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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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VIRTUAL MEETING

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TUESDAY,

MARCH 16, 2021

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The meeting was convened via Video-Teleconference, at 10:05 a.m. EDT, Dr. Darlene F. Metter, ACMUI Chairman, presiding.

ACMUI MEMBERS PRESENT:

DARLENE F. METTER, M.D., Chairman

VASKEN DILSIZIAN, M.D., Vice Chairman

RONALD D. ENNIS, M.D., Member

RICHARD L. GREEN, Member

MELISSA C. MARTIN, Member

MICHAEL D. O'HARA, Ph.D., Member

ZOUBIR OUHIB, Member

MICHAEL SHEETZ, Member

MEGAN L. SHOBER, Member

HARVEY B. WOLKOV, M.D., Member

NRC STAFF PRESENT:

KEVIN WILLIAMS, Director, NMSS/MSST

CHRISTIAN EINBERG, NMSS/MSST/MSEB, Designated Federal Officer

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

SUZANNE DENNIS, OEDO/AO

DANIEL DIMARCO, NMSS/MSST/MSEB

LISA DIMMICK, Team Leader, NMSS/MSST/MSEB

STEPHANIE DINGBAUM, OIG/AIGA/NMW

ROBIN ELLIOTT, R-I/DNMS/MLAB

MONICA FORD, R-I/DNMS

SARAH FORSTER, R-III/DNMS/MLB

CASSANDRA FRAZIER, R-III/DNMS/MLB

ROBERT GALLAGHER, R-I/DNMS/MLAB

FARRAH GASKINS, R-I/DNMS

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VALERIE GRAY, NMSS/MSST/MSEB

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LATISCHA HANSON, R-IV/DNMS/MLDB

VINCENT HOLAHAN, Ph.D., NMSS/MSST

DONNA-BETH HOWE, Ph.D., NMSS/MSST/MSEB

IAN IRVIN, OGC/GCLR/RMR

KELLEE JAMERSON, ACMUI Coordinator, NMSS/MSST/MSEB

DONNA JANDA, R-I/DNMS/MLAB

JANELLE JESSIE, COMM/OCMJB

CYNTHIA JONES, COMM/OCMAC

PENNY LANSZIERA, R-I

KATHY MODES, NMSS/MSST/SLPB

JANICE NGUYEN, R-I/DNMS/MLAB

ROBERT ORLIKOWSKI, R-III/DNMS/MLAB

VERED SHAFFER, RES/DSA/RPB

KATIE TAPP, Ph.D., NMSS/MSST/MSEB

CAROLYN WOLF, OCA

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PUBLIC PARTICIPANTS:

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JINSY BABU, Department of Veterans' Affairs

JAIME BARNES, Cook Children's Medical Center

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JOSH MCILVAIN, Diagnostic Technology Consultants

SCOTT MCKEE, U.S. House Committee on Appropriations

ASHLEY MISHOE, Novartis

CHRISTOPHER MITCHELL, Kettering Health Network

JEFF MOIRANO, University of Washington

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PAT ZANZONICO, Memorial Sloan Kettering Cancer Center

C-O-N-T-E-N-T-S

P R O C E E D I N G S

10:05 a.m.

DR. METTER: Thank you very much. And good morning and welcome to the 2021 Spring ACMUI meeting. I am Darlene Metter, the ACMUI Chair and diagnostic radiologist.

I would like to acknowledge the new ACMUI recently appointed Vice Chair, Dr. Vasken Dilsizian. Thank you, Dr. Dilsizian, for your continued commitment and dedication to the work of ACMUI.

I would also like to thank the NRC staff and ACMUI members for their dedication in continuing the Committee's work, especially during these challenging times, and also for their tireless commitment to our patients and the public.

I would also like to acknowledge the dedicated work of our healthcare professionals, hospital and clinic staff who unselfishly care for their patients regardless of the potential serious risks to their own health. It is my hope that the next time we meet, it will be in person, and that this pandemic will be in our rearview mirror.

And now Mr. Chris Einberg will open the meeting, and Mr. Kevin Williams will provide opening remarks.

Mr. Einberg?

MR. EINBERG: Thank you, Dr. Metter.

Good morning. As the designated federal officer for this meeting, I'm pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes. My name is Chris Einberg. I am the Chief of the Medical Safety and Events Assessment Branch, and I have been designated as the federal officer for this Advisory Committee in accordance with 10 CFR, Part 7.11.

Participating today we have Lisa Dimmick from our Medical Radiation Safety Team and Kellee Jamerson, our ACMUI Coordinator, as the designated federal officers for the ACMUI.

This is an announced meeting of the Committee. It 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 or recorded by others. The meeting was announced in the February 10th, 2021, edition of the Federal Register, Volume 86, page 8929.

The function of the ACMUI is to advise the staff on issues and questions that arise on the medical use of byproduct material. The Committee provides

counsel to the staff members, but it does not determine or direct the actual decision of the staff or the Commission. The NRC solicits the views of the Committee and values their opinions.

I request that whenever possible, we try to reach a consensus on the various issues that we discuss today. But I also recognize that 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 would like to perform a roll call of the ACMUI members participating today.

Dr. Darlene Metter, ACMUI Chair and diagnostic radiologist?

DR. METTER: Present.

MR. EINBERG: Thank you.

Dr. Vasken Dilsizian, ACMUI Vice Chair and nuclear cardiologist?

DR. DILSIZIAN: Present.

MR. EINBERG: Dr. Ronald Ennis, radiation oncologist?

DR. ENNIS: Present.

MR. EINBERG: Mr. Richard Green, nuclear pharmacist?

DR. GREEN: Present.

MR. EINBERG: Dr. Hossein Jadvar, who was

unable to attend due to other commitments, so he is not in attendance.

Ms. Melissa Martin, nuclear medicine physicist?

DR. MARTIN: Present.

MR. EINBERG: Michael O'Hara, FDA representative?

(Pause.)

MR. EINBERG: Maybe he can join us later.

Mr. Zoubir Ouhib, radiation therapy physicist?

(Pause.)

MR. EINBERG: Mr. Ouhib is trying to call in, so he should be joining us shortly.

Mr. Michael Sheetz, Radiation Safety Officer?

(Pause.)

MR. EINBERG: Ms. Megan Shober, state government representative?

MS. SHOBER: Present.

MR. EINBERG: Very good. Thank you.

Dr. Harvey Wolkov, radiation oncologist?

DR. WOLKOV: Present.

MR. EINBERG: We do have a quorum, so we have at least six members present.

All members of the ACMUI are subject to federal ethics laws and regulations and receive annual training on these requirements. If a member believes that he or she may have a conflict of interest -- and the term is broadly used within 5 CFR, Part 2635 -- with regard to an agenda item to be addressed by the ACMUI, this member should divulge it to the Chair and DFO as soon as possible. ACMUI members must recuse themselves from participating in any agenda item in which they have a conflict of interest unless they receive a waiver or prior authorization from the appropriate NRC official.

Due to the ongoing COVID-19 public health emergency, the NRC is continuing to allow flexibility in telework status. As such, we are all working remotely and each individually calling in to this meeting. NRC staff members who are participating by phone today are Kevin Williams, Kellee Jamerson, Dr. Davis (phonetic), Dr. Howe, Dr. Tapp, Lisa Dimmick, Dr. Hallahan, Ian Irvin, Daniel DiMarco, and Valerie Gray.

Members of the public who notified Ms. Jamerson that they would be participating in the teleconference or registered for the Webex will be captured as participants on the transcript. Those of

you who did not provide prior notification, please contact Ms. Jamerson at kellee.jamerson@nrc.gov. Kellee is spelled -- or the email is spelled K-E-L-L-E-E, dot, Jamerson, J-A-M-E-R-S-O-N, @nrc.gov.

Today's meeting is being transcribed by a court reporter. We are utilizing a bridge line for today's -- for the audio of today's meeting, and the phone number is 1-800-369-1898. The participant passcode is 8157030. Once again, the passcode is 8157030.

This meeting is also using the Webex application to view presentation material real time. You can access this by going to usnrc.webex, W-E-B-E-X, dot com, and searching for event number 1999109533. Once again, the event number is 1999109533.

The meeting material and agenda for this material can be accessed from the NRC's public meeting schedule. Dr. Metter, at her discretion, may accept comments or questions from members of the public who are participating with us today. Individuals who would like to ask a question or make a comment regarding a specific topic the ACMUI has identified or discussed should dial star-one to signal the operator that you

wish to speak. Please clearly state your first and last name for the record.

Comments and questions are typically addressed by the Committee at the end of a presentation. After the Committee has fully discussed a topic, we will notify the operator when we are ready for the public comment portion of the meeting.

At this time, I ask that everyone on the call who is not speaking to please place your phone on mute. If you do not have the capability to mute your phone, please press star-six to utilize the conference line mute and unmute functions. I would also ask everyone to exercise extreme care to ensure that the background noise is kept at a minimum, as any stray background sounds can be very disruptive on a conference call this large.

I will now turn the meeting over to Mr. Kevin Williams, Director, Division of the Material Safety, Security, State and Tribal Programs, for some opening remarks.

Kevin?

MR. WILLIAMS: Good morning, and thank you, Chris.

I'd like to welcome everyone to the ACMUI Spring 2001 meeting. As Chris stated, my name is Kevin

Williams, and I am the Director for the Division of Material Safety, Security, State and Tribal Programs.

I first want to begin by thanking the ACMUI for all your hard work and support to the NRC. We truly value your contributions and expertise as it relates to the medical use of radioactive material. This is our third remote meeting with ACMUI, and I think they've all gone extremely well. And I may go a little off script here, but I think a lot of it is to Kellee Jamerson's hard work to make sure that we are knowledgeable and aware of all activities that are going on.

So, thank you very much, Kellee.

I hope that you are all remaining safe and healthy, and I look forward to when we can conduct these meetings again in person. I would like to highlight a few items that may be of interest to the ACMUI and the meeting participants.

With regard to Commission-related activities, on February 24th of 2021, the staff developed SECY 21-0013, which is a rulemaking plan to establish requirements for rubidium-82 generators and emerging medical technologies. The staff developed this rulemaking plan to give the Commission rulemaking options to establish calibration and dosage

measurement requirements for rubidium-82 generators and to enhance the regulatory framework for well-established emerging medical technologies.

The staff is recommending a rulemaking that would establish a performance-based requirement for rubidium generators and all current well-established emerging medical technologies, and would also broadly examine 10 CFR, Part 35, to determine where we could update our prescriptive requirements to revise them to be more performance-based. SECY 21-0013 is currently under review by the Commission, and the staff will not take any actions related to the rulemaking and directed by the Commission.

So, status of NRC activities, training and experience -- as mentioned during last year's meeting on January 13th of 2020, the staff submitted a notation vote to the Commission providing a rulemaking plan to revise the training and experience, or commonly referred to as T&E, requirements for use on unsealed byproduct materials in 10 CFR, Part 35.

The Commission is still deliberating on this topic, and once Commission direction is received, the staff will take appropriate action.

Abnormal occurrence criteria -- on July 27th of 2020, the Commission approved the staff's

recommended option to develop and propose to the Commission a limited revision to the abnormal occurrence, or AO, criteria in a medical event in source security areas only. The NRC staff is drafting a revision to the AO criteria and is expecting to provide it to the ACMUI AO Subcommittee for review shortly.

Extravasation. The ACMUI Subcommittee provided recommendations on extravasations and infiltrations at the September 2019 meeting. Currently, the staff is finalizing its independent evaluation and plans to provide it to the ACMUI for review by the end of this month.

Phase II revision of Regulatory Guide 8.39. The Phase II revision to Regulatory Guide 8.39, which is a release of patients administered radioactive material to update the dosimetric equations, methodologies, tables used to calculate dose to members of the public from released patients is in progress, and the staff plans to provide a draft of Reg Guide 8.39, Phase II, to the ACMUI Subcommittee for review in early May.

Reporting nuclear medicine injection and extravasation as a medical event. The petition for rulemaking on May 18th of 2020 -- a petition for rulemaking was submitted requesting that the NRC revise

its regulations to require nuclear medicine injections and extravasations that exceed 50 rem dose equivalent to tissue as a medical event. The petition is currently under review by the staff, and the rulemaking division and the medical team is coordinating their evaluation of extravasations with (audio interference) what happened, essentially, the latest ACMUI fall of 2020 meeting.

On November 18th, 2020, the ACMUI briefed the Commission on a variety of topics, including an overview of ACMUI activity, the staff evaluation of training and experience required to administer radiopharmaceuticals requiring a written directive, patient intervention, extravasations, and trends in radiopharmaceuticals.

My observation of that meeting is I thought that the meeting went extremely well. The Commission really enjoyed the opportunity to engage the ACMUI, and the ACMUI did a great job of addressing some very tough or difficult questions.

Organizationally, the NRC has made a number of changes within the recent new administration. On January 22nd of 2021, Chris Hanson became the Chairman of the NRC. And the outgoing Chairman Svinicki, she left the Agency, thereby creating a

vacancy in the Commission, which the President shall fill shortly.

Changes in ACMUI, since the fall meeting, two members, Mr. Gary Bloom and Dr. Schleipman formally resigned from the ACMUI. We really appreciate everything that they had participated in in our activities. Their contributions were extremely valuable to the NRC, and we will miss their insights.

The resignation of Dr. Schleipman also left a vacancy for the ACMUI Vice Chair. As we noticed just last week, we are pleased to announce that Dr. Vasken Dilsizian has been appointed to serve as the Vice Chair of the ACMUI. We congratulate him on his appointment and look forward to his leadership there.

The NRC staff is working to fill the Patients' Rights Advocate and Healthcare Administrator positions. Nominations for these positions have closed. However, nominations for the Healthcare Administrator are being accepted until April 5th of 2021.

So the following presentations will be provided today. Dr. van der Pol of Maastricht University located in the Netherlands will provide an overview of case studies on the consequences of radiopharmaceutical extravasations and interventions.

Dr. Katie Tapp will provide an overview of the NRC staff's evaluation of patient release consideration associated with temporary brachytherapy devices. And Dr. DeWerd, a representative from the American Association of Physicists in Medicine, will give a presentation on calibration procedures for brachytherapy sources.

