One abstention. That has been voted down. Do we have another motion on this since we need to come to resolution? Anybody? Yes, Dr. Alderson?

VICE CHAIR ALDERSON: Well, I want to move, but what I think Pat was saying is that the person who places the seed should be under the supervision of an AU, but they need not be themselves an AU.

CHAIRMAN THOMADSEN: Is that --

MEMBER ZANZONICO: Yes.

CHAIRMAN THOMADSEN: Do we have a second for that?

MEMBER ZANZONICO: Seconded.

CHAIRMAN THOMADSEN: We have the second for that. Discussion? Ms. Weil?

MEMBER WEIL: So, under the supervision, does this mean in the same room, or does this just mean that -- that doesn't mean that?

CHAIRMAN THOMADSEN: Not necessarily.

MEMBER WEIL: So, that is of course another opportunity we could explore, whether the placing of the seed could be done by someone who's not an AU. If the AU is in the room directly supervising reminds me a little bit of the Gamma Knife in the Perfexion units

where you want the authorized user in the room at the console.

MEMBER SUH: That is a little different because you're talking about therapy versus diagnosis purposes.

MEMBER WEIL: Okay.

MEMBER ZANZONICO: I mean, right, just to echo that comment, again we're talking about low-activity, long-lived sources. So you have the luxury of time, of a considerable amount of time to deal with an issue that you don't have in the case of Gamma Knife.

CHAIRMAN THOMADSEN: Other discussion? Yes, Dr. Metter?

MEMBER METTER: With the ACGME; and, Chris, you can correct me, they have definitions of supervision, direct or indirect supervision. And my question would be if you have an individual who is not an authorized user, should they have for example three cases with direct supervision, then followed by indirect supervision just so that they can -- for the first time you should actually have somebody who might understand the radiation safety aspects of things.

CHAIRMAN THOMADSEN: And that was the situation that Dr. Zanzonico discussed and that we have in the University of Wisconsin. We have a comment.

MR. SHEETZ: Mike Sheetz again. We have the same type of program as Dr. Zanzonico has at Memorial Sloan Kettering. We have our authorized users and then we have approved radiologists who can implant seeds under the supervision of the authorized user. The individuals who implant seeds under the supervision, I think, one, should be a radiologist. They can't be a surgeon. They can't be an internist. And they also have to have radiation safety training on the procedure and they also have to have supervised case study requirements. That's my recommendation.

CHAIRMAN THOMADSEN: Would you accept as an amendment to your motion that the person implanting the seeds would have to have the typical 80 hours of radiation safety training plus three proctored courses by the supervising authorized user?

VICE CHAIR ALDERSON: What do you think, Pat? I'm not sure.

MEMBER ZANZONICO: I would not go as far as that as all.

VICE CHAIR ALDERSON: Yes, I think that's too far, also.

MEMBER ZANZONICO: Yes, I think that's too far.

VICE CHAIR ALDERSON: No, I won't accept

that.

CHAIRMAN THOMADSEN: Okay.

VICE CHAIR ALDERSON: I won't accept that.

MEMBER ZANZONICO: And the reality, these are -- at least for -- these would be breast radiologists and --

MEMBER WEIL: Not necessarily.

MEMBER ZANZONICO: Well, for the current context.

CHAIRMAN THOMADSEN: And that's why the 80 hours of training in radiation safety would be satisfied by the breast radiologist?

MEMBER ZANZONICO: Yes, for sure. I mean, this gets into the area of granting clinical privileges, which is often a departmental or institution-specific issue. And I would leave it to the institutions and the departments to define what "under supervision" means at their respective institutions, proctored cases and so forth. I would not be overly prescriptive about this.

VICE CHAIR ALDERSON: Yes, I agree.

CHAIRMAN THOMADSEN: Okay.

MEMBER ZANZONICO: I think just saying "under supervision" is adequate.

VICE CHAIR ALDERSON: I agree. And it leaves latitude.

CHAIRMAN THOMADSEN: Yes, Dr. Metter?

MEMBER METTER: And as a radiologist you already have 80 hours or more, so --

CHAIRMAN THOMADSEN: That's why I --

MEMBER METTER: Yes, so I think --

CHAIRMAN THOMADSEN: Yes.

MEMBER METTER: -- a radiologist should be the one placing it.

CHAIRMAN THOMADSEN: Although without anything like what we've said, we have not specified that in this motion and a surgeon could be the person doing that.

MEMBER ZANZONICO: Actually that's a slippery slope because someone can jury-rig 80 hours who is not a radiologist.

CHAIRMAN THOMADSEN: Absolutely true.

MEMBER ZANZONICO: I would leave it to the respective institutions to define their clinical privilege requirements.

CHAIRMAN THOMADSEN: Okay. Other comments? Yes, Dr. O'Hara?

MEMBER O'HARA: I have a question. With respect to the seed, I thought I heard you say that could be implanted any place in the human body.

CHAIRMAN THOMADSEN: Yes.

MEMBER O'HARA: Okay. So it's not --

MEMBER ENNIS: Hence my concerns.

MEMBER O'HARA: -- just to breast?

CHAIRMAN THOMADSEN: No.

MEMBER ENNIS: Right now it's mostly being used to breast, but it's already being in theory anything and anywhere, either with some kind of imaged guidance or not necessarily, just by touch, which is why I had my view.

CHAIRMAN THOMADSEN: Ms. Weil?

MEMBER WEIL: I think we also have to consider that these are procedures that may not be happening in the academic medical center, that they could be happening in community settings, community cancer centers where the credentialing issues may be less effective in making sure that the appropriate training has taken place.

MEMBER ENNIS: I think this is exactly what NRC is supposed to be doing, not leaving it up to the department when it comes to radiation safety. It requires a higher level of oversight in care. This is why we exist, why the NRC exists as opposed to just regular medical procedures.

CHAIRMAN THOMADSEN: Mr. Costello?