At this time, I will turn the meeting back over to Dr. Metter. Thank you.

(Pause.)

MR. WILLIAMS: You're on mute, Dr. Metter.

DR. METTER: Thank you very much for that reminder.

So thank you very much, Mr. Einberg and Mr. Williams, for your very nice review of the NRC staff's work and the ACMUI's work this past year and ongoing activities.

Our next item on the agenda is Ms. Kellee Jamerson, who will be giving a review of the past ACMUI recommendations and provide NRC responses.

Ms. Jamerson?

MS. JAMERSON: Good morning, everyone. I will be providing the old business report and giving a status update on some of the items from the ACMUI's recommendations and action items, beginning with 2019,

Item 17. This item was partially accepted by the staff, if you recall from a September 14th, 2020, closure memo.

This particular recommendation from the Appropriateness of Medical Event Reporting Subcommittee suggested that NRC staff, in coordination with ACMUI, should provide additional information to NMED users regarding the best practices for preparing NMED reports for medical events through an IN or through presentations through professional society meetings.

So the staff has drafted an information notice and has shared this with the ACMUI Subcommittee. So we are working to get the feedback from the Subcommittee. And with the internal coordination and time required that it takes to publish an information notice, staff is recommending that this specific recommendation remain open and has changed the target completion to summer/fall 2021.

For Item Number 18, the ACMUI endorsed the evaluation of Extravasation Subcommittee report at --

OPERATOR: Hi. This is Sandy. I'm your operator. Are you part of the group that needs to be in the speakers group? Hello? Please check your mute button. Hi.

MS. JAMERSON: -- to provide this to the

ACMUI for review by the end of this month. And the staff is recommending that this particular recommendation remain open with a target completion date of summer/fall 2021.

Item Number 4, the ACMUI endorsed the Patient Intervention Subcommittee report as presented. This was at the spring meeting of 2020. This item, like Item Number 18 of 2019, is also related to the extravasation report. And the staff is considering the ACMUI's recommendation from its report and plans to provide the ACMUI with an independent evaluation of extravasation (audio interference). The staff is recommending that this item remain open with a target completion of summer/fall 2021.

For Item Number 10, the ACMUI endorsed the Medical Event Subcommittee report as presented. This was at the fall meeting of 2020. The final report of the Subcommittee, dated September 24th, 2020, is available on the ACMUI Subcommittee Reports web page. And with that, the NRC recommends that this item be closed.

For Item Number 11, as part of a nonmedical events report provided by Mr. Mike Sheetz at the Fall Meeting 2020, the ACMUI recommended to the NRC staff and/or the National Materials Program to evaluate the

issue of detection of short-lived medical isotopes in municipal waste. The staff has presented the ACMUI's recommendations to the Organization of Agreement States Board, and the Board would like to survey the Agreement States to determine the interest and need for this recommendation.

So, this will be occurring soon. The survey will be provided to the Agreement States soon. And depending on their response, we'll determine how this recommendation will move forward. For this reason, the NRC recommends that we keep this recommendation open with a target completion of fall 2021. And we will keep the ACMUI informed of the Agreement States' decision.

For Item Number 12, the ACMUI tentatively scheduled its spring 2021 meeting for March 15th through the 16th with an alternate date of March 22nd or 23rd, 2021. Given the availability of the ACMUI members and NRC staff, this meeting is obviously being conducted today on March 16th. So the NRC staff recommends that this item be closed.

And, Dr. Metter and ACMUI members, this completes the old business report and review of the ACMUI's recommendations and action items. I have proposed closure for two items, so is there a motion

to accept the report.

DR. WOLKOV: So moved.

DR. METTER: This is Darlene Metter. I second that.

MS. JAMERSON: Do I have -- is that Harvey?

DR. WOLKOV: Yes. I made the motion. This is Harvey Wolkov.

DR. METTER: And this is Darlene Metter. I second it.

Do I have any discussion?

Okay. Anybody opposed to approving the motion as delineated by Ms. Jamerson?

(No response.)

DR. METTER: Hearing none, Kellee, I believe it has passed.

MS. JAMERSON: Thank you.

DR. METTER: And that concludes your session. Thank you, Kellee, for your complete review of the past ACMUI recommendations and NRC responses.

Now our next session will be a special guest speaker on extravasations in nuclear medicine. At this time, I would like to thank Mr. Michael Sheetz, the ACMUI Radiation Safety Officer, who through his research, determination, and innovative initiatives

has brought the author of a major international article on nuclear medicine extravasations to speak with us today at our ACMUI meeting.

Thank you, Mike.

And now I turn this over to Mr. Sheetz.

MR. SHEETZ: Thank you, Dr. Metter. Can you hear me okay?

DR. METTER: Yes, we can.

MR. SHEETZ: Is our guest speaker on the Webex, Kellee?

MS. JAMERSON: He has not joined yet.

MR. SHEETZ: Okay. Then I'll proceed with my introduction in hopes that he can join us shortly.

Again, my name is Mike Sheetz. I'm the Radiation Safety Officer representative on the ACMUI. And in 1980 rulemaking, the Commission made the policy decision not to require licensees to report radiopharmaceutical extravasations to the NRC, which is the current position today.

The issue of whether radiopharmaceutical extravasations should be subject to any type of regulation by the NRC has been researched, evaluated, and debated multiple times over the past 40 years. With the introduction of new diagnostic and therapeutic

radiopharmaceuticals and a recent petition for rulemaking has prompted the NRC to again reevaluate whether the extravasation of radiopharmaceuticals should be reported to the NRC after medical events.

Our next speaker is an attending nuclear medicine physician at the Maastricht University Medical Center in the Netherlands. Prior to becoming a medical doctor, he completed training as an electrical engineer. His special interest in medical imaging allows him to link the two worlds that he loves of technology and medicine.

His clinical areas of interest were neurological, oncological, and cardiovascular imaging, and his research area of interest is in cardiovascular disease. He has researched and authored what is probably the most definitive and comprehensive study on radiopharmaceutical extravasations, which was published in the European Journal of Nuclear Medicine and Molecular Imaging in 2017. The article has been accessed almost 4,000 times and has been cited in over 30 publications.

He and I have corresponded several times about this article, and he was very gracious in seeing this presentation. He has also agreed to entertain some specific questions on extravasation that we wanted

him to address. So it is with great pleasure and appreciation to introduce Dr. van der Pol, who will share his perspective on extravasations in nuclear medicine.

MS. JAMERSON: Dr. Metter, this is Kellee. He has not joined yet, and I just sent him a reminder.

DR. METTER: Okay. Thank you, Kellee.

Well, while we're waiting for Dr. van der Pol, let's go ahead and go to the next item on the agenda until he joins. Or has he joined already?

MS. JAMERSON: No.

DR. METTER: Okay. I'd like to go to the open forum, where the ACMUI will identify medical topics of interest, perhaps, for the future.

Is there anybody on the call that would like to introduce a topic that will be of interest for future discussion on the ACMUI?

DR. DILSIZIAN: Dr. Metter, this is Vasken. Maybe I can start a little discussion on the extravasation topic.

DR. METTER: Okay. Go ahead. Thank you, Dr. Dilsizian.

DR. DILSIZIAN: Well, despite numerous discussions with the Subcommittee and the Committee of ACMUI on this topic of extravasation in nuclear

medicine and letters from major organizations like ACR, SNMMI, Radiation Oncology to request that extravasations not be considered as medical events, which has been the case for over 40 years, but rather be passive patient intervention -- and the question is why are we still discussing this extensively, and what is the concern?

And I guess, in my opinion, perhaps the publications represented thus far really indicate institutional experiences and does not necessarily capture the denominator or the millions of procedures that are being performed annually. And our guest speaker, who's done a fantastic job, Dr. van der Pol, who's going to be presenting meta-analysis of such publications -- we all know, while that meta-analysis was very much appreciated in scientific communities, it's simply summation of individual data that is institutional-based.

So extravasations of small quantity are not uncommon, as we all know. Usually, when it does occur, the dose is strained by the lymphatic system and ultimately is taken up by the organ of interest. And so it's really not an issue. On the other hand, if the extravasation is significant and the images therefore become poor and poor quality -- and those

are the cases where study may have to be repeated.

And in my opinion, it is this data that the NRC should capture. That is, how often is an extravasation an issue that results in poor-quality or poor-count images that the study has to repeat it? Now, the reason of that significance is that not only it suggests that you're capturing that extravasation was significant, but number two, by repeating the study, you are providing the patient extra radiation exposure as a consequence of the extravasation of the dose.

So I suspect this is going to be very small. At least in my experience over 30 years, I would say very few, less than five in my number of procedures I've performed, that we've actually required to repeat a study. It's a very, very few.

And the issue about the false positivity of findings if there is an extravasation like axillary node, well, that's part of the residency training. It is what we train our residents to differentiate true abnormalities from artifacts. These are things that are not limited to extravasation. It happens with a number of other things, like soft-tissue attenuation, subdiaphragmatic visceral activity, and it's really part of medical practice and medical training. And

some of these false positives are even part of Board questions.

So, in my opinion -- maybe I can have a discussion about this -- is that the NRC should actually look at the number of cases where an extravasation has required a repeating study the next day. And that should give an idea, of the millions of procedures that are being performed, how common is a significant extravasation and whether this is an issue or not. Thank you.

DR. METTER: Thank you, Dr. Dilsizian. That was a very nice summary of the issue involved, and that's a very good point that you made. And I agree with you that it's not infrequent that we do have extravasations, and very rarely do we have to repeat the study. Thank you very much.

Kellee, did Dr. van der Pol join?

MS. JAMERSON: He has not joined us yet.

DR. METTER: Okay. Thank you.

Anybody else on the Committee, any other comments or -- they would like to make regarding extravasation?

(No response.)

DR. METTER: Dr. Dilsizian, let me ask you, as far as what your Committee has looked at on

extravasation, if they -- the majority of procedures we do in nuclear medicine are diagnostic. And these generally tend to be smaller doses and mainly aimed at imaging. What about the issue of therapeutic extravasations? Have you all looked at that?

DR. DILSIZIAN: Well, as you know, the therapeutics of IV administration is relatively new in the field of nuclear medicine. So we don't really have a lot of experience. But what I'm proposing is that perhaps the NRC staff should start requesting sites to report both diagnostic and therapeutic.

I mean, I know the diagnostic dose is small. It's not the issue. But the dose of the radiation exposure that's necessary for the patient -- we do understand that it's limited, but simply to capture this idea that whether extravasation is an issue and whether it's significant enough to impact the image quality to repeat the study.

I think that by just simply gathering this data, this issue probably can be addressed much more objectively, rather than having -- publications are limited to specific institutions and doesn't really reflect the entire denominator of the procedures performed.

DR. METTER: Thank you. That's -- thank

you very much, Dr. Dilsizian.

Any other members on the Committee who would like to make a comment on that?

(No response.)

DR. METTER: Okay. Hearing none --

OPERATOR: I have one from the general public, if you would like.

DR. METTER: Yes, please.

OPERATOR: Okay. Our first question comes from Mary McCormack.

You may go ahead.

MS. MCCORMACK: Yes. So I don't understand if we're -- can you hear me okay?

DR. METTER: Yes, we can.

MS. MCCORMACK: Okay. I know medical event is wrong route, more than 20 percent dose and 50 rem to an organ. So, with just regular old tech 99m, that's happening. If we give them two doses of, you know, 20 millicuries into the -- under the subcutaneous, and then we give then 20 millicuries IV, they've gotten double the dose, greater -- that's greater than 20 percent. They're 100 percent extra. And then the exposure is going to be over 50 rem with the way tech decays with some beta.

Yeah. So I don't understand how, I mean,

just based on the definition of medical event, how that's not -- that doesn't fall into that category, not to mention FDG, which I've seen full doses be infiltrated, you know, with a positron emission under another double dose, subcutaneous and then another IV. So I don't understand how it doesn't fall into that category based on the definition of medical event.

DR. METTER: Dr. Dilsizian or another Committee member, would you like to take that question?

DR. DILSIZIAN: I would request the NRC staff to address that.

MR. EINBERG: Yeah, so this is Chris Einberg.

Yeah, I would suggest, then, Dr. Metter, that yeah, let's have the ACMUI deliberate first, and then we can accept comments from the members of the public later on. At this point, we're in the listen mode and we're happy to take these comments, but we're not here to respond to questions at the moment.

MS. MCCORMACK: Okay. Thank you.

MR. SHEETZ: This is Mike Sheetz.

DR. METTER: Yes. Mike, go ahead.

(Simultaneous speaking.)

MR. SHEETZ: -- respond to that question. I feel that the medical event recording rule is

intended to capture errors on the part of the licensee that exceeded a certain dose threshold. Performing the administration of radiopharmaceuticals is a practice of medicine issue that involves both technical skills and challenges with patient anatomy.

So to classify an extravasation as an error is not consistent with its original intention. Also, the .5 sievert tissue dose threshold was implemented in 2002 to eliminate errors in diagnostic administrations from being recorded as medical events, so they did not rise to the level of causing any patient harm. This .5 sievert dose threshold is not intended to be applied to small lines of tissue such as that surrounding an extravasation, which did not result in any patient harm.

So a medical event reporting extravasations will not likely contain a root cause analysis or provide any generic causal information that will be applicable to other licensees in helping them to prevent other extravasations. And so I recommend to the Medical Extravasation Subcommittee and the Patient Intervention Subcommittee it is most consistent and appropriate to classify extravasations as a type of patient intervention. That way, it will capture those that actually result in patient harm or

tissue damage by requiring them to be reported.

Thank you.

MR. EINBERG: So, Dr. Metter, this is Chris Einberg. As Kevin mentioned -- Mr. Williams mentioned in his opening remarks, the staff is working on the independent evaluation of extravasations, and we will be providing that report to the ACMUI Subcommittee at the end of March. And the ACMUI Subcommittee will have the opportunity to provide comments on the NRC staff's and the independent analysis of extravasations.

We're not prepared at this moment to go into any discussion regarding our evaluation. So I would suggest that the topic of extravasations -- you know, or I would just say that you'll have ample opportunities to deliberate extravasations in the future, and we will hold a -- at the appropriate time, once the ACMUI Subcommittee provides their recommendations, we will hold a public meeting to fully discuss extravasations and what the ACMUI and NRC staff positions are on extravasations.

DR. METTER: Thank you. Thank you, Mr. Einberg, for that and for that guidance.

And I would just like to say that the comment that Mr. Sheetz gave was also the same comment

he had in his report to the NRC staff and the ACMUI Subcommittee. But I do appreciate that, and I really appreciate the NRC staff looking at this issue that is a concern for our licensees and our users.

At this time, has Dr. van der Pol joined the Committee meeting?

MS. JAMERSON: He has not joined the Webex, and I'd like to go to Sandy, our operator.

Do we have -- has he joined the conference line?

OPERATOR: No. He's not joined on the phone either.

MS. JAMERSON: Okay.

OPERATOR: If he has joined and he's come in under the guest passcode, please press star, zero, and I'll grab him.

DR. METTER: Let's give it a few more minutes to see if he is on the call and just actually will be able to join us shortly.

MR. EINBERG: Can the operator please repeat what Mr. van der Pol needs to do if he's on the public line?

OPERATOR: If he's on the line as a guest, he can press star-zero, and I can go ahead and move him into the speaker conference.

MR. EINBERG: Thank you.

So, yes, Dr. van der Pol, if you're on the line, please press star-zero, and the operator will get you.

DR. METTER: Operator, has anybody attempted to join the meeting through that method?

OPERATOR: No, no one has.

Once again, if you're on the line, please press star-zero, and I will grab you and move you to the correct location.

One moment, please.

(Pause.)

OPERATOR: Okay. That was not them.

DR. METTER: Okay.

Mr. Einberg, let me just ask you, since this session was targeted for an hour and we -- it is 20 minutes past the time it's supposed to start, would you be opposed if we proceeded on to the next item, or should we go ahead and go according to our schedule? And that next item is at 11:30.

MR. EINBERG: Yeah. I think let's just go ahead and move forward to the next agenda item.

DR. METTER: Okay. Thank you.

The next agenda item is the open forum, and this is where the ACMUI members will be able to

identify topics that are of interest to the ACMUI for further discussion. Are there any such topics that the ACMUI members would like to bring up at this time?

(No response.)

DR. METTER: Okay. Hearing none, do I have -- I would like to see if the NRC staff has any items. Mr. Einberg did bring up the issue of extravasations, and I think that will be at a later point in time. But any other issues that you might see that maybe, potentially, the ACMUI may be asked to review?

MR. EINBERG: Yes. Thank you, Dr. Metter. Yes. As I indicated, we will be providing the extravasation report to the Subcommittee for their review and comment before we finalize our recommendation to the Commission. So that's one item.

We also will be providing you, as Mr. Williams pointed out -- and let me pull up his opening remarks earlier. We'll be providing you with Phase II of Reg Guide 8.39, which is the release of patients administered radioactive materials. The Committee will be receiving that in early May time frame.

And so the other thing that we're working on -- and we thank the select members of the staff who've been assisting Dr. Howe in revising the abnormal

occurrence recording criteria. And we have Dr. Howe on the line, and maybe Dr. Howe can speak to the status of the AO reporting -- revisions to the AO reporting criteria and when that will be provided to the ACMUI.

Dr. Howe?

DR. HOWE: Thank you, Chris. Can you hear me?

DR. METTER: Yes.

MR. EINBERG: Yes.

DR. HOWE: Good. The working group has essentially developed its draft of the proposed changes to the abnormal occurrence, and we are currently in the process of preparing it to send it to the Organization of Agreement States to get the Organization of Agreement States' comment on it. And then we will also be sending it to the ACMUI Subcommittee, and that should be getting to the Subcommittee very soon. We sent it through our Office of General Counsel for just a very quick look at it before it goes out to anyone else.

So you should be getting it soon, and then you will have 60 days to comment on it. And the Organization of Agreement States will have, I believe, 30 days to comment on it, but it has to go through the Office of Budget Management in order to send it to the

Agreement States.

So we believe we have a good proposal. We've gone back and done a retrospective study to see how the new proposal would have captured medical events in the past to see if they were abnormal occurrences because one of the problems with our current abnormal occurrence is that it captures events that are significant to some extent, but it does not capture only those events that are significant from public health and safety.

So the group has worked very hard, and we're close to sending it out for comments. And once we have those comments, we'll send it to the Commission for their approval. So that's where we are with the abnormal occurrences. Thank you for your time.

DR. METTER: Thank you very much for that update.

Mr. Einberg, I did get a note from the chat box that -- it was actually interesting that possibly in the Netherlands, Dr. van der Pol may not be aware that we are on Daylight Savings Time. That is actually a -- perhaps --

MR. EINBERG: Okay. Well, let's continue on, and if he does join, then perhaps we can accommodate the schedule because I know that he has a very tight

schedule and was gracious enough to join us.

MR. WILLIAMS: Hey, Chris, this is Kevin and Dr. Metter. I was wondering, is there any desire to talk about Y-90 at all? I know that comes up every now and then, but I was just wondering if there was any interest or thoughts in regards to that.

DR. METTER: Y-90 in relation to the procedure itself or to the medical events?

MR. WILLIAMS: To the medical events.

DR. METTER: Yes --

MR. EINBERG: So, Dr. Metter, can I --

DR. METTER: Sure. Please.

MR. EINBERG: -- responded to that first?

So, Kevin, or Mr. Williams, once a year, the NRC staff provides the evaluation of all the medical events and presents that to the ACMUI. And at that point, we look at it to see whether there is an increase in certain medical events and, for instance, if there is a -- we noticed an increase in Y-90 events.

We've delayed that presentation at this time, and we're going to have a separate telecon on that to do some further analysis of the medical event data that we have. So we can anticipate having a telecon to discuss medical events in the future, and Y-90 is one of those medical events that seems to be

fairly prevalent.

But at the fall meeting, the ACMUI evaluates the data that we have provided them and does their own independent trending analysis of the events to see if they notice trends or if there's any recommendations for regulatory actions or guidance to be developed in these areas.

And with that, Dr. Metter, I'll turn it back to you.

MR. WILLIAMS: Thank you, Mr. Einberg.

DR. METTER: Yes, thank you, Mr. Einberg.

Also, in regard to that topic, the ACMUI is also looking at intervention radiologists for their expertise in perhaps the technical aspects that may be related and attributed to some of the medical events that are occurring due to Y-90 administration.

So are there any other issues that would like to be brought up for future topics?

MR. SHEETZ: Yes, Dr. Metter. This is Mike Sheetz.

DR. METTER: Yes.

MR. SHEETZ: I have a question about the SECY paper 21-0013. I wasn't sure if that was going to be discussed any further later in the meeting or if it's appropriate to ask questions about it now.

DR. METTER: I'm sorry. What was it?

MR. SHEETZ: The SECY paper 21-0013, the rulemaking plan to establish requirements for rubidium-82 generators and emerging technology.

DR. METTER: Lisa Dimmick, I believe you're going to be speaking about that or mentioning it.

MS. DIMMICK: Yeah. I was going to do it in the open forum this afternoon, but I can do it now if you would like.

MR. SHEETZ: No, I'll wait for the afternoon forum. That's fine.

MS. DIMMICK: Okay. Either way.

MR. SHEETZ: Thank you.

DR. METTER: Thank you. Thank you, Mr. Sheetz, for bringing that up.

Any other topics that the ACMUI would like to talk about and bring up for future meetings?

(No response.)

DR. METTER: Okay. Hearing none, would it be all right if we go ahead and go to our next item with Katie Tapp since she is on the agenda? And then when or if Dr. van der Pol joins in, she can -- her talk can be completed, and then he can follow?

DR. TAPP: That is okay with me. This is

Katie Tapp.

DR. METTER: Okay. Thank you. Okay. Let's go ahead, Dr. Tapp. And you'll be talking about patient release evaluation and emerging brachytherapy sources.

DR. TAPP: Thank you.

DR. METTER: Thank you.

DR. TAPP: I think Kellee's going to bring up the presentation, I think. Yep.

All right. As Dr. Metter mentioned, today I'm going to be talking about patient release considerations associated with temporary brachytherapy devices.

Next slide, please.

Start my video for you guys. This presentation will provide an overview of temporary implant devices, the scope of the staff's evaluation of patient release for those temporary implants, the many regulatory questions the staff intends to answer through its evaluation, and the next steps.

I would like to comment that this presentation is meant to provide the beginning of our evaluation and the questions we intend to be answering as we go through our evaluation. This presentation is not meant to be providing our answers for evaluation,

as that is ongoing at this time.

Next slide, please.

As a reminder for the patient release regulations, they can be found in 10 CFR 35.75, which states, a licensee may authorize the release from its control of any individual who has been administered implants containing byproduct material if the dose to any other individual from exposure to the released individual is not likely to exceed five millisieverts. A licensee shall provide a released individual with instructions on the actions recommended to maintain dosage to other individuals as low as reasonably achievable if the dose to any other individual is likely to exceed one millisievert.

Next slide, please.

The patient release regulations were only allowing release of patients who had permanent implants before 2002. In 2002, the regulations were amended to allow patients to be released with all types of implants if the dose limits were met. This included temporary implants in addition to permanent implants.

The Reg Guide 8.39 does not provide guidance specific for temporary implants for these patients to come back. The Reg Guide is specific, assuming the dose rate -- or assuming that these

patients will be exposing others the entire time as the decay occurs with the implant. They do not have temporary implant consideration in that Reg Guide.

Next slide, please.

Temporary implants are expected to be removed from a patient at a specific time to deliver the prescribed dose. If they stay in longer, the temporary implant then would give more than you would expect for the prescribed dose if the patients do not return. If the implant was to come off early, they would be given less than the prescribed dose.

Some examples of temporary implants include eye plaques, some types of brachytherapy seeds, and some emerging brachytherapy devices, including the Alpha DaRT and CivaDerm. It is these new emerging brachytherapy devices that has caused the NRC to want to take a closer look at how temporary implants enter regulatory questions relating to release of patients with temporary implants.

Next slide, please.

I'm going to go over an overview of some of these temporary implants. This is a very high-level overview. I'm sure many on the Committee have a lot more knowledge on these than this overview is intended to give. It's just to make sure everyone is aware what

we're kind of talking about.

For eye plaque brachytherapy, plaques are temporarily attached to the wall of the eye. These plaques contain brachytherapy sources, and there's shielding on the back side to prevent exposure away from the body. The eye plaque brachytherapy is licensed under 10 CFR 35.400, and patients are currently released under 10 CFR 35.75.

Next slide, please.

In addition, there's brachytherapy seeds that have been used for temporary implant brachytherapy before. Some iridium-192 seeds have been used in ribbons for temporary implants. In the past, many of these patients have stayed in hospitals during the treatment, especially before 2002. There's also iodine-125 seeds, which are used for radioactive seed localization. These patients are normally released from the hospital after the implant and then were returned to have the seeds excised at a later date.

Next slide, please.

A new emerging technology is called the Alpha DaRT. The Alpha DaRT is the first manual brachytherapy device which uses diffusing alpha-emitting radiation for therapy treatment. The Alpha DaRT contains radium-224 seeds that are affixed

to -- the radium-224 that is affixed to the seed.

Inside the tumor, as the source decays, the radium-224 atoms decay. The decay chain becomes into a gaseous form and goes and diffuses into the tumor volume. Therefore, it diffuses away from the seed itself and becomes more unsealed inside the tumor volume.

Next slide, please.

Currently, this therapy utilizes temporary implants. These seeds are contained in ribbons. In the future, they may be used for permanent therapy, but right now we're looking at it for the temporary implant portion and the release of the patient.

There's a lot more questions with the Alpha DaRT, as I was trying to explain there. And staff is looking at that in addition to the patient release. We are working on a draft, 10 CFR 35.1000, licensing guidance for the Alpha DaRT and the use of the Alpha DaRT. And we're hoping to provide that to the ACMUI for review in early summer for all the issues surrounding the Alpha DaRT.

Next slide, please.

The CivaDerm is another temporary brachytherapy device. It uses palladium-103 sources

which are affixed to the skin's surface. The patient will need to return to have these sources removed. These sources are self-shielded and have a cold and hot side. As shown in this picture here, there is a cold side, which is -- gold is cold; the gold side is the cold side -- and the blue side, which is the hot side.

Staff is still evaluating a licensing pathway for this use for the CivaDerm.

Next slide, please.

For the CivaDerm, the sources are placed on the surface of the body. They are placed on clean, dry skin, and they are attached with a surgical bandage, secured with an additional radiation shield cover, and covered with a waterproof shield. This picture here shows the fixation for these type of devices. As you can see, this is more of a surface application than many of the others that we have seen in the past.

Next slide, please.

Now I'd like to go into the regulatory evaluation the NRC is conducting and the areas that we're looking through and the questions we're asking for temporary implant brachytherapy patient release.

Next slide, please.

The first area I'd like to cover is public exposure.

Next slide, please.

As I stated before, 10 CFR 37.75 allows licensees to authorize the release from their control any individual that has been administered implants containing byproduct material. I think it's a focus on any individual. The licensee is releasing the individual that could expose people, other individuals, to a dose of less than five millisieverts or not likely to exceed five millisieverts.

Because this is a release for any individual and not for the source itself, licensees needed to be confident that the source is not going to become dislodged. If the source becomes dislodged, especially a higher source, it is possible that a loose source could exceed this limit. The assumptions that you use for patient release are assuming that the source is on a person and you're looking at the interactions that person is having with another person.

So we're really looking at what would happen if a source becomes dislodged, what is the risk to the public, and what is the likelihood of that source becoming dislodged? These are some of the questions we're asking.

Next slide, please.

In addition, the public dose limits in Part

20 exclude exposures to individuals administered radioactive material and released under 10 CFR 35. Due to the public dose limits in Part 20, which is 100 millirem per year, a lower limit than the patient release limit, the public dose limits do not exclude doses from sources not attached to a patient. So we're conducting further regulatory evaluation to determine if the public dose limits listed in Part 20 apply to sources dislodged from patients after the patients are released under 35.75.

This here is more of a regulatory exercise, trying to figure out which regulations apply, and then as well, which ones are the safe ones to be considering.