MEMBER COSTELLO: Yes, I would be in favor

of the new approach. I think what we're doing is putting our faith in the authorized user, but when the authorized user -- is doing under the supervision of the authorized user, that they're only going to choose someone to supervise who's been properly trained, that they're not going to pick an internist and say could you do this for me? And so, if the authorized user is doing this and supervising this, that they're only going to be doing it because they're somebody that is trained to do it properly.

CHAIRMAN THOMADSEN: Mr. Bollock?

MR. BOLLOCK: I'm sorry, but if we're going to continue this, I'd like to --

CHAIRMAN THOMADSEN: I was just --

MR. BOLLOCK: Yes.

CHAIRMAN THOMADSEN: Yes, I was --

MR. BOLLOCK: Because we have to keep in mind this is a public meeting.

CHAIRMAN THOMADSEN: Yes.

MR. BOLLOCK: We're on a schedule, so we don't want to --

CHAIRMAN THOMADSEN: I understand. And --

MR. BOLLOCK: -- be speaking outside of the schedule time.

CHAIRMAN THOMADSEN: Right. So at this moment, I close the discussion and take a vote on this motion and see if we have a decision yet.

MS. HOLIDAY: And which motion is this?

CHAIRMAN THOMADSEN: This motion is that the person implanting the sources can do so under the supervision of the authorized user. All in favor, say aye?

(Chorus of aye.)

CHAIRMAN THOMADSEN: And opposed, no?

MEMBER ENNIS: No.

CHAIRMAN THOMADSEN: Abstentions?

PARTICIPANT: Yes, abstention.

CHAIRMAN THOMADSEN: So that motion carries. One last motion, which at this point should be perfunctory, which is the motion to accept this report as the report for the ACMUI. I think we've had enough discussion on this. We can just call the question. All in favor, say aye?

(Chorus of aye.)

CHAIRMAN THOMADSEN: And opposed, say no?

(No audible response.)

CHAIRMAN THOMADSEN: Abstentions?

(No audible response.)

CHAIRMAN THOMADSEN: All right.

Clarifying, we are well behind schedule. If you can, please try to eat and be back by no later than about five after 1:00. Thank you very much.

(Whereupon, the above-entitled matter went off the record at 12:16 p.m. and resumed at 1:05 p.m.)

CHAIRMAN THOMADSEN: And we start this session with discussion of the Interagency Working Group on Alternatives to High-Activity Radioactive Sources, GARS by Mr. Herrera.

MR. HERRERA: Yes, hi. Good afternoon. My name is Tomas Herrera. I am the Sealed Source and Device Review Team leader here at the NRC. I was asked to provide an overview of this new working group, GARS that the NRC is supporting. It is a relatively new working group.

The working group was established by action by the White House's National Science and Technology Council. And as you can see, it is a Committee on the Homeland and National Security Subcommittee on Nuclear Defense Research and Development.

Essentially, the reason for establishing this working group, again, goes back to the overall security concerns about the potential for diversion of high radioactive sources and the potential use in a radiological dispersal device. And by high-activity

sources, we are referring to Category 1 and Category 2 sources that come under the NRC's security requirements in 10 CFR Part 37.

Now, this working group is focused on the federal agencies and the uses by the federal agencies. The idea is to look and assess at what the federal agencies currently use in terms of higher active radioactive sources and other non-radioactive alternatives. To do this, the working group is made up of several different government agencies and they are going to work to develop ideas on how to potentially transition to alternative technologies.

Now one of the main drivers behind this new working group comes from a recommendation that was made in the radiation source protection and security task force report. Their last recommendation came out in 2014. Basically, the idea behind that recommendation is that the government should look at ways to transition to alternative technologies with the focus on the government should lead by example with the government looking at the government's current uses of the high-active sources and transitioning to potential alternatives.

The working group is co-chaired by three agencies. It is the DOE's National Nuclear Security

Administration, the National Institutes of Health, and the NRC. Josie Piccone is the co-chair of this working group.

To date, there has been two meetings. As I mentioned, they are relatively new. We are looking at, right now, developing and finalizing an outline of what the working group will be looking at and looking at the scope and what areas the federal agencies are interested in.

To date, we have two different presentations; one by the Department of Homeland Security. They are looking at -- they also have a parallel working group looking at alternative technologies and also a presentation by the NNSA and looking at the research that they have been doing in terms of alternative technologies.

So, as I mentioned, the idea is the federal government is looking at leading by example. The focus, though, is mainly on medical applications. And by medical applications, again, looking at the higher radiation sources that are used, whether it is for blood irradiation, sterilization, or stereotactic radiosurgery.

And the idea is they are looking at the current -- doing an assessment on the current state of

research and development of alternative technologies compared to the current uses of radioactive sources and looking at ways to explore -- to support transition to these alternative technologies. The ideas are what kind of incentives can be shared with the other federal agencies in terms of maybe any type of administrative hurdles or potentially any kind of procurement hurdles that the agencies could encounter when potentially trying to look at transitioning to alternative technologies.

One of the issues or topic areas is basically the working group will look for a way to start looking to enhance competency on building effective, nonradioactive technology, also looking at supporting their commercialization and availability.

Now, from the NRC standpoint, we are a co-chair, however, as you are more than aware, we don't promote the use of radioactive material; we just regulate the safe use of it. So, this is something that we would not really have much input on but it is something that we are obviously staying engaged in so you will be aware of the current status.

The end product, essentially, is to develop a Best Practices Guide to share with the different federal agencies to potentially transition away from

the use of radioactive material over to alternative technologies with the idea, however, that it does meet the technical needs, operational, and are cost-effective.

As you can see, the membership is mainly made up of just about all the different departments in the government. We would have HHS, which does have representations from the CDC, NIH, as well as the FDA. And there is also a couple of groups from the Department of Energy, the Office of Science, as well as the NNSA.

The time line, essentially, the working group is chartered through December 2016. The idea is to have a completed draft by July -- excuse me, the document is finalized by July 2016. The idea is because there will be a change in administration, so they want to complete this work before the national elections.

There is also some discussion of reaching out to outside groups to potentially have a meeting later in 2016. So, that is something that is still being finalized at this point.