Next slide, please.

The licensees, as they're evaluating the approval of releasing patients with temporary implants, are going to need to consider the ease with which the source is becoming dislodged and the public exposure potential if those sources become dislodged. As you can note, the CivaDerm, as I mentioned, is more of a surface implant. So we're really looking closely at that because that one has, I think, a higher potential of becoming dislodged.

And note here from the maximum activity -- the maximum dose rate from the maximum activity sheet

-- that the sources are very hot if the unshielded side was exposed to the air. And 100 centimeters is the maximum dose rate. You're looking at 31 millirem per hour. So we're really needing to look at this carefully and consider what would happen if the source becomes dislodged and what is the possible likelihood of that happening.

Next slide, please.

Next consideration we're looking at is medical events for temporary implant brachytherapy.

Next slide, please.

10 CFR 35.41 requires licensees to have procedures that ensure high confidence that each administration is in accordance with the written directive. These procedures must address the following items: verifying the administration is in accordance with the written directive and determining if a medical event occurred.

Next slide, please.

If a source becomes dislodged or a patient does not return at a specific time, it is possible that a medical event could occur as defined in 10 CFR 35.3045. The first criteria that could happen is that a prescribed dose could be more than 50 rem to an organ or tissue, and a total dose delivered can differ from

the prescribed dose of 20 percent or more.

This could happen if a patient has the sources attached or has the sources implanted and decide -- that patient does not come back, it is possible that they could exceed this criteria. It is also possible the sources become dislodged and there would be an underdose, and it could also meet this criteria.

Next slide, please.

Another criteria that's important for temporary implant sources that a licensee may find they have a medical event is a dose to skin or organ or tissue other than the treatment site that exceeds 50 rem or more to the expected dose to the site from the procedure if the administration had gone in accordance with the written directive and 50 percent or more of the expected dose to that site if the procedure had gone in accordance with the written directive.

This could happen if a source became detached or moved, in a sense, and started treating another site, and when a patient comes back to have the source removed, the licensee notices that it had moved. It might be difficult at this time for the licensee to determine how long that source had been moved, but this is a possible criteria that could be

hit if one were to discover the source had moved during treatment when the patient was out and about. So it's important to consider that this is a potential medical event for temporary sources that we may find.

Next slide, please.

An item that's always important for a medical event is patient intervention. Patient intervention means actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing the treatment devices or prematurely terminating administration. If a source comes off by an action by the patient, it could be considered patient intervention and not medical guidance.

The idea that we're considering is the term, action. If a patient were to actually just say, I'm done with this, and remove the source, that is a clear action by a patient that is changing the course of the treatment, and patient intervention could be considered.

The question would be if a patient is going about their normal day and maybe is out in a rainstorm, and the licensee didn't affix the bandage properly or didn't give the patient instruction, and it's just the patient's action to be out in a rainstorm that causes

the source to fall off, is that really considered an action by a patient or should that be considered a medical event?

The NRC staff believes that we should evaluate this and provide guidance to licensees to be able to determine when patient intervention is occurring because I believe there will be several situations where this could be questioned in the future.

Next slide, please.

The next regulatory consideration is lost source.

Next slide.

If a licensee is unable to retrieve a temporary brachytherapy source, the source could be considered lost. 10 CFR 20.2201 requires licensees to report lost and licensed material above specified limits. Many of these sources are going to be above those specified limits in Part 20.

The temporary reports need to be made within 24 hours or 30 days depending on the activity themselves.

Next slide, please.

And written reports may be required 30 days after the initial telephone report and are going to

need to describe the circumstances in which the source was lost, a statement of the probable location or deposition of the source, exposure to individuals, actions taken to try to recover the source, and procedures to prevent another lost source. This would be a new consideration for many of our medical licensees for temporary brachytherapy therapy sources that we're looking into.

Next slide, please.

In addition, we have 10 CFR 35.406, which requires licensees to maintain accountability at all times for all brachytherapy sources in storage or use. If a source is lost, the licensee will not be able to account for the sources or be able to complete the record required by 35.2406 for temporary implants. Again, we believe more guidance is needed to describe how a licensee would be expected to meet this regulation for sources that are temporary implant brachytherapy sources.

Next slide, please.

The last regulatory consideration would be just other considerations we're looking into.

Next slide, please.

Brachytherapy source accountability requires a licensee to record the location of use for

all temporary implant brachytherapy sources per 35.3406. Again, this is something we're just looking at guidance for how a licensee would be expected to meet this requirement in these types of situations.

And then, finally, as the implants are temporary, the written directive will need to include dose, unlike permanent brachytherapy implants, which just need to include source strength. This is an important consideration for sources like Alpha DaRT, which might be being used temporarily and, in a situation, permanent. But they may have slightly different written directive requirements.

Alpha DaRT is a little bit interesting. That will be a 35.1000, so it may have its own. But for other types of brachytherapy that may have temporary and permanent, this is just a consideration for people to be aware of.

Next step. Next slide, sorry, I meant.

So here's the next steps, which is the staff is going to continue to evaluate these regulatory questions regarding the release of patients. We plan to provide the ACMUI with this evaluation when we're completed with it and any associated licensing guidance documents that come out of it, as well as if we have any questions going forward before we issue any

documents, we will bring it to the ACMUI's attention.

And then finally, as I mentioned earlier, we do have a licensing guidance that we're drafting for the Alpha DaRT, and we will be providing that to you guys hopefully this early summer timeframe for the Alpha DaRT.

That's the end of my presentation, and I'll open it back -- or turn it back over to Dr. Metter.

CHAIR METTER: Thank you, Dr. Tapp. That was a very interesting presentation and an exciting one for the future of (audio interference) therapy sources. Are there any questions from the ACMUI members regarding Dr. Tapp's presentation?

MEMBER OUHIB: This is Zoubir, can you hear me?

CHAIR METTER: Yes.

MEMBER OUHIB: Okay. I think is a very exciting topic, in my opinion. And I believe we can learn so much from the Khan study regarding the eye plaque where a lot of precautions were put in place. Granted, these were fairly secured applicators that, for them to fall from the eye is almost impossible -- never heard of. However I think that there will be some additional guidance that will have to be

implemented to make sure that none of these applicators are either accidentally removed, or perhaps involuntarily -- we're in the middle of the -- you know, basically sleeping and all the sudden they reach and something is itching, and they try to grab something -- whether or not -- there are a lot of circumstances that could perhaps occurs there. So I think we have so much to learn and provide some feedback to the NRC staff on that.

DR. TAPP: Thank you. Yes, that -- any knowledge that you guys have is -- is always great and welcome.

MEMBER ENNIS: This is Ron. This -- yes, these technologies are very exciting and -- full disclosure, I've had some conversations with the Alpha DaRT people about their product and -- and we are thinking about collaborating on some research. A -- it's a great example of what this whole body does, because we -- you know, it's really -- going to be a challenge to strike the right balance between patient safety without stymying -- you know, innovation that could help patient care. I see this really straddling that. And I could envision regulations in the name of patient safety that essentially stymied a development and --and the availability to the American

public. But I could also see where -- you know, lack of regulation leading to medical events. So it's going to be a fine line, I think, here to -- to strike the right balance. I hope that we can do that. And that we can do it relatively timely so that these new innovations can be tested in the clinic and -- and help patients.

DR. TAPP: If I could add a little onto that. This guidance for the patient release aspect for these services and evaluation -- what we're considering is doing something -- a generic guidance out. We do believe that these -- that should not stop the use of these materials at this time. The licensing guidance for Alpha DaRT is coming out -- I guess this summer -- hopefully have the draft for the licensing and the authorization of use. But the overarching evaluation for the temporary implant -- that final guidance may take us some time to hopefully -- it will just address some issues that we may have to just deal with individually as they arrive before that final guidance is done. The rule is out there. 35.75 is a published rule for patient release. It's just, I think, licensees need guidance, so we don't just constantly have questions going forward. So I'm hoping that we will -- don't stop anything as we're

doing an -- an evaluation of this.

And of course, the 35.1000 guidance for the Alpha DaRT is something that -- it looks at a lot of other things. I don't think that would fit under our other regulations right now for authorization.

MEMBER MARTIN: Katie, this is Melissa Martin. I have a couple of questions -- and I am sorry. The -- the superficial applicator, the one that's not the Alpha DaRT?

DR. TAPP: CivaDerm.

MEMBER MARTIN: CivaDerm. Two questions. Do you -- can you tell us what total activity is actually in that sample? In other words, it looked like there were nine or twelve of the little, individual seeds -- what activity are we actually looking at? And my other question is, are you looking at the training and education requirements for the users of that? Because I can see where the dermatologist would really want to use this in addition to radiation oncologists.

DR. TAPP: Yes. Just let me go back through my slides. I do not have right in front of me the maximum activity. I just have the maximum dose rate. And I don't want to speculate.

MEMBER MARTIN: Okay.

DR. TAPP: I have an idea in my mind, I don't want to take a guess. But I can get that information to you. As for the training and experience, with CivaDerm we have not finalized our determination yet on which licensing pathway it falls under. But it really does feel like a 35.400 with patient release issues. So therefore if it -- it is a 35.400 -- a manual brachytherapy source -- it would follow the training experience that we would expect for a manual brachytherapy.

MEMBER MARTIN: Okay. That's what it looks like. I agree.

DR. TAPP: Yes.

MEMBER OUHIB: This is Zoubir. Just to add to Melissa. Melissa, there is a -- a working group that has -- I told you, has been formed within the AAPM under BTSC. It's actually being chaired by Antonio Damato who actually is leading this project, per se, so there will be a lot of work and a lot of information that's going to be available in that aspect. As far as the dosimetry and -- and so on and so forth.

PARTICIPANT: Thank you. And then, I think, we may be going back to Dr. Van der Pol. Did I see that he's actually on here?

PARTICIPANT: I believe that is him, yes.

But are there any other final questions before we start our next session?

PARTICIPANT: Thank you, Katie.

CHAIR METTER: Thank you very much -- thank you, Katie. Mr. Michael Sheetz, do you want to go ahead and make a short introduction for Dr. Van der Pol, please?

MEMBER SHEETZ: Yes, that would be great. Thank you, Dr. Metter. In a 1980 rulemaking, the Commission made the policy decision not to require licensees to report written forms of extravasation to the NRC, which is the current position today. The issue of whether really considerable extravasation should be subject to any type of regulation by the NRC has been researched, evaluated, and debated multiple times over the past 40 years. But the introduction of new, diagnostic and therapeutic radiopharmaceuticals and a recent petition for rulemaking the response of the NRC to then reevaluate whether the extravasation of radiopharmaceuticals should be reported to the NRC as medical events.

Our next speaker is an attending nuclear medicine physician at the Maastricht University Medical Center in the Netherlands. Prior to becoming a medical doctor, he completed training as an

electrical engineer. This special interest in medical imaging allows him to link the two worlds he loves of technology and medicine. His clinical areas of interest are chronological, oncological, and cardiovascular imaging. And his research area of interest is in cardiovascular imaging.

He has researched and authored what is probably the most definitive and comprehensive study on radiopharmaceutical extravasations, which was published in the European Journal of Nuclear Medicine and Molecular Imaging in 2017. The article has been accessed almost 4,000 times and has been cited in over 30 quotations.

He and I had corresponded several times about this article and he was very gracious in agreeing to give this presentation. He has also agreed to entertain some specific questions on extravasation that we wanted him to address. It is with great pleasure and appreciation to introduce Dr. Van der Pol who will share his perspective on extravasations in nuclear medicine. And Dr. Van der Pol, I apologize for the United States still adhering to daylight saving time.

DR. VAN DER POL: Well no -- no apologies needed. Thank you very much for your very kind

introduction. Can you all hear me clearly?

CHAIR METTER: Yes, we can.

DR. VAN DER POL: Okay. So -- let me just share these slides. Oh, here it is. So well there's not a lot of further introduction needed, I suppose. But I -- I made these slides anyway. So I'll share with you it -- it also shows where Maastricht is in the Netherlands in relation to Amsterdam. But let's just start with the main part of the presentation because you asked me to tell you something about extravasation, which I did a literature study, as Mr. Sheetz already told.

So the -- actually came following a discussion on an extravasation case during my -- the other part of my training to become a nuclear medicine physician. And there was no protocol -- no local protocol on how to act in case of extravasation. So we had a lot of questions on that. So, like, can -- can extravasation actually cause deterministic effects such as skin burn or other symptoms? Should you apply any kind of therapy, like cooling or should it be warming? And should you perform dosimetry and how should that be done? And a lot of other questions.

So we started looking in -- in guidelines from all kinds of association -- the Dutch Association,

of course. But also the European Association. The SNMMI and also the German Association of Nuclear Medicine. But none of those had guidelines on extravasation. So we -- we -- the only thing we could do was try to -- to search in the literature for ourselves. So we did quite an extensive literature search. And after all the work we said we should share this information. So why not publish this -- this data? And this actually led to a publication in the European Journal of Nuclear Medicine and Molecular Imaging in 2017.

So we did this extensive search on Pubmed and Embase with the following search strings. It was a combination of extravasation and several synonyms, like infiltration, misadministration -- combined with a variety of isotopes which are used in nuclear medicine -- also spelled in different ways to -- to make sure everything was included. And it combined with radiopharmaceuticals. So radio isotopes. And it yielded 2,153 results in Pubmed and 3,493 in Embase. And of course were a lot of doubles. So we -- we merged all the results of Embase and Pubmed and of course excluded all the doubles. And we screened all those abstracts -- myself and another person. And if the abstract mentioned human radioactive tracer

extravasation, then the publication was marked for further analysis which were subsequently retrieved from online sources from different university libraries, or by just tracking down the authors' email addresses and just ask for the publication.

And afterwards, bibliographies were screened to compliment the search. So when we have collection, these data were extracted -- a number of cases -- to tracer involved injection place, estimated extravasation following an activity, estimated tissue dose, follow-up duration and method, applied medical interventions, and if these were advised or discouraged by the authors.