It is really, as I mentioned, still early stages. They are developing, as I mentioned, finalizing the outline and also working to develop writing teams in the different sections.

So, at this point, if there are any

questions.

CHAIRMAN THOMADSEN: Dr. Ennis.

MEMBER ENNIS: I have two. First, so the issue, as I understand it, is the concern that what more can we do that we haven't already done. Now, the conclusion of what to do about that seems to already have been, I would hope that this group would discuss what to do about that problem as opposed to what sounds like a foregone conclusion that the solution is to just try and eliminate high activity sources from being used.

So, that disappoints me and I am confused why enhanced security, and a variety of other potential solutions that one could be thinking about beyond just eliminating high-activity sources. That is number one.

Number two is in your list of impacts, you did not list brachytherapy.

MR. HERRERA: Right -- oh, excuse me.

MEMBER ENNIS: And that would have a huge impact and one of the biggest challenges, if one is trying to think about ways to eliminate sources and come up with alternatives. That would be, I believe, one of the greatest challenges.

DR. PICCONE: Tomas, let me respond to that.

It is the NRC's position and has been the NRC's position that the sources we have regulations in place to ensure the safety and security of these sources. So, NRC is not promoting either the use of sources or the disuse of these sources.

And yes, this is one area where NNSA believes that eliminating the risk completely, okay, would eliminate the problem. This effort is meant, as Tomas indicated, to have the federal government family show by example to the rest of the community that this can be done or what are the issues in doing this.

So, this document is going to look at the challenges, also, in going from one technology to the other. It is very, very limited in what it is looking at and what it is promoting with the other agencies. So, they have limited this to blood irradiators, where there is some alternative technology, and medical device sterilization, and stereotactic radiosurgery, so Gamma Knife. And there are no federal facilities, that we know of right now, that have a Gamma Knife facility.

So, what they are really looking at right now for this working group or to show by example would be in the blood irradiator and sterilization. But the document, per the outline, is going to look at or

identify the challenges, as well. And as Tomas indicated, there is another DHS working group just looking at that. And some of you might be involved in that effort as well in determining what are the challenges. There are many challenges, depending on who you talk to. There are challenges in the research area, the medical area, in procurement. So, this document is meant to cover many of those challenges, how would you go about doing it.

How I see NRC's role in this whole effort is -- and I am one of the three co-chairs -- there is much of this document that we cannot contribute to. We don't, as NRC, we don't procure these sources. So, they want the folks who are involved in procuring this technology to help write this document. But what we can contribute to is to ensure the scope remains the scope as chartered by the White House and also on what are the regulatory requirements or what would need to be done in decommissioning a radioactive source to one of these alternative technologies.

CHAIRMAN THOMADSEN: Mr. Costello.

MEMBER COSTELLO: Well, I would like to, I just might agree with you, Josie, Dr. Piccone, that our current regulations, that Part 37 and with managed States still increase controls, and the efforts of the

NSA around the country to further secure these devices result in a situation where they are perfectly secure there and, in my mind, there is not a problem that needs to be fixed. And so this whole effort I will know about.

My only advice to the NRC when it participates as co-chair, is to make sure that the document that comes out makes it very clear that they are currently secure and safe and protected against unauthorized use and not to let anyone in this document exaggerate the risk that exists today, because today it is under control.

DR. PICCONE: And in fact, those were our opening presentations at the start of this effort. And I think the presentation today was just an informational presentation for you to know that this effort is going on and we happen to sit on this group as well and FDA is on this as well.

CHAIRMAN THOMADSEN: Are you using the report from the ACMUI on the irradiators at all in this work?

DR. PICCONE: The report on what?

CHAIRMAN THOMADSEN: The ACMUI report on cesium irradiators.

DR. PICCONE: No, that hasn't come into play. We will take a look at that to see.

CHAIRMAN THOMADSEN: I can send you that.

DR. PICCONE: Yes.

MS. COCKERHAM: This is Ashley. I was going to say I know what you are talking about, Dr. Thomadsen and we can get that to Tomas. I think it is very relevant to what this project is about and what the ACMUI's position would be on the effects in medicine.

CHAIRMAN THOMADSEN: Could you get that to us?

MEMBER COSTELLO: Well, we could say what it was, not what it would be now because the technology has changed.

DR. PICCONE: Yes.

CHAIRMAN THOMADSEN: I think a lot of the points that were made in that report could be used on this, too.

DR. PICCONE: And there are a lot of efforts going on right now, in terms of developing alternative technologies, many of these through Department of Energy, as well.

So, we certainly will take a look at it.

VICE CHAIRMAN ALDERSON: Just as another informational comment, I think that the recent news this week is current, about people having been captured over in the Mideast trying to get radioactive sources to

people who would do ill with them, I think that is more likely going to be the source than the various medical things that you, that this agency currently protects. But I do think that a big void, and it is not an issue probably that the NRC is going to address, or even GARS, but is education, education both of the public and of responders to things like this. Because despite what these good efforts are going to be, I think there is still a reasonable risk that at some point something like this will happen in this country.

DR. PICCONE: Right. The other thing that I will just piggyback a little bit on is Tomas indicated that the group is looking at how to bring in input from other external organizations. And because that would involve a public meeting, they are working on the details of that but I think I can say at least this much. That the co-chairs and some of the other members of the working group have identified other groups that can provide valuable information to this effort. So, we have identified groups like the Organization of Agreement States, the CRCPD, because most alternate technologies would require licensing by the State organizations, the Health Physics Society, AAPN, ASTRO. So, all of these groups have been identified -- did I cover your organization -- okay, have been identified

as valuable in providing input to this effort.

CHAIRMAN THOMADSEN: Dr. Suh.

MEMBER SUH: Just to clarify. So, you had mentioned on the slide it says initial focus on medical applications and it states stereotactic radiosurgery. Then you made a comment that in the government there is not a Gamma Knife unit. So, is this still going to be evaluated as an alternative approach? Because as you know, Gamma Knife radiosurgery is used at over 100 centers right now and has been shown to be very clinically effective for a number of disease sites. And I would hate to see a report saying that because of its potential risk, we should switch to some other alternative technology.