So we had 4,523 abstracts and a lot of those were rejected because there were animal studies -- and I think I should add that only a few animal studies were actually the subject of extravasation of a radiopharmaceutical dosimetry study. A lot of excluded abstracts were because they reported about extravasation or infiltration of a substance other than a radiopharmaceutical. Also, excluded when extravasation was mentioned as a technological finding which was actually not associated with the injection of radiopharmaceutical. And 603 abstracts were excluded because radionuclides were used for other

purposes than medical imaging assays.

And so we eventually retrieved the full text of 81 included publications. So we were actually able to retrieve all the full-text PDFs, or -- or printed versions of those publications. And we added 27 publications to a total of 108 publications. And 44 of those actually reported on extravasation of radiopharmaceuticals. So actual cases. And 37 of those reported diagnostic and 8 therapeutic. That makes for a total of 45, but one did both diagnostic and therapeutics. Ten expert opinion manuscripts were also included based on publications, but they did not report a case of extravasation.

So this table summarizes the results of the diagnostic traits for extravasations. And -- and you see the -- the largest number we're seeing in FDG as well as Tc bone tracers. And to be honest, that number is an overestimation because in one article there were actually a lot less extravasations reported then. And we reported in our article, that's actually something Mr. Sheetz found out. So we made a mistake. But still a decent number of reported extravasation.

And so I'll give you some examples -- of course, I cannot give you all those publications in -- in just 30 minutes. But I'll give you some examples

to show you what kind of publications these are. So starting by this publication by Wagner, et al. from 2011. And actually a lot of -- lot of cases we included were case reports in which axillary lymph nodes was visualized after a extravasation. So see in the right, lower quadrant, in the MIP image that there is an extravasation at the right arm. And you see a lot of intensity over there.

And you also see this lymph node, which accumulates a lot of tracer. And they reported this case because they had a petechiae from before the lymphoma treatment. And that actually didn't show any activity and they didn't see any anatomical evidence for a pathological lymph node. It should be a more mass-like nodule without hilum. So based on the CT image and based that there was no morphological change, they concluded that this was actually benign lymph nodes and probably the cause of the tracer extravasation.

The other similar example by Alibazoglu -- they are from 1998. And we see a lymph node pointed out, over here, with a tracer extravasation over here. And, you know, repeat study. Which is displayed in C and D. You don't see that lymph node anymore on this repeat study was done a few days after the first PET.

So that -- that's -- because an important finding because you have to be aware that extravasation can cause a false positive lymph node in oncology studies, which could lead to over staging of disease. And this is an example of by Hall et al. from 2006. And that's another type of studies. So these are more patients series in which they also measure the amount of activity at the injection site. In this case there were 190 FDG PETs evaluated and 39 of those, which is a fraction of 21 percent, had a visible focus at the injection site. And 36 of those only had less than 1-percent injected dose. And three of those had more than 1 percent. And in those three, the -- as the SUVmax actually ranged from -- the change in SUVmax actually ranged from zero to 21 percent. So that's, I think, another important lesson that significant tracer extravasation can actually give you a variation in SUVmax which is also something you have to be aware of when you're reading a nuclear medicine scan and have to choose PET scan, or another PET scan.

So this is a similar study with 400 FDG PET scans evaluated and also in about ten -- 10, 25 percent there was no visible extravasation. And five studies had repeat studies, so they gave numbers about these five patients with two FDG PETs -- one with

extravasation and one without. So they saw a change of about 10 percent in -- with Mediastinal SUV and Hepatic SUV. So this -- it's a minor change in SUVmax in those studies.

So now let's proceed to the technetium tracers, or the bone tracers -- example of a similar (audio interference) reports I showed you. So it's something you can't see in a severe extravasation case that there is lymph node drainage of the tracer and as a result, the lymph node will -- can't really be seen as a focal spot of activity in this patient.

So a lot of those other technetium tracers shows similar case reports of focal activity in a lymph node -- or just a painful experience for the patient. So let's proceed to the three cases which showed actually clinical symptoms, because all those cases -- they did not -- did only say there are extravasation. Of course they didn't report any follow up. So that's something you should know -- there isn't really much known about a follow up of basic tracer extravasation. Of course, if there would be severe consequences, you would expect with the high number of -- of nuclear medicine students all over the world every day, you should expect that someone should have published more severe symptoms, if there were any.

Now let's proceed to the patients with symptomatic extravasation. So one actually is from a case with iodocholesterol, which is used in an adrenal gland study. So after 13 days this patient developed an erythematous puritic patch, as you can see in the photo. And they measure it -- almost complete tracer retention. So this tracer had the property that it really adhered in that injection place and didn't go away -- and actually deposited all the radiation in that place. And gave the symptoms.

This is the second tracer with the reported symptoms, which is Thallium-201. And in this case, almost after two years of the injection of the extravasation of the patient also referred to -- also with an ulceration. So that -- these are the cases with diagnostic tracers. And these are the cases from therapeutic tracer extravasation. So in seven publications -- sorry, eight publications, ten cases were actually published in literature, which also generally showed more severe symptoms like this very early publications from Dr. Patton in 1950 with skin ulceration from hydroxycitrate complex, 90-Y, hydroxycitrate complex. And this one by Williams in 2006, which showed these combination -- this combination after Yttrium-90.

So the conclusions of our literature study were that extravasation of tracers is common. But I also think it depends on your definition of extravasation because if you only count a spot at the injection site, that's actually very common. But if you look at the -- at the -- at the PET studies, you see that the tracer extravasation cases with more than 1 percent are actually just a few. So it really depends on what you define to be a extravasation or a clinically significant extravasation.

I think the most important for us that -- us looking at is as physicians -- that there were no adverse effects of 18F, 99mTc, 123 Iodine, Gallium-68. And I think we should also add Indium-111. Now reported in literatures, which is good news because you don't even -- you don't have to expect any symptoms -- radiation symptoms in those tracers whenever there is an extravasation.

Sporadic reports of other diagnostic tracers, like Gallium, have described soft tissue lesions. And multiple reports of severe events following therapeutic tracer extravasation were reported. So like Mr. Sheetz -- so then as introduction you had a number of questions for me to give our perspective on.

So the first of these is, what is the frequency of extravasation in nuclear medicine, and what criteria should be used for identifying an extravasation? So first of all, the frequency is -- is of course not very known. The only thing -- it's a few case series which -- from which I presented a few studies. So ranging up to 20, 25 percent in some studies. But depending on the definition, I looked at our report of radionuclide extravasations in our hospital. And in the period from 2007 to 2018. And actually, only three extravasations were reported well. I -- that must be some underestimation, but we only reported the extravasation case in which there was a clear clinical substrate. So when a patient's had pain and -- and you know, that's -- that's -- even that is quite rare in our clinic with the precautions we take.

And to put it in perspective, we do around 6,000 nuclear medicine studies per year. And another perspective is that the report of contrast extravasation in -- in radiology in our -- radiology department in MUMC is 91 in the same period, between 2007 and 2018. And we estimate it to be about 50,000 procedures per year.

So of course, there must be some

under-reporting. But I think, if we do the right -- if you have the right precautions then extravasations is definitely something that can be -- yes, that can be -- I'm looking for the right word, sorry. Something that doesn't -- it's something that doesn't have to happen.

So there's no national registration which -- from which I was able to -- again, get the numbers on a national level. So the second part of the question, what criteria should be used for identifying extravasation? Visualization, fraction of the injected dose -- well, I think there should be multiple criteria, of course. First of all, the clinical criteria -- is there a painful injection? Is there swelling? Is there a redness or pallor? A visual and -- with visual, I mean, on the skin itself directly? So can you see injection sites in relation -- or do you see -- skin quality? Of course, skin quality that can be -- can possibly be attributed to extravasation. And the injected dose, of course, quality -- in my opinion, is a parameter in nuclear medicine physicians who monitor. So I don't think, if you have a fraction of the injected dose, that there is actually a possible threshold under -- over which you say that you should repeat the study. I think that something in which --

do if you -- if you judge that your quality is too low, then you should always consider a repeat study.

Also, if the quality is degraded by other costs. One caveat to this -- the studies with the FDG PETs do show that there is a possible effect from SUVmax, so I can imagine that percentage, or a fraction of the injected dose actually -- can actually be helpful in estimating the difference in SUVmax if you have more data available on what the influence is on your SUVmax, and even better if your scanner actually provides a correction on the SUVmax based on the percentage of injected dose in your injection spot. I think that could be a future -- a future that would be very interesting for a future as you use PET scanners and software.

In case of a therapeutic extravasation, any extravasation noted at any time point should be adequately treated and registered, irrespective of the dose. But what we do is we -- we register it locally. And we don't necessarily register in any national or -- register, or in -- to the authorities. I will come back to us in one of the later slides.

So what of the appropriateness of reporting extravasation that we saw in a certain dose threshold as a medical event? Well, if you ask me that

question then I am really curious about the method you use -- dose will be calculated because there is a huge variety in calculated dose based on the variation -- on the small variation of different parameters. I will come to that shortly.

If you want the threshold -- and I don't personally see any use in 0.5 Sieverts. You could use the erythema threshold of 2.5 Sieverts, but then again, if you don't have adequate method of very accurately measuring the -- the effective dose, then I don't think it's -- it's really useful to have a threshold in place, as a rule.

So how has the -- the European community address reporting of extravasations? There is no European legislation on healthcare. That's something the EU let's -- let's the nations -- the member states decide for themselves. So every member state has a -- state has its own legislation on healthcare. So I can give you the Dutch perspective on that. There is no definition or mentioning of extravasation, let alone where your pharmaceutical extravasation. So our laws are quite -- yes -- have a broad interpretation on what -- what is an adverse event. There are two different definitions we use, which is a complication -- an incident, or a calamity.

So a complication is an unintentional and undesired outcome during or following the actions of a medical care provider which demands adaptation of the medical procedure, or causes irreparable damage. So in this case, a medical care provider worked according to the medical standards and there was an unintended outcome -- undesired of course -- but which can actually be expected. It's a known complication. So we call that complication and (audio interference) in general to be a complication.

So we also have incidents, and calamities and incidents is an unintentional or unexpected event that is related to the quality of healthcare. And that could have led to the death of a patient, or serious harmful consequences. And calamity -- which has a very similar definition but in this case the -- the event actually has led to the death of the patient, or serious harmful consequences for the patient. So we only report calamities to healthcare authorities, and incidents of complications are reported and registered locally as advised by healthcare professional societies.

Unless one nature is not clear, and calamity is not ruled out, then we should let the authorities advise on the type of event. So next

question. If -- what are the issues and challenges in determining the tissue dose for an extravasation. So first of all -- geometry. So you see that in -- in some case reports they actually try to do a dose calculation and most of the time they use a sphere model, or a disc-shaped model. So of course it's most easy to work with a point source, but it's not realistic when the source is within the patient. So you have -- you have to work with other types of shapes. But -- especially the disc-shaped source is already giving you very complex mathematics.

And totally a very coarse model of the reality. Furthermore, which associated with geometry is that activity concentration is a very great factor in those calculations. And actually I have calculated some tracers in a sphere volume model. So you see on the x-axis, different sphere volumes ranging from zero to 100 cubic centimeters. On the y-axis, you see the amount of tissue dose, which actually should be effective dose in millisieverts but it's -- I made a mistake there. It's milligray on this slide, but it's -- it is millisieverts. For four kinds -- for four -- excuse me. For four different amounts of activity, one, ten, 100 and 1,000 megabecquerels and a variety of tracers.

So you see that, of course in all those amounts of extravasation sheet, that of course these therapeutic tracers, the Alpha emitters, and the beta emitters are on top. And then the PET tracers, which are also beta emitters, follow and after that, technetium -- the pink line -- it's the lowest line. So I also plotted two horizontal lines, one dotted line, and one solid line. And the solid line represents 0.5 millisieverts and the dotted line -- so the solid line is 0.5, the dotted line is 2.5 millisieverts.

So you already see in only one megabecquerel that if the volume is small enough -- which is actually quite realistic for the amount of volume used in tracer studies -- then in these theoretical cases, you already are well beyond these dotted line -- especially if you look at the gross for a more realistic amounts of tracers. Which shows that the activity concentration is -- is fairly important in calculating radiation dose. And it's fairly sensitive for small changes in volume, especially for the volume we use for tracer studies.

You -- and of course, if it's, in a way, a worst-case scenario and an unrealistic geometry. But the point is that the activity concentration is

a great factor.

So what about cystic distribution with -- which mean that the tracer can actually be in between layers, for a large part, and then actually there is quite a -- an amount of self radiation of the tracer fluid. So I mean, this fluid is in a sense between different layers of tissue. And the energy is the deposited within the fluid itself.

Another point is the homogeneity of the distribution, which can be fairly -- and in the real world, of course, you also have very complex geometry, which if the saying on time point one asked -- in time implies ten minutes or one hour or three days. It's any -- it evolves. It's not a simple disc shape, which remains the same during -- I mean, all the time. So it evolves.

Biological half-life -- that's -- that's also a very important tracers. Very important factor. It's probably somewhat less relevant for short half-life PET tracers. But still, very important. But it's more relevant for tracers with longer half-life. So if -- if you want to do a good -- go calculation, then you should know a lot about the dynamic behavior of the tracer about the biological half-life. And the unique -- like I said in the last

slide, you should also know the difference in -- in the shape of the extravasation during that time.

So what personnel training qualifications and quality assurance should be placed and monitored to prevent extravasation in medicine. Excuse me.

(Pause.)

DR. VAN DER POL: So a technician should be appropriately trained for obtaining -- obtaining the IV access and that should be something only a nurse or a doctor can do. But we have this special exception. So technicians can also do that. They should be trained how to do that and how to check if the patient is -- is okay. See if there's any obstruction, or see if -- if there -- if you can draw some blood. And you use a cannula instead of just a straight needle injection.

For a nuclear medicine physician and radiologist, you should always check the image quality, which is also something that the technician should be looking -- as well, of course. And if they're not adequate, regardless of the result, you should repeat the study.

And always look for signs of significant tracer accumulation near the injection site. And the radiation safety officer should keep a local

registration of extravasation cases. And the only goal of that is to improve the quality and to train technicians, or any physician for the bad track records. And of course also to assist in cases where there's actually a -- a symptomatic tracer extravasation in -- for instance, therapeutic tracer extravasation.

So that's it. I think we can move on to the discussion now.

CHAIR METTER: Thank you, Dr. Van Der Pol. I -- that was a very interesting presentation. And very thorough. Thank you for answering our questions that we -- Mr. Sheetz posed to you and in a very nice fashion. Are there any members on the ACMUI Committee that has a question for Dr. Van Der Pol?

MR. SHEETZ: Hello, this is Mike Sheetz:

CHAIR METTER: Yes, go ahead.

MR. SHEETZ: Thank you very much, Dr. Van der Pol, for the excellent presentation. I appreciated the issues and complexity in calculating the dose that you brought up. And I actually appreciated the cystic model that you mentioned and I -- my opinion is that's probably the more realistic model to follow in trying to calculate tissue dose from extravasation will be contained within layers of

tissue. And the tissue will not be uniformly mixed throughout the extravasation. And so, by sending it to via sphere or even a disc in calculating the dose within that sphere disc, there is a gross overestimate of the dose. And in the tables you showed how it exceeds millisieverts very early on from a small amount of activity.

And an actual dose to -- to the tissue, or to the skin -- wouldn't be reaching that level, I think. I'm going to ask your opinion, we haven't been seeing these tissue reports occurring. But the fact that we do not see these occurring routinely means -- that little dose is really just not being achieved to the determined tissue or skin. Thank you.

DR. VAN DER POL: Yes -- did you finish your question? Or do you --

(Simultaneous speaking.)

DR. VAN DER POL: Yes, yes -- I definitely agree with that. And that's actually the basis of our conclusion of our publication four years ago. Since there is just no evidence literature of symptomatic radiation damage in these traits -- in a lot of traits that are used which I mentioned before, on the same basis. I find it very unlikely that these cause these levels of radiation needed to -- to give symptoms --

radiation symptoms.

CHAIR METTER: Thank you, Michael. Are there any other questions from the ACMUI members -- from the subcommittee, or the ACMUI committee itself?

(Simultaneous speaking.)

CHAIR METTER: Go ahead.

PARTICIPANT: Go ahead.

MEMBER DILSIZIAN: Sorry, should I go first?

PARTICIPANT: Yes.

MEMBER DILSIZIAN: Thank you. Dr. Van der Pol, congratulations for putting together the meta-analysis. You know, these are not comments in anything to do with your publication. I just want to highlight some of the things you said, and summarize it, and maybe you can give your opinion about the four points that I'm going to make.

One is clearly we should separate diagnostics and therapeutic extravasations. The criteria probably should be different and just something that, you may, want to give your opinion about. Second, in general, it's much more difficult to publish negative studies. So all the -- all the publications are biased. So it's those that potentially have something to say about

extravasations, otherwise, no paper would be published. If I just present all of my experience from Mayo, for example, with only one repeat study that's over the last 20 years, that would not be published. On the other hand, if you have a paper with 400 pieces where five of them were repeat studies, then it becomes interesting -- even though that number is 0.01 percent of repeating studies.

So in my opinion, then, you know, the way you presented it -- there's extravasations and there's extravasations. The small ones -- they are inconsequential, even if you have an actual lymph node -- the couple of examples you gave -- we're all learned that and educated to know that. We can differentiate an extravasation inside a drainage from real malignancies. That's not confusing.

So the ones that are important, in my opinion, are the ones that were repeated. So of the FDG PET studies that you presented, five of them were repeatable of 400. That's 0.01 percent. That's pretty low. But that's -- to me, the repeat ones are the most significant ones. And yet, those were very, very small. Obviously, if clinical symptoms -- symptomatic extravasations are important, then we should be -- you know, knowledgeable about it and report

it. And regarding the SUV, we all know that the SUV counts per inject of dose per weight. I think that all of us who use SUVs are educated enough to understand not only does it depend on the injected dose -- and the extravasation, obviously, it would confuse an SUVmax -- but also it's based on weight.

A lot of oncology patients that we follow are losing weight every year. So we are very familiar that the SUV values are not an absolute -- that it's all clinically based, and we don't rely on SUV completely when we interpret images. So it's nice to say that, but it's not as critical because we're all very well educated on knowing the changes of SUV max based on injected dose and weight.

So in summary, I think in my opinion it seems to me that, just -- regular minor, extravasations is not clinically relevant. Those with -- who are repeated studies would be relevant, but except I think in this type -- these publications, only 0.01 percent. Clinically symptomatic extravasation should be paid attention to because obviously, it's rare but it's significant. And in my opinion, I think therapeutics, which is a new area, should be different from diagnostics. Maybe you can comment on all of those points.

DR. VAN DER POL: I'll try. So I think your first point was -- should you only discriminate between a diagnostic and therapeutic? I think that would be most convenient. But the problem is that we found some diagnostic cases with actual symptoms. So that's why -- and -- and if you read the article, then you would see that we also devised a protocol in our hospital, which we published. We -- we basically say those four tracers I mentioned earlier -- in those cases you can just ignore possible effects of radiation -- or, not ignore. You don't have to expect any clinical symptoms. So in these cases, you don't -- yes, that's no -- no reason to assume that there -- be any clinical symptoms. But there might be some tracers. Like F-Fluoride which could possibly give you radiation burns.

So in those cases, I think it's a different -- that's a different plane because I think actually, if you know there's a tracer extravasation, that would be worthwhile to just follow that patient and let him come after a few weeks and see if there are any symptoms. And if you do see symptoms and comes up with a -- plastic surgeon, for instance. So I would like to only discriminate between diagnostic and therapeutic tracers, but to discriminate between the tracers for

which no evidence is found that they give radiation symptoms, and the other tracers -- only two, actually -- for which there was some publications for -- with symptoms of radiation burns.

Do you agree on that? Or would you like me to --

(Simultaneous speaking.)

MEMBER DILSIZIAN: No, I agree obviously. I -- diagnostic -- as long as using symptomatic extravasation rather than diagnostic or therapeutics, I think it's important.

DR. VAN DER POL: Yes, okay. So your next point was on the amount of evidence. Yes -- no, the evidence was very, very sparse. And that's also a conclusion of our study. And that's -- it would be very much -- it would be very worthwhile if we would have more studies. And most of those could be quite basic. If you only -- in case of bone scan with osteo patients -- and by telephone, if you could two weeks later and gather this data. You can also say -- you can already say some more about tracer extravasation. Or in case of the SUVmax, I think that's a good point. There are only a few cases in those studies filed as a repeat study. So if you want to learn more about SUVmax then you should -- you should want more -- more

research done.

So about negative results, yes that's true, there's always publication bias. I can't deny that. So the -- yes. That might be a reason for a lot of scientists not to undertake these kinds of studies. But I think since there are some tracer studies with FDG PET showing that there is some change in SUV max, you know, it's interesting to repeat that on a larger amount of repeat studies. And if you aggregate multiple hospitals and multiple studies, then you should be able to come up with some -- dozens of results. And -- which basically would be interesting to publish -- actually negative -- publication would be, but I think there might be an incentive still if you take the right angle.

So your next point was --

(Pause.)

MEMBER DILSIZIAN: No, I think -- no I think you covered them all. I appreciate -- I appreciate all of your responses. The bottom line I think is that the repeat studies, which is the most important part. Because the images will contour, not reliable -- even in a positively published paper, was only 0.01 percent.

DR. VAN DER POL: Yes, and I agree actually

with your point of view on that SUV max is just something that can help you.

(Simultaneous speaking.)

MEMBER DILSIZIAN: -- we don't use it as a diagnostic end tool, right? We just -- it's an adjunct to our read. It's not a -- and we -- we are on the way about issues related to SUVmax.

DR. VAN DER POL: That's true but there are some -- some diseases like neurofibromatosis in which there are thresholds knowing about which there is --

(Simultaneous speaking.)

MEMBER DILSIZIAN: There's always an overlap, there's no such thing as a threshold --

DR. VAN DER POL: Yes.

MEMBER DILSIZIAN: If -- if there's a -- there's an overlap -- of data.

DR. VAN DER POL: Exactly, yes.

MEMBER DILSIZIAN: Thank you.

DR. VAN DER POL: You're very welcome.

CHAIR METTER: And thank you, Vasken. There was another question, I believe, when I made a comment from the ACMUI?

MEMBER OUHIB: Yes, this is Zoubir. First of all, thank you for this -- a great, great

presentation. Valuable information. And more importantly, clarification -- the myth of extravasation. I was -- I have to admit I was -- I was very encouraged when you reported your own data over many years, which was very, very small percentage. Like it was -- like in one category it was 0.01 and in the other category was -- it might have been like, 0.6 -- 0.7 percent or something in that nature.

I like the idea of -- I didn't -- I like the idea of registration versus medical event reporting. I think that's really valuable and we can already learn, perhaps, from that. Which leads me to another point is your -- in your very first slide was like -- there was a bullet point on how to act in the case of extravasation. But I think I was hoping -- which you actually covered in part -- regarding the how to prevent these types of situations. And so that leads me to, do you think there might be a need of some sort of a practice guideline to actually help and assist people who -- as you quoted, in bad situations -- that's what they -- I think that would be really valuable. I'll stop there and let you comment.

DR. VAN DER POL: Yes, well I -- I think the way you perform your trace injections -- it's very important, of course. And I know from my older

colleagues who already retired a few years ago that -- not so long ago, for instance, they used straight needle injections and they saw a lot of extravasations in that line. That's where we use the (audio interference), which in -- it doesn't seem to be a much problem anymore. And I think there must be some -- some other reporting, like I said before, of -- local reporting of extravasation as well because that's the reasons of which you're enjoying your daily job, you're busy, and -- and it's something that -- it's possibly forgotten. So you have to think of a system, how to -- to do that in a very user-friendly way. And actually we have integrated these kinds of local reporting in our PET system and that -- we hope in the future that makes it easy and doable for anybody to -- to -- to report any -- any kind of events, like tracer extravasation.

CHAIR METTER: Thank you. Any other questions or comments from the ACMUI members?

MEMBER MARTIN: This is Melissa Martin. I was just wondering -- thank you, first of all, for a wonderful presentation. We really appreciate it. But there tends to be a punitive aspect to documenting extravasations -- sometimes dealt with primarily on -- or by, or with the technologist. And I was just

wondering how you handle that process. Do you penalize your technologists for extravasations? Do you track how many each technologist is doing? Or -- what is the attitude that you would recommend that we handle reported extravasations?

DR. VAN DER POL: Well, I think that's -- that's a personal -- an opinion for myself. But I don't think it works to penalize people in any way to -- in order to -- to improve their work. I think you should always do it in a very positive way. And -- yes. Again, that's how we work. We don't penalize, but we try -- for instance, we have an open complication meeting every -- every three months. So in the Netherlands, we are already merged with -- with radiology. So we have one big medical imaging department. So we do a complication meeting for all the complications on the department. And that way we know the -- we try to take care of it in a positive way and -- we don't try to penalize anyone if it's presented. And we have -- it's a meeting in which every event is respectfully presented and I think in such a positive atmosphere, then it's -- anyone should be able to -- to understand the importance of sharing such adverse events -- and the importance of understanding how -- how often it -- it happens. And to -- to see

if there's need to change the way people work.

MEMBER MARTIN: Thank you very much.

CHAIR METTER: Thank you. Any other comments or questions from the ACMUI?

(No audible response.)

CHAIR METTER: Okay, hearing none -- Dr. Van der Pol and Mr. Sheetz, thank you so much for a very important and practical presentation on an issue that's really very important to educate our new clients and community on this important -- quality of imaging in the care we give our patients. And I want to thank you -- thank you very much for looking at this because it's -- the topic that needed to be looked at and I appreciate your time and your expertise. Thank you very much.

DR. VAN DER POL: You're welcome.

(Simultaneous speaking.)

MEMBER EINBERG: This is Chris Einberg, I'm with the NRC. And on behalf of the NRC and -- we wanted to thank you for your research in this area. And then, yes, you know -- your valuable time making this presentation. This has helped clarify, you know, things in our mind as we move forward to look at the regulatory structure -- whether extravasations need to be reported as medical events. And our Advisory

Committee -- they will be receiving a report shortly on our evaluation. We do an independent evaluation on this as well. So -- thank you so much.

DR. VAN DER POL: You're absolutely welcome. And I -- I would like to hear if you have -- if you are going to change the regulations or not. Perhaps, Mr. Sheetz -- with whom I am already corresponding can -- can get me some information about that. I would be very interested in that.

(Simultaneous speaking.)

PARTICIPANT: Thank you.

CHAIR METTER: If I could keep in touch with you and keep us up to date on what's happening -- and we really appreciate your expertise and your time. Thank you very much.

DR. VAN DER POL: Thank you, good bye.

(Simultaneous speaking.)

PARTICIPANT: Thank you very much, Dr. Van der Pol. Appreciate it.

PARTICIPANT: Good bye, thank you.

CHAIR METTER: Okay, so it looks like it's time for our lunch break. And I'm -- are there other issues before we go? It's regarding the open forum that we were -- we had started.

(No audible response.)

CHAIR METTER: Okay, hearing none. Let's go ahead and break until -- the time is until 1:00 if that's all right with -- Chris, if that would be all right with you. We'll start at 1:00 with Ms. Jamerson doing her report on ACMUI reporting structure.

MEMBER EINBERG: Yes, that would be perfect. And that will get us back on track. And so let's start at 1:00 Eastern Time.

CHAIR METTER: Thank you, and you all have a good lunch. And thank you again Mr. Sheetz for that -- bringing Dr. Van der Pol -- it was an excellent presentation.

(Whereupon, the above-entitled matter went off the record at 12:23 p.m. and resumed at 1:00 p.m.)

DR. METTER: Good afternoon and welcome back to the afternoon session of the 2021 Spring ACMUI meeting.

Our first presentation for the afternoon will be Ms. Kellee Jamerson of the NRC, who will be reviewing the ACMUI reporting structures. Ms. Jamerson?

MS. JAMERSON: Good afternoon, everyone. My name is Kellee Jamerson. And as Dr. Metter mentioned, I will be providing the review of the ACMUI's

reporting structure.

This presentation will go over the current reporting structure, a discussion of our annual review, the frequency of our meetings and we'll have discussion by the ACMUI.