DR. PICCONE: No.

MEMBER SUH: Just for clarification.

DR. PICCONE: The document is supposed to be a best practices guide in transitioning from radioactive material to alternative technology. They identified these -- and it is meant for federal agencies, for the federal agencies to transition.

So, you see VA is on here, Health and Human Services, whatever. But when we went to see are there any Gamma Knife units out there in the federal agencies, our records do not show any. And they probably did not

know that when they put this together. We notified them of this.

MR. HERRERA: We notified them once we were able to confirm that federal agencies don't have the experience with Gramma Knife.

MEMBER SUH: Sure. So, one of the concerns would be the trickle-down effect of having this report come out and then to insinuate that technologies such as Gamma Knife radiosurgery, which, again, has been shown to be very clinically effective for a treatment of a variety of conditions within the brain all of a sudden gets relegated because a document comes out.

And that is why when I saw stereotactic radiosurgery that is a big -- at least for me, being very involved with radiosurgery, it is a big red flag for me because that would be a huge disservice to the nation and to physicians.

DR. PICCONE: Yes. And again, the scope of this document is not intended to mandate anything to the federal agencies but to encourage them to consider going from RAM to alternative technologies and to provide some best practices on how they could do that.

And there is no document yet. There is an outline that is still being worked on but what we did, NRC, is we pointed out that if they wanted to focus on

these areas, that there are no Gamma Knife's in federal facilities right now.

But there are blood irradiators, many of them. There are many sterilization, other sterilization units. They may not be to sterilize medical products but Department of Agriculture has many.

MEMBER COSTELLO: I know they have one.

DR. PICCONE: They have several.

MEMBER COSTELLO: Okay.

CHAIRMAN THOMADSEN: Dr. Zanzonico.

MEMBER ZANZONICO: One source that I know that was missing I think was industrial radiography systems. I mean some of those use very high activity sources and it is kind of a low profile application of high activity sources but it is one that does exist. Is that incorporated into your game plan?

DR. PICCONE: No. No, this effort was very specific and narrowly focused and they called it medical applications, using cesium-137 and cobalt-60.

MEMBER ZANZONICO: It just strikes me as an overly narrow focus. I mean it leaves unaddressed a large number, a lot of resources that are as susceptible to theft and so forth as others.

DR. PICCONE: Yes, but I think I mean I

can't say what they were thinking. Okay? I can surmise that some of the thinking behind keeping the focus in this narrow area is that there are known alternative technologies for these two things, for blood irradiators and sterilization. And, again, the focus is on federal agencies. Can we get some of the federal agencies to use some of these alternative technologies? And then if they are great, they work out, they are wonderful, that the word would get out.

So, that is why I believe there is this narrow focus.

CHAIRMAN THOMADSEN: Dr. Ennis.

MEMBER ENNIS: Do you anticipate the report presenting the NRC's view that the safety of the sources is adequate and that transitions are not necessarily needed?

DR. PICCONE: We don't go as far as to say transitions aren't needed. That is not our call. That is your call and the researchers' call and the organization's call. But we continually stress that the sources are safe today.

MEMBER ENNIS: I think it would be important that language like that is included to get to Dr. Suh's point. It could easily be understand, if not that all three organizations endorse the idea that we

need to transition and could have a cascading effect that was not necessarily intended.

DR. PICCONE: Point taken.

CHAIRMAN THOMADSEN: Other questions or comments? Hearing none, thank you for your update.

DR. PICCONE: Thank you, Tomas.

Dr. Palestro, you are back in this chair. And we will be hearing about the Subcommittee on Yttrium-90 Microsphere Brachytherapy Medical Event Criteria.

MS. HOLIDAY: Dr. Thomadsen?

CHAIRMAN THOMADSEN: Yes?

MS. HOLIDAY: This is Sophie.

CHAIRMAN THOMADSEN: Yes.

MS. HOLIDAY: Before we jump into Dr. Palestro's presentation, I just wanted to make a comment.

CHAIRMAN THOMADSEN: Yes.

MS. HOLIDAY: I know that we ran over time discussing the last two presentations before lunch and the last thing we were talking about was the Radioactive Seed Localization Guidance.

CHAIRMAN THOMADSEN: Yes.

MS. HOLIDAY: As some of you or most of you are aware, there was an NRC/Agreement State Working

Group that was formed to look at revising this guidance. So, the report that the Committee endorsed today will, of course, be fed to this working group, of which I am one of the co-chairs. All of the working group members were watching the meeting via webcast. So, I just wanted to let you guys know that your efforts, obviously, were not in vain. But as with most things, staff, in this respect, the working group, will consider what was outlined in the report as part of our looking to revise the new guidance.

Thank you.

CHAIRMAN THOMADSEN: Well, thank you.

Dr. Palestro.

MEMBER PALESTRO: All right, well this is in follow-up to a very comprehensive report that was presented, I think, about a year ago, perhaps a little bit more, by the then-chair of this subcommittee, Mickey Guiberteau, about the potential for revising the criteria for medical events.

So, the subcommittee members include Frank Costello, Sue Langhorst, and Bruce Thomadsen, in addition to myself.

And our charge was to review and provide comments on proposed revisions to the Yttrium-90 Microsphere Brachytherapy Licensing Guidance.

Recommendation 1 that had been named was that the specification of acceptable GI tract and lung dose or activity in the written directive prior to yttrium-90 microsphere embolization procedure should not be required. Instead, the total treatment activity of yttrium-90 microspheres to be infused or administered should be to require compliance measure.

And in the proposed revised guidance, the statement, the written directive should specify the maximum dose or activities that would be acceptable to the specified site or sites outside the primary treatment site due to shunting, for example, lung and gastrointestinal tract, has been removed.

Recommendation 2, GI and lung irradiation for yttrium-90 microsphere brachytherapy should be considered known risks of the procedure. Revised guidance reads as follows.

The revised medical event reporting allows an exception for shunting outside the authorized user's control. Exceptions for documented stasis and emergent patient conditions clarified, criteria for wrong radionuclide, patient, route or mode of treatment maintained.