This slide provides a graphic of the current reporting structure. The ACMUI reports directly to Mr. Kevin Williams, who is the Director of the Division of Material Safety, Security, State and Tribal Programs. The Medical, Safety and Events Assessment Branch, Chris Einberg is the Chief, also reports directly to Mr. Kevin Williams.

And our Division, MSST, reports to Mr. John Lubinski in the Office of Nuclear Material Safety and Safeguards. And it goes up the chain to our Executive Director of Operations, Margaret Doane and to our Commission.

While the ACMUI does not report directly to MSEB, this branch specifically, the Medical Radiation Safety Team, helps to support the day-to-day activities of the Committee.

During the presentation of the Bylaws in September of 2012, the ACMUI recommended to have an annual review of its reporting structure. At that time, the ACMUI was presented with the option to

continue to report into NMSS or to report directly to the Commission. And the subcommittee report provided in 2012 stated that the working relationship between the NRC and the ACMUI remained excellent, and the reporting structure through the NRC staff continued to function effectively.

The subcommittee and ACMUI agreed at that time that the associated logistics with direct reporting to the Commission, such as more frequent meetings, did not and does not justify any change in the ACMUI's reporting structure.

The ACMUI currently holds two meetings at NRC headquarters each year, one in the spring and one in the fall, typically it's March/April time frame or September/October. And the ACMUI meets via teleconference approximately two to three times between these meetings on an as needed basis.

At this time, I would like to turn it over to Dr. Metter and the ACMUI for discussion for the Committee to decide or discuss whether it's satisfied with the current reporting structure as a standard as reporting directly to Mr. Kevin Williams and MSST and to hear any feedback from the ACMUI whether there are any issues with the frequency of the face-to-face meetings and what changes, if any, would the ACMUI like

to see?

DR. METTER: Thank you, Kellee. Are there any comments from the ACMUI regarding Ms. Jamerson's presentation and her questions regarding the current reporting structure of the ACMUI in relation to the NRC staff and the Commission?

Oh, Kellee, I do have a comment. I think that the NRC staff has been very, very supportive of the ACMUI. And I really think the working relationship has only excelled the amount of work that we do and the quality of work that we both provide together.

And I think that the current structure is very appropriate for the work we have to do and the support that your staff gives to our Committee members is incredible. And I really thank you for that. And, Chris Einberg, I really thank you also for your help and direction and guidance.

As far as the reporting to the Commission, I think it's currently -- once a year is adequate. And I think that the topics chosen are really very appropriate. And the interaction with the Commission during that time gives us a lot of insight into what their interest is and they see what we are proposing in their investigations, in some cases, for rulemaking.

So that's my opinion. And I thank you very

much for all of your support and your help over 2020 and before. Thank you.

MS. JAMERSON: Thank you, Dr. Metter.

MR. EINBERG: Chris Einberg here. Any additional insights from the ACMUI members?

MS. MARTIN: This is Melissa Martin. I would just agree with what Dr. Metter said. I think the working relationship we have right now seems to be working very well. And I really appreciate the support that we get from the NRC staff.

DR. METTER: Thank you, Melissa. Any other comments from the ACMUI members? Even accolades is fine, too.

DR. ENNIS: This Ron. So I'm satisfied and happy with the reporting structure. And I think Kellee is doing a great job.

DR. DILSIZIAN: This is Vasken. And I just wanted to also add that during the subcommittee meetings, the expertise and experience of the NRC staff members have been very valuable in guiding us in the right direction.

DR. O'HARA: And this is Mike O'Hara. I agree with the fact that we have a good working relationship.

MR. SHEETZ: This is Mike Sheetz. I

second all of the comments, exceptional support and cooperation with the NRC staff members. Thank you.

DR. METTER: And regarding -- this is Darlene Metter again. And regarding that, and thank you for accommodating, for example, our Netherlands special guest speaker today on extravasation and really that was very well coordinated.

Thank you, Kellee, and your staff for helping with that. And it was just a very, very good discussion and an excellent presentation. And thank you for working with Mr. Sheetz in setting this up.

MR. EINBERG: This is Chris Einberg. Yes, this is Chris Einberg. And, yes, I wanted to thank the ACMUI staff for all their efforts and all their hard work.

And it's a pleasure for our staff to work with the ACMUI members, and I think we do have a good collaboration going. And I'm always looking, you know, for opportunities to, you know, increase the collaboration and strengthen that relationship.

There is one question given that we have been operating in a COVID environment. We've been doing the virtual meetings. I wanted to know or get your thoughts, you know, when things get back to normal, would -- you know, these video Webex meetings have been

very useful. And I think we've all accommodated these very well. Would you like to see in-person meetings or virtual meetings or a hybrid of the two?

DR. DILSIZIAN: Vasken Dilsizian here. I don't think there's a replacement for an in-person meeting. As you can see, sometimes when Dr. Metter is asking questions, we don't even know if someone is muted or unmuted or they're answering. There's a big silence.

I think that an in-person meeting where we're in a circle and we're facing each other, the dialogues and the discussions are much more effective and continuous rather than abrupt stopping and then continuing. So I'm in favor of in-person meetings.

MS. MARTIN: This is Melissa Martin. I would totally agree. I just don't think -- I think we've done an amazing job to accomplish what we have for the last year. But I don't think there is a replacement for an in-person meeting if at all possible.

DR. WOLKOV: This is Harvey Wolkov. I fully agree. In-person meetings, I think should be available, safety permitting.

MR. GREEN: This is Richard Green. I'd like to concur with those previous thoughts. I think

there's a lot that occurs outside of the formal meeting with dialogue between members of ACMUI amongst themselves in hallways, at lunches. I think there's a lot of opportunity to further the goals of ACMUI and consult the NRC staff that is outside of our meetings.

DR. METTER: This is Darlene Metter. And I totally concur. I think the collaborative and networking that goes with face-to-face is really irreplaceable. And (audio interference) is much more fruitful. And, you know, getting the non-verbal cues from other members is very important, too. And I really think that an in-person meeting would benefit the work that we do. Not that we're not doing a good job. I think we're doing a great job. But I think it could further enhance the quality of discussion and the work that we provide for this Committee.

MR. EINBERG: Chris Einberg again. Thank you, everybody, for that valuable insight. As the NRC moves forward when we're looking into, you know, going back to the office, we're having these same kinds of discussions. Well, what's the new normal going to look like? And what does it look like when we go back?

And so this is very valuable. I do concur that face-to-face interactions are very beneficial. And there's a lot of non-verbal cues that we get from

each other and that's part of the communication as well.

DR. METTER: I do have a question for the Committee. If we were to have a face-to-face meeting, would any of your institutions not allow you to come because I would be able to come to a face-to-face meeting at this point in time.

MR. OUHIB: There are no restrictions at this point in our institution. This is Zoubir.

MS. MARTIN: Yes. This is Melissa. I'm not restricted.

DR. METTER: Okay.

MR. DILSIZIAN: Darlene, I was just -- I'm assuming -- I was assuming that, you know, obviously once we have herd immunity and a majority of the people are vaccinated, the institutions are back to the "normal" travel and no restrictions, I was assuming that we were going to go back to face-to-face meeting.

I think in the absence of that, it would be unfair for some of the ACMUI members not to be present because of institutional restrictions.

DR. METTER: Thank you, Vasken. And it is restricted for now. And, you know, people are being -- more and more individuals are being vaccinated.

MR. GREEN: Dr. Metter? This is Richard.

(Simultaneous speaking.)

DR. METTER: Yes, Richard.

MR. GREEN: This is Richard Green. I think now that we've mastered this Webex platform that it has functionality and will bear fruits for us in subcommittee meetings. Rather than pure telephonic, we can actually see each other and get some of that verbal cues. I think we've mastered this and can now use it during our subcommittee meetings.

MS. MARTIN: Good point.

DR. METTER: Good point. Kellee, you've got more work.

MS. JAMERSON: Thank you, Mr. Green. That's an excellent point.

DR. ENNIS: This is Ron. I agree with Richard's comments. In terms of restrictions, so my understanding of my institution is all of the restrictions are in place. I think, though, the restrictions really just are on university funds as opposed to actually constraining what you do. So given NRC pays the travel, I might even now be able to do it. But I was also assuming, like Vasken, that we were talking about, you know, the world post-vaccination over a high proportion of the population.

DR. METTER: Thank you. Any other comments from the ACMUI regarding this topic?

DR. WOLKOV: This is Harvey Wolkov. We did have travel restrictions that were imposed early on in the pandemic, and they have been lifted.

DR. METTER: Thank you. Does that help you, Chris, on --

MR. EINBERG: Yes. That was very helpful. You know, I would just note that currently the NRC could not have any in-person meetings, you know, an ACMUI meeting because we would have restrictions at this time.

But, you know, six months from now, we're in the fall, you know, things hopefully are much different.

DR. METTER: Okay. So thank you. So we'll see what happens in six months but thank you very much. Are there any other comments to make before we go on to the next topic?

MS. JAMERSON: Dr. Metter, this is Kellee.

DR. METTER: Yes.

MS. JAMERSON: So just to conclude my presentation, it's just a matter of some points of contact, which you all have this information. And I thank you all for your feedback and insights. And this will be greatly useful moving forward. So thank you.

DR. METTER: Thank you, Kellee.

MS. JAMERSON: That concludes my report.

DR. METTER: Okay. So our next presentation will be by Dr. DeWerd who will be presenting content on calibration procedures for brachytherapy sources. Dr. DeWerd will provide the presentation on the calibration procedures for existing brachytherapy sources and considerations for emerging manual brachytherapy sources. Dr. DeWerd? Kellee, is Dr. DeWerd on the call?

MS. JAMERSON: I do not think he has joined us yet. Sandy, has he joined the line, the phone line?

OPERATOR: No, he is not on the line.

MS. JAMERSON: Okay.

OPERATOR: Unless he came in under a guest. In case you have, Dr. DeWerd, please hit star 0, and I'll advance you to a speaker.

MS. JAMERSON: He may be joining momentarily since we are a little bit ahead.

MR. OUHIB: Yes. He's scheduled for 1:30.

DR. METTER: Okay. Well, we can go ahead and I think we've talked about the open forum for topics. Let me look at my notes quick. So let's just go ahead and move on to a section, the following section on the open forum.

At our last open forum, we talked about extravasation and the issue of impact and the quality of the study and the possibility of repeating the exam.

The Phase 2 Reg Guide 8.39 on dosimetry and the equations thereof was also brought up. The abnormal occurrence, the NRC is looking at that. And they are going to probably send it to the staff to review for about 30 days and then to the ACMUI subcommittee to review for a period of 60 days.

And then we have patient intervention and then the issue of Y-90 medical events was also brought up. Anything else that anyone can think of that we could discuss or bring up for future topics?

MS. MARTIN: Do we want to bring up the letter that we received from the ACR or is that a future topic?

DR. METTER: I believe that was for information only, wasn't that Kellee?

MS. MARTIN: Okay.

DR. METTER: Yes. I think that was information regarding their position on the topics that we have discussed, the training and experience and those topics there. Thank you for bringing that up, though, Melissa.

MR. GREEN: Dr. Metter, this is Richard

Green. Just for clarity, regarding the comments regarding medical events with Y-90, yttrium-90, we should be specific. I think we're talking about microspheres.

DR. METTER: I'm sorry.

DR. GREEN: Not the issue of Y-90 ZEVALIN.

DR. DILSIZIAN: Correct, yes.

DR. METTER: Yes, I'm sorry. You're correct. Thank you very much for making that clear. It's the yttrium-90 microspheres and the TheraSpheres, yes, the hepatic embolization, radioembolization procedures. Thank you for that clarification.

Okay. Any other things that the NRC staff would like to bring up or Mr. Einberg?

MS. JAMERSON: Dr. Metter? I'm sorry to interrupt. This is Kellee. I believe our speaker has joined.

DR. METTER: Okay.

MS. JAMERSON: Dr. DeWerd?

MR. OUHIB: Hi.

DR. METTER: Well, thank you, Dr. DeWerd for participating in our afternoon session for the spring ACMUI meeting and for speaking on calibration procedures for brachytherapy sources. Thank you very

much. And you may begin. Are you unmuted?

OPERATOR: This is Sandy. I have not -- he's not called in.

MR. OUHIB: He's on the screen.

MS. JAMERSON: Yes. He's on the Webex, but he hasn't joined the phone line yet. Hang on.

DR. METTER: Kellee, is there a way we can get ahold of him or can we get ahold of him on the chat?

MS. JAMERSON: Yes. I'm sending him a message now.

MR. OUHIB: I do have his cell number in case you want me to call him also.

DR. METTER: Go ahead, Zoubir. Go ahead and try and call him. We'll try both ways.

MR. OUHIB: Okay. He's not answering.

DR. METTER: Okay. Thank you. We'll just wait.

MR. OUHIB: Larry? Hey, Larry, can you hear me?

DR. DeWERD: I can hear you now, but I can't get on the line here.

MR. OUHIB: Let's see if we can resolve this. Kellee, what would you like him to do?

DR. DeWERD: I'm going to try audio connection.

MR. OUHIB: Mm-hmm.

DR. DeWERD: It says participant use following bridge line. It gives me a dial number, passcode. And then it says following entry of passcode, okay.

OPERATOR: He needs to dial in. That doesn't work from the Webex.

DR. DeWERD: Do you want me just to call in on that number?

MR. OUHIB: Hang on one second. You need to call the number, yes. Kellee, is this you speaking, right?

OPERATOR: This is Sandy, the operator.

MR. OUHIB: Okay. What would you like him to dial on the phone?

OPERATOR: He needs to dial the 800 --

MR. OUHIB: Okay. Hang on a second, Larry. Larry, I'm going to give you the number, 800 --

OPERATOR: -- 369 --

MR. OUHIB: -- 369.

OPERATOR: -- 1898.

DR. DeWERD: Yes.

MR. OUHIB: 1898.

DR. DeWERD: All right.

OPERATOR: And then he needs to use that passcode he used earlier.

MR. OUHIB: The pass --

DR. DeWERD: 157030.

MR. OUHIB: That's correct, right, yes? The passcode that ends with the 3-0, yes, 3-0.

OPERATOR: And I'll be waiting for him.