Recommendation 3, that implantation of the microsphere brachytherapy sources is considered to be

in accordance with the written direction, if the total administered or infused activity does not vary from the activity prescribed in the written directive by 20 percent or more, except in situations in which activity administered is limited by determination of the procedure due to stasis.

The revised guidance allows for an exception to medical event reporting when the administered or infused activity varies from that prescribed in the written directive by more than 20 percent because of stasis or emergent patient conditions provided that this is documented.

And the subcommittee's recommendation: The subcommittee unanimously agrees with and endorses the changes made in response to the subcommittee's original recommendations.

On review, the subcommittee has additional recommendations. In the training and experience under A.3.iii.e, reference is made to an appendix in NUREG-1556, Volume 9, Revision 2. The subcommittee recommends changing to Appendix S to the current revision of NUREG-1556, Volume 9 and so forth.

Similarly for A.3.iii.f, reference is made to an appendix in NUREG-1556, Volume 9, Revision 2 and we recommend changing Appendix N to the current revision

of NUREG-1556, Volume 9.

And the rationale for this is that in the updates of NUREG-1556 volumes, the appendices letter designation kept constant. The proposed change would clarify that licensees could use the most up-to-date revision in applying the licensing guidance.

CHAIRMAN THOMADSEN: Thank you very much. Comments and questions from the committee? Dr. Zanzonico.

MEMBER ZANZONICO: It all sounds very reasonable.

(Laughter.)

CHAIRMAN THOMADSEN: Thank you for that comment. Hearing no others, I again -- oh, Ms. Weil.

MEMBER WEIL: I keep finding that I want to make the same comment. Again, this is aligned with the patient intervention definitions, the passive patient intervention techniques that were discussed earlier.

So, we are talking about anatomical or physiologic abnormalities that cause shunting. I mean that is what this is sort of after, that there may be patient-sited conditions that cause shunting to the GI tract or the lung.

And again, there is pretreatment stuff that has to happen to determine whether or not those

abnormalities exist and how they might best be mitigated. And I am not comfortable that that isn't alluded to in a statement. Can somebody help me here? It doesn't vary from the activities described.

Emergent patient conditions are clarified -- it just troubles me that we aren't putting front and center that there are certain predetermined activities that should take place when infusing these things, if we are assuming that there is a certain acceptable risk of shunting to the GI tract or the lung.

CHAIRMAN THOMADSEN: In the written report, although I don't know if this is the current one or the one that this is following, that was discussed in great detail as being expected.

MEMBER WEIL: Okay.

CHAIRMAN THOMADSEN: Dr. Zanzonico.

MEMBER ZANZONICO: I also think that an implication of this report is that, and this in fact occurs, when all of the pretreatment dosimetry and so forth has been done and done properly, there are instances where the procedure is overtaken, stasis is encountered or other problems are encountered, despite everyone doing everything properly. And the prescribing information, the package insert and so forth describes all of the required pretreatment

analysis. But again, despite that, you sometimes have to stop the procedure or something because of unforeseen and impossible to know circumstances.

MEMBER PALESTRO: All of that, I'm almost sure was in the guidance and these really are excerpts looking at our specific recommendations. But all of that information is provided in the comprehensive guidance.

MR. BOLLOCK: Actually Ashley can answer a lot of these questions.

CHAIRMAN THOMADSEN: Oh, hi. I couldn't see you.

MS. COCKERHAM: That's okay. No, I just raised my hand. So, this is Ashley Cockerham.

We did specifically tie it back to the manufacturers' procedures for the pre-implantation diagnostic imaging.

MEMBER PALESTRO: Thank you.

CHAIRMAN THOMADSEN: Other comments? I am assuming, again, the subcommittee is moving that the full committee accept and endorse its report as its own. Do you want to make that into a motion?

MEMBER PALESTRO: Yes.

CHAIRMAN THOMADSEN: Fine. Any discussion before we vote? No more than there was

before. In that case, all in favor say aye.

(Chorus of aye.)

CHAIRMAN THOMADSEN: Opposed say no.

(No audible response.)

CHAIRMAN THOMADSEN: Abstentions?

(No audible response.)

CHAIRMAN THOMADSEN: It passes.

MS. COCKERHAM: Dr. Thomadsen, can I just make one -- I just wanted to thank the Committee for looking at the guidance again. I know that you have seen it several times but I hope that we implemented what you intended us to implement. I think we are in a good place. And just as a heads up on next steps, the guidance will go out to the Agreement States for their review and comment. And so we will hear what our Agreement State partners have to say about these same topics. And then the working group will reconvene, consider those comments and then we hope to issue final guidance in December of this year.

CHAIRMAN THOMADSEN: Thank you for the clarification of the procedure.

Yes?

MEMBER COSTELLO: I think we should really compliment the staff. I think they took what our subcommittee came up with and made it better. So, it

was really a joint between us and the agency and what they came up with is, I think, a very significant improvement. I thank the staff for all the work on this.

CHAIRMAN THOMADSEN: Thank you. And I think we will all appreciate your comments to the staff and agree with that.

Well, now strangely enough, after going so late and rushing lunch, I'm going out in a blaze of glory. This is completely out of control.

(Laughter.)

CHAIRMAN THOMADSEN: We have a topic coming up where we may have people coming in on the bridge lines at two o'clock. So, we will be on break now for about the next 18 minutes. Please don't wander too far away so that we can start that on time.

(Whereupon, the above-entitled matter went off the record at 1:42 p.m. and resumed at 2:01 p.m.)

CHAIRMAN THOMADSEN: Dr. Daibes, welcome. And it is good to have another update on the current status of the Germanium/Gallium-68 Generators.

DR. DAIBES: Thank you, Dr. Thomadsen. First of all, thank you for the opportunity provide you an update on where you are. Let me start with an overview of our intent today. I am going to provide you

a brief overview and a very brief background behind gallium-68, as well as the current status of our initiatives, what we are intending on doing, our regulatory option and recommendation as well.

I'm going to be very brief on the utility behind gallium-68. I believe this has been brought up to the Committee multiple times. So, I am going to be very, very brief.

As we have heard from ACMUI in the past, and especially Mr. Mattmuller, the advantages of gallium-68 currently are superior to current clinical agents for neuroendocrine disease, in this case, neuroendocrine tumors. We understand that gallium-68 PET imaging provides greater sensitivity and specificity for this type of disease.

Despite being very widely available in Europe, in the States it is still an investigational new drug in at least 11 centers around the States.

We understand as well as the FDA's review and application, because they have said so in SNM and a few other professional meetings. However, we also understand that they have not acknowledged this, as is their policy.

Facilitating this review is a very vast, large amount of data and mainly from the research done

in Europe. In addition, the FDA has designated this an orphan drug, which in this case it provides to a sponsor further support for moving or, in any case, reviewing this potential agent.

So, what is happening is behind this? Well, basically in order to generate a gallium-labeled radiopharmaceutical, a site will need a generator, in this case, a germanium/gallium-68 generator. However, the gallium-68 produced from this generator is, in its nature, is a radiochemical and is not a radiopharmaceutical yet.

So, what happens is that this has to -- it is extracted and it is basically further processed to generate this gallium-labeled radiopharmaceutical and the generator itself, it operates very closely or resembling in a similar manner to a tech-99m generator. So when you can visualize it, it is something close to that. At least, based on what we have seen in professional organization meetings.

So, the current status of staff's initiatives. So the parent radionuclide in this generator system is germanium-68, which has a half-life of 270 days because of this specific half-life, which, in this case, is a very long half-life and the fact that this is an unsealed radioactive material per 10 CFR

30.35, a decommissioning funding plan is needed and it must be developed in order for a licensee to possess or be able to possess this generator.

What is a DFP? A DFP is a financial assurance plan that is based on a site-specific cost estimate for decommissioning the licensed facility. And this DFP must incorporate every single radionuclide in the facility.

So, why is it that a DFP is needed? Well, the situation stems from the change to the regulations in 2005, when the definition of byproduct material was revised to include accelerator-produced radionuclides, such as fluorine-18, cobalt-57, and lesser known radionuclides as germanium-68. During the rulemaking process, a value for germanium-68 was then added to Appendix B of 10 CFR 35.30. However, this was a missed opportunity, since there is no value in 10 CFR Part 30, Appendix B for germanium-68, the default quantity of ten millicuries is used. Because if a typical gallium-68 generator contains approximately 50 millicuries of germanium-68 upon delivery, at least this is what we heard during the SNM meeting, a DFP requirement is triggered.

We have heard as well, and we have heard this from multiple attendees at SNM and from ACMUI as

well, that a DFP may be costly and it may create limitations to access and this is based on what ACMUI said in its report.

So, our regulatory options. Staff believes that granting an exemption from their requirement for a licensee to develop a DFP is justified in this case and in the best interest of public and safety. An exception in this case will allow more access to the gallium-68 radiopharmaceuticals that could be generated from this generator. An exemption will be granted to the DFP requirement with a specified limited scope applicable only to the possession and use of the germanium/gallium generator and only when we, in turn, place a guarantee that the generator manufacturer or distributor will remove the old generator when a new one is delivered.

Staff is developing a plan that will enable the NRC regions to provide this exemption to licensees and applicants who request it and provide the information necessary to ensure that these certain conditions are in place. If this plan is approved, it will be allowed for the exemption to be granted in licensing space, rather than rulemaking space. I need to make that clear.

Staff believe that the plan of action will

be sufficient to ensure public health and safety until a more permanent regulatory solution is reached through rulemaking in the near future.

So, our recommendation. Staff recommends that NRC regions be authorized to grant an exemption from the DFP requirements, when requested under certain conditions. And if approved, guidance will be generated providing licensee radiation safety recommendations for safe generator handling and concurring to this initiative appropriate generator communications and outreach activities will be implemented to inform licensees of special regulatory requirements associated with this licensing of this generator.

And this is our plan forward to the committee or what we intend right now to pursue in the short-term. And we believe this is something more practical and it will be less time that on direct final rule when we see it in a time frame or we evaluate it from that perspective. Questions?

CHAIRMAN THOMADSEN: Thank you. Mr. Costello.

MEMBER COSTELLO: Yes, a number of questions.

First of all, with the exemption, exempt

licensees from all financial assurance considerations for the generators. For example, if a licensee has other materials and the possession of the generator put them over the amount necessary for a statutory amount of financial assurance, you know $300,000 or $1 million, or whatever it may be, will the exemption mean they don't have to consider these things in determining whether financial assurance is necessary?

DR. DAIBES: That will not be the case. We are currently working on the plan and as soon as we have it available, we will make that available to the committee.

MEMBER COSTELLO: Because it is not just DFP.

DR. DAIBES: That is correct.

MEMBER COSTELLO: It is all of the other levels of financial assurances. Okay.

And the second thing is, and so, yes, I was hoping for a direct or final rule, but that's okay, most of these facilities you are talking about are Agreement State facilities. Right?

So, I assume that you are going to be sending something out to the States encouraging them to do the same thing. Because in order to really have this effect like 90 percent of the licensees in the country,

it has to be implemented by the Agreement States and they would have to be the ones really given the exemptions, not the regions.

DR. DAIBES: This relationship will definitely consider Agreement States and we are going to work very closely with them.

MEMBER COSTELLO: Thank you.

CHAIRMAN THOMADSEN: Other questions? Dr. Zanzonico.

MEMBER ZANZONICO: I have a question that is somewhat off topic but this concept of a license-specific exemption seems awfully powerful. And I know, again, it is off topic but we got into the issue of the training and experience for radionuclide therapy and we were told that the change from the 700-hour regulatory requirement would require rulemaking.

Why is that qualitatively different than this instance? Why not a license-specific -- if one agreed that 700 hours was not the optimal amount of training, what would prevent implementing a license-specific exemption for licensees in that respect?

MR. BOLLOCK: Basically, in this case, what actually your subcommittee provided was a safety

analysis in the previous subcommittee report teleconference. And that is the other piece. You know after reviewing I believe Dr. Langhorst came up with it, after reviewing that, we are still in the process of getting to this point. But basically that makes sense showing the safety analysis that is not a safety concern and that will allow us to -- that basically is a big help in allowing us to do this, giving guidance to an exemption because we do have that.

So, there is a couple that, Mike, you might want to add.

MR. FULLER: Actually, can you all hear me? This is Mike Fuller, Team Leader of Medical Radiation Safety Team. And Doug is correct.

Saying it another way is that the hurdle, the regulatory hurdle for granting an exemption, whether it be this type of an exemption or something more general is very, very high. You have to really make the case that in doing so in no way will public health and safety be compromised and, as Doug said, the safety and risk analysis that was done by this body of the subcommittee and reported out in June -- no -- August was really the piece that was missing on germanium/gallium generators and was very, very helpful to us.

So, we think, we believe at this point, we still have a ways to go, but we believe, at this point, that we have what we need to meet that regulatory or to get over that regulatory hurdle of demonstrating that this is in the best interest of public health and safety and in no way will safety be diminished.

And so whether or not it would apply in all cases that is the hurdle that must always be overcome. And most of the time, that is a very, very difficult thing to do.

MEMBER ZANZONICO: Yes, I understand but my understanding has been that there was sort of an absolute distinction between what required rulemaking from what did not. And it seems that that distinction is not as absolute as I understood it.

MR. BOLLOCK: Yes, to make the long-term solution to this is rulemaking.

MEMBER ZANZONICO: Right but the short-term solution --

MR. BOLLOCK: It is a case-by-case basis. Now, they would have to, in their license, say that they are going to, for instance, they get two generators in, they return it to the vendor who supplied it. Those things in the license that we can hold them to, hold them accountable to.

So, there are a number of things that make this like I said not really, you know get over that regulatory hurdle, that it is not a safety issue.

In bringing up the training requirements, right now the training requirements are 700 hours. In the last case they are 700 hours and we don't have that analysis to say --

MEMBER ZANZONICO: Right but that is not to say that new charge of the subcommittee, if I understood correctly, was to address the issue of what was the adequate training and experience. And presumably a component of that would be a safety analysis in some form.

So, again, I'm just trying to understand what -- this seems like a mechanism which would not require the rule changing, if it were decided, and I'm not arguing in favor of that but if it were decided that for radionuclide therapies, like Bexxar and Zevalin, less than 700 hours was acceptable or would not compromise public safety, et cetera, et cetera, that license-specific exemptions could be pursued.

MR. BOLLOCK: In just general terms, exemptions are exactly that, it is an exemption. So, it would be a case-by-case basis that have to be shown in each case and this is each license.

With the germanium, how many licenses do we have? This is, just for the licensees, if you limit the licensees, they are each going to have to do this, this is something that is widespread, every hospital, in the case of the training requirements, each one of them would have to put in a license exemption. That would be up to them. It is an exemption and it is right there. It is generally speaking, if shown to get over those hurdles, there could be an exemption. That is why we have the ability to do that but it is rare, extremely rare.

In this case, we believe that ACMUI, that you all have shown a lot of good scientific data, all reasonable, to show the assurances and it is like Mike said, we are not done yet with our evaluation but it looks like this is something that we can do to get over those hurdles because it is for the good of the public without that risk.

CHAIRMAN THOMADSEN: Oh, Mr. Costello.

MEMBER COSTELLO: It is rarely done because regulating by exemption isn't a very good idea. That is why it is rarely done.

For short-term, I am okay with this, although I really, really like the rulemaking because the way it is right now, you will have, not counting the

NRC, 37 different regulators evaluating exemption requests from more than the licensees. And I am sure that the NRC, when they come out with the exemption, will have suggested criteria that the Agreement States will use but different reviewers look at things differently and the chance of having lack of uniformity in the approach that is taken by the 37 Agreement States is pretty good.

And Doug, I agree with you on your question about the 700 hours and the alpha and beta emitters. The reason not to do that is regulating by exemption is a really bad idea. It really is a bad idea. You could do it in some very limited but it is a slippery slope because it is a way of avoiding of the rulemaking process. There is lots of reasons why you don't want to do it that way.

Again, I am okay with doing it -- I am personally okay with doing it now but it is an addictive thing you don't want to get used to doing. They say well, we will just exempt everybody from it and just have bad rules in the rulebook.

So, I encourage the NRC to work with some vigor and direct a rulemaking and then the 37 Agreement States won't be fielding these like every other week.

CHAIRMAN THOMADSEN: Mr. Bollock.

MR. BOLLOCK: Thank you. And to address that, sorry I didn't indicate the end goal is to get this in the rulemaking. We understand that but that is the best thing that is the permanent solution so that we are not continuing for years and years having to do this by exemption. It is rare.

And that is our goal but given the fact that this is something that is coming out short-term in the next maybe year or so, it is a way for us to not be a hindrance when this is for the public good and not a safety concern.

MEMBER COSTELLO: There is a good reason why it's rare.

MR. BOLLOCK: Yes, absolutely. And I believe Mike, do you want to --

MEMBER ZANZONICO: But rare is not never. To think that making available a treatment for a fatal disease, if that is not a compelling reason, I don't know what is.

And again, I'm not endorsing that but this strikes me as a mechanism that become very relevant to that issue because part of the argument against that was that it would delay the ongoing rulemaking. And it seems an option that circumvents that difficulty.

MR. BOLLOCK: Right but we don't have the

information to say that it is safe now.

MEMBER ZANZONICO: Right, but that is not to say that the information is going to accruing.

MR. BOLLOCK: And also in that case, that is something has been in practice for ten years. We know there are authorized users available that could use it and do use it. The case with the germanium, this is new here in the U.S., other than basically essentially research trials, not in use.

So, there are some specific differences. I mean I see your point. I absolutely see your point but yes, it is a rarity. There are enough differences here. And again, a lot of what helped us, realizing we have known all along the only way to change the tables that were discussed and I know Mr. Mattmuller has discussed in previous meetings that Part 30 tables would be -- we have to change them in rulemaking and that is the final answer.

But knowing that could take, even direct final rule, perhaps a year, there is a lot that factors into that. And this is just -- so I admit he spoke -- I don't know if it was in the slide, but that is the end goal is to continue to go more towards rulemaking. But in the world that we are in right now, I don't know that we are going to be able to get to step two and do that.

And this would be a separate rulemaking than the draft final rule we have in place now, just to be clear.

CHAIRMAN THOMADSEN: Dr. Daibes.

DR. DAIBES: If I could add, going back to what Doug was saying, there is a very, very vast body of data of peer review scientific papers that provide basis on the efficacy of this radiopharmaceutical. And we are trying to work and find a pathway that allows access. We are just simply working with licensees in finding something that allows immediate access. And there is quite a bit of data to support that. And your data or analysis provides even further basis for that. I believe that is why we have opted to pursue this option.

If you see the regulatory options that the NRC has in its framework, an exception is one that if you go to their website you can see this information and we are simply following the process and seeing what options we have we are pursuing that and seeing if, indeed, we can work with licensees and others to make this available.

MEMBER ZANZONICO: I appreciate that and I don't want to belabor the point but, for example, Dr. Cultrera quoted data that indicated, for example that

Bexxar is among, if not the most effective single region treatment for non-Hodgkin's B cell lymphoma. So, the point is, it sounds like all the conditions that have been satisfied for the license exemption in the case of the germanium-68, can potentially be satisfied with some instance.

DR. DAIBES: And I think we differ from that opinion in this case that we, if I may, like when we see this from the patient, from the public and safety perspective and access to a patient, there is a full spectrum of different aspects that have been evaluated and we did that. And at least I don't have that information available based on the presentation today, so I cannot comment on that specific. But we definitely did our homework and made sure that we are complying with what we needed in order to pursue this.

MR. BOLLOCK: Right. And in the case, if I may, based on their case with the Zevalin, they didn't make the case. They haven't made a strong enough case to say that the 700 hours or the 80 hours is enough. I mean we don't know. That is why we are looking forward to the subcommittee's report on that evaluation and come spring-time because it is that type of information that we would need to be able to make a decision based on the size, based on evaluation to be able to move forward with

something like that. So, in that case, that is missing.

CHAIRMAN THOMADSEN: Mr. Costello.

MEMBER COSTELLO: That's why I brought up regulating by exemption is not a good idea because it could be very subjective. It is a way of avoiding the rulemaking process. And there will be many cases on a case-by-case basis where providing exemptions to regulations will appear much faster and much more attractive than following the rulemaking process because few things are less attractive following the rulemaking process.

One comment on the germanium and the gallium, as far as the technical basis goes, I think the fundamental technical basis is that the risk implied on a Part 30 value of germanium-68 overstates it by a factor of a thousand because properly, from the safety point of view, the proper value is in Part 20. It was a thousand times higher than the value in Part 30.

So, I think that I am fine with exempting it but I think it is not just the fact that this is a very good treatment but for a risk-based point of view, you don't require financial assurance of DFPs for the amount that would be required by the amount that is currently in Part 30.

But I'm agreeing with your terms.

CHAIRMAN THOMADSEN: Yes, Mr. Mattmuller.

MEMBER MATTMULLER: Yes, I was the chair for this committee and I don't know if when we last spoke if I took the time to thank my individual committee members, which I would like to do now.

Doctors Langhorst, Palestro, Zanzonico, and Mr. Costello who helped tremendously in this effort. So, I am very appreciative of that.

Just one slight correction I would like to make in regards to Said's or Dr. Daibes comments is that he said that the DFP may restrict the use. And I would say it already, and I think our report indicated this, it already has limited the use of this generator.

And then a promise to the Committee. As you all know, I am on the hot seat and I will be gone by the next meeting. If you can have this done by the last meeting, I will go very quietly.

(Laughter.)

CHAIRMAN THOMADSEN: Any other comments? Well, thank you very much.

MS. HOLIDAY: There might be someone on the phone.

CHAIRMAN THOMADSEN: Oh, do we have somebody on the phone who would like to comment?

(No audible response.)

CHAIRMAN THOMADSEN: Well hearing none --

MEMBER COSTELLO: I have one last question, if I could.

CHAIRMAN THOMADSEN: Yes, please.

MEMBER COSTELLO: This approach of doing this by exemption, has this been run by the Office of General Counsel?

DR. DAIBES: I made something very clear and I said that, if approved, this will be passed by that office.

MEMBER COSTELLO: My experience is that OGC is often not thrilled with the idea of regulating by exemption.

MR. BOLLOCK: Yes, we agree and we will have to. But part of it will be us making the best case. And so we do have a process to send it up to them.

CHAIRMAN THOMADSEN: I think on behalf of the Committee I can express gratitude to the NRC for picking up this problem and trying to come up with the most expedient solution as possible.

DR. DAIBES: And that is the objective. Yes, that is the main objective.

MR. MAILMAN: This is actually someone on the phone.

CHAIRMAN THOMADSEN: We do! Okay, very

fine. Please go ahead. Identify yourself first.

MR. MAILMAN: Sure. This is Josh Mailman. I am the President of NorCal CarciNET Community and also the past Chair of the Society for Nuclear Medicine and Molecular Imaging Patient Advocacy Advisory Board. And I would like to thank the Committee and the NRC for taking this up and making this available or working on making the availability of the germanium-68 generator by exemption for the centers that need to use that as this is a very important upcoming diagnostic test that will be available for patients in, hopefully, in the not too distant future.

So, I wanted to thank you on behalf of the patient community.

CHAIRMAN THOMADSEN: Thank you for your comment. We appreciate that.

Any other comments from the committee? In that case, again, thank you. And at this moment we stand adjourned for the public session.

We return here, the Committee does, at three o'clock for the closed session on training.

(Whereupon, the above-entitled matter went off the record at 2:30 p.m.)