MR. OUHIB: And she'll be waiting for you. Sandi will be waiting for you, and she will transfer you.

DR. DeWERD: Okay.

MS. JAMERSON: Thank you, Zoubir.

MR. OUHIB: You're welcome. Go ahead. Go for it. I'll stay on the line with you. Okay?

DR. DeWERD: All right.

MR. OUHIB: Oops. He disconnected.

DR. METTER: How are we doing? It looks like he's speaking.

MR. OUHIB: Yes. Sandy was going to connect with him and transfer him.

DR. METTER: All right.

DR. DeWERD: All right. Can anybody hear me?

MR. OUHIB: All right.

DR. DeWERD: All right. That was

excitement. So where are we? What's going on?

DR. METTER: Dr. DeWerd, this is Darlene Metter. I'm the Chair of the Committee. And thank you so much for coming to speak with us today on calibration procedures for brachytherapy sources. And you may begin your presentation.

DR. DeWERD: Okay. Very good. So I presume everybody can hear me. And can we just talk about calibration procedures for brachytherapy sources?

And basically, what I'm going to cover is what's in place right now for photon sources especially and then also about other sources and draw a distinction here between quantities as well as basically talking about the future TRT type sources.

So, yes, the next five year quantities are the desirable quantity, and the AAPM requirement is absorbed dose to water. This quantity is determined from the other quantity air kerma strength. And that quantity is determined from AAPM, or the absorbed dose to water is determined from AAPM Task Group 43. It's a protocol to determine dose to patient.

So the calibration quantity from the National Institute of Standards and Technology, NIST, is air kerma strength. And that, of course, is

converted with a dose rate constant and note that the quantity activity, which is usually years, in other words millicuries or it should be becquerels, is not used for brachytherapy sources because we're concerned about the absorbed dose to the patient first off and activity does not give absorbed dose. It gives an activity. And so I'm trying to make a distinction here that I hope is clear.

So as we provide dose to patient, we want to know what the organ or the tissue is receiving and it's, of course, generally done through water as a standard material.

So the air kerma strength is the quantity of radiation emitted from the source after the cladding of the source, taking the activity, the contained activity and trying to convert it to an output or taking the output and trying to convert it to an apparent activity is not adequate because the activity, the cladding, could be different in each case.

So therefore air kerma strength is the general quantity used for photon sources. Brachytherapy sources have absorbed dose to water measured directly. And I'll talk about the TRT at the end of this.

Next slide. So the output quantities for

photons versus air kerma strength, and you can see that their beta sources or absorbed dose to water are usually at a depth. They use an extrapolation chamber to make this measurement at NIST, and it's usually two millimeters of depth of water.

I'm going to talk mostly about photon sources because of time constraints and some future calibrations.

Next slide. So we divide the brachytherapy sources generally into two sections, so low energy photon sources, but there we have both high and low dose rate sources, and high energy photon sources used for high dose rate brachytherapy, high and low dose rates as well and then, of course, beta dose or beta sources ophthalmic applicators, intravascular brachytherapy. And intravascular brachytherapy is still done. The manufacturer still sells some units, and so they are still calibrated.

Eye plaques for tumors, there's beta sources, new ones out, a concave bi-plaque. And there's ophthalmic applicators used to treat the eye. And these at strontium-90 sources. And the strontium-90 sources that come from these have been -- the NRC has said you had to get them calibrated and that was about 12 years ago.

There is no traceable calibration for them, new calibrations for them. So if they're calibrated, fine, you're okay because they're a 30 year half-life but basically otherwise they're not calibrated.

So a majority use in brachytherapy though is low energy, low dose rate or high energy, high dose rate sources.

Next slide. So just looking at the two sources that I mentioned there, the low energy, low dose rate, those are LDR seeds, iridium, palladium, cesium-131.

And the primary calibration is the wide angle free air chamber. That's what WAFAC stands for. That's from NIST. They have actually two wide angle free air chambers. They calibrate it, and they send the calibrated sources to the Accredited Dosimetry Calibration Labs, ADCL, who then calibrates well chambers to be used for the clinic.

The high dose rate, high energy sources are generally HDR afterloaders. Most of the time iridium-192, cobalt-60 is not here in the states yet but has been talked about coming via a number of manufacturers. There is no calibration for that right now for lack of cobalt.

The calibration primary standard for HDR is an ion chamber measuring out at 7-distances and then calculating what the dose air kerma strength would be for the source at 1 centimeter.

Next slide. The use of the free air chamber is for low energy. The use of a thimble chamber and air for high energy, high dose rate sources, the thimble chamber is what's calibrated, traceable to NIST, and, of course, an extrapolation chamber for beta sources.

Next slide. So why am I making such a difference here, especially for absorbed dose? Because when we're talking about effective treatment to neoplastic disease, we have to quantify the dose to the tissue of interest. And the dose, again, is not activity. It's a different quantity.

Standards should be specified by a clinically relevant metric and therefore is air kerma strength or in Europe it's called the reference air kerma rate, RAKR. And basically, the reference to kerma rate and the air kerma strength is the same number out at 1 meter. That's the only difference, basically, between those two. The quantity is energy deposited per mass, joule per kilogram at a distance in vacuo, in vacuum.

Next slide. So the air kerma strength is the characterization of a source output in terms of dose delivered to air FE1. The exposure, basically by W/e and the average energy produces an iron pair in dry air.

This is the quantity endorsed by the AAPM for use in the treatment and planning protocols and adopted in TG-43.

Next slide. This is the Task Group 43, the methodology, the protocol to determine the dose. And so the dose there, the air kerma strength is S sub K. I'm sorry. I'm trying to rush, I think. And the lambda is basically the dose rate constant. Those two, the air kerma strength and the dose rate constant converted to dose in water.

And there's geometry factors, radial dose function, anisotropy function, each of these to correct for the source, which would be located in a tissue. These are generally sources at length. And therefore, that's where geometry comes in. And a radial dose function is how it falls off in the tissue. And anisotropy is around the parameter of the seed.

Next slide. Air kerma strength, of course, is a well chamber for the clinic, traceable to NIST. The dose rate constant is measured by a TLD,

a Monte Carlo, and then averaged. A radial dose function, an anisotropy, all TLD and Monte Carlo. G is geometry, that's just basically for the Sievert integral.

All of these are consensus values and there's a website that you can go to to find the values for the given type of seed or source that you're using.

Next slide. This is a picture of the wide angle free air chamber at NIST. And the part on the right there, there's the seed. You're not going to be able to see it. But that's where you put the seed and then you measure it.

It's a low dose seed, a low energy seed. And it goes into the WAFAC there, which is a semi-free air chamber because there is a window in the front so it's not totally free air.

Next slide. So the low energy brachytherapy, the standard is 50 centimeters. This is an x-ray brachytherapy. I'm sorry. The source, for example, has been calibrated also at NIST. This is not, of course, great concern to the NRC because it's an x-ray source. But just for completion of the information, it's the same sort of equation protocol, and it's another free air chamber used for that. That's the end of what I'll say about x-ray

brachytherapy.

Next slide. So the medical physicist needs to calibrate the source or multiple sources are used, 10 percent of the sources, generally, for like prostate implants of low dose seeds. There's 10 percent of the sources out of 100 sources. Generally, there are 100 sources, not necessarily 100 implanted, but sometimes they are.

There's been examples of dead seeds in a batch and some seeds with twice the output. So the average comes out right. But, you know, if you put a dead seed in, you're obviously not treating the patient.

So basically, my point here, and I'll give you another example, if the manufacturer does their job well, and I don't mean to criticize manufacturers here, but you don't trust the numbers the manufacturer gives you. You should measure it. That's what all the physicists want to do for treating patients.

Calibration differs among sources because of the cladding, and there are at least 5 percent differences out many times.

Next slide. This is the iodine spectra. There are a couple of different sources here. 6702 is no longer made but that doesn't have a silver base.

In the silver base, you have the k alpha lines. That's what that first peak on the left there is showing.

Next slide. So the absolute standard, NIST does for the WAFAC, the wide angle free air chamber, transfers the calibrations to the ADCL. The ADCL's secondary labs all -- you know, we intercompare, and they all fall within the .6 percent. ADCLs are our traceability to NIST and the beta sources. Secondary laboratories fall within 2 percent and proficiency tests always 2 percent or so that K=2.

You will notice the reason here, the percentages are very precise. And they are kept that way because we have patients involved and so we want to know the dose as well as we can.

Next slide. Now I want to give you an example of a palladium-103 source. I won't tell you the manufacturer, but this manufacturer introduced it right at the beginning. And they did not have a NIST standard. They just said here's the dose, use it. And they used a cadmium source to calibrate the palladium-C.

The manufacturer then changed calibrations a number of times because he got a different calibration source. Self-shielding of the source encapsulation was different. There were a

number of changes.

All of a sudden there's a 9 percent shift in calibration, and this caused all kinds of consternation among the physicists that were using it. So the manufacturer communicated this by letter and that got everybody upset.

Next slide. It shows this is from Wayne Butler, who did a number of studies across a year. Now when they first started with this seed, they basically wanted 115 grey delivered to the patient. Well, you notice the first source that they sent out is actually delivered 119 grey according to the manufacturer's calibration.

They changed the cadmium source and then instead of 115 it was delivering 117 grey for a while. They changed cadmium source again, and it went to 114 grey instead of 115.

Another change, 118 grey and another change, 113 grey. And finally this is where the 9 percent change came. They changed the cadmium source again, and it was delivering 125 grey instead of 115.

They finally then calibrated at NIST and the NIST calibrations began to be used. And so when they first calibrated, there was a change. They said, okay, now it delivered 125 grey. Well, they changed

the source again and so there was, like, the 115 is the solid line at the bottom, 107 grey, 110. Finally, they got to 115 grey. If they went to the 125, which they said they wanted to do, you're delivering to the patient 116, 120 and then finally 125 grey when everything settled down.

And this took them a period of five years to sort of settle down in the source that they were doing. This is the reason that we don't want manufacturer calibrations. We want to have a NIST traceable calibration when we do this.

Now you say why five years when they got to calibrate it right away? Because they were changing a source. They were making a source different. But the user in all of these cases had a calibrated NIST source. And so they used their calibrated factor when they measured the sources given to them from the manufacturer instead of using the manufacturer's output.

So the patients were being treated correctly so to speak but not according to what the manufacturer was doing, not sending 115 grey source.

Next slide. So it changed many times, a 9 percent shift. That shows the importance of the standard and that physicists need to calibrate their

sources.

Next slide. So the clinical calibration uses a well chamber. And the insert of the well chamber is part of the calibration. Chambers and methodology for brachytherapy calibration is different from a nuclear medicine PET, and they use a dose calibrator.

Now I want to make a clear difference here of dose calibrator versus well chamber. Well chamber is air communicating. The dose calibrator is generally, you know, sealed.

So the dose calibrator generally reads an activity - this is the distinction I'm trying to make here -- not in dose or air kerma. And the energy dependence of a dose calibrator is more severe than a vented well chamber.

And so the comparison, I think, is the next slide. Next slide. I guess uptick so the quantity used for nuclear medicine is activity, becquerels. The quantity is not dose. The activity is measured -- generally administered by a syringe in a nuclear medicine field.

And I know the dose received by a given tissue is different. You know how much you gave into the patient. But where does it go? And if you're imaging, 10 percent is fine. But when you're trying

to treat, therapy-wise, this can be a problem. You want to know it better than 10 percent.

Next slide. Well chambers, ADCLs can calibrate well chambers, provide the most convenient, accurate, precise way. And you measure LDR, HDR. The well chamber is there no matter what. And the pressurized chambers, the sealed ones can leak, 1 percent per year. We've noticed this. If they leak 1 percent, of course, your calibration changes by 1 percent.

So basically you need to calibrate dose every year or keep track, do good quality assurance to see if you're leaking. And obviously, you need to use an electrometer that can measure low enough signal.

Next slide. So if a single SAGE was used, then you get one reading and that's where the calibration is. If you have multiple SAGE, you have M times that reading. And basically, you can do strands or sources by measuring them in a well chamber that way.

Next slide. And people have said, well, how about needles? You know, needles are used to insert the sources. And what about if we measure it in a needle itself? The variation of thickness of needles, their tolerances in other words, there was

a 15 percent variation by the output, through the needle this is.

So you cannot measure sources and needles. You really have to have separate sources. This is why for the third-party to do these measurements, you really need to have a separate needle that you can take apart and measure the sources themselves for the physicist in the clinic.

Next slide. So the energy response of inner chambers is not severe compared to pressurized chambers. And here's the curve.

Next slide. This is the pressurized chamber, a sealed chamber. And you will notice a big energy response, depending what you're trying to measure, for going down for low dose rate sources, like 25 keV.

And you'll see 50 is the peak. And it falls off very rapidly there. So it becomes very difficult to maintain a calibration and to make things work. This is only one example of a sealed chamber, of course. It's probably the worst example. But still it shows you energy response.

Next slide. This is a vented chamber. And you will notice the energy response is very linear, very flat, in comparison.

Next slide. Next slide. So now let's -- whoops. Whoops. Let's go -- there we go. HDR high energy sources require other techniques because the free air chambers, you would have to make too big of one to use it for HDR iridium-192 source, energy around 397 keV.

A chamber with a known volume can be used, and the chamber with a flattened calibrated energy response is obviously still the way to go. So you need a known volume. And there's different ways of accomplishing this. The traceability through NIST is to do two energy points better known and then interpolate between them.

So next slide. So as I mentioned, this doesn't offer primary calibration. So 7-distances in air is how you determine the air kerma strength. But you need a NIST traceable calibration via the calibration of the ion chamber itself. And traceability is provided by an interpolated chamber calibration factor.

And the next slide. This is what the spectra looks like. A number of lines and when you take a weighted average, it turns out to be 397 keV on average.

Next slide. So it requires two steps.

The calibration of the ion chamber and then use that chamber to calibrate the source.

NPL, the nuclear in England, the UK, has a known volume chamber that they use to calibrate. But you need a chamber with a flat energy response and two points interpolated to weighted average energy is all that's really needed.

So the next slide. You calibrate it at two points. And the two points generally in the U.S. are M250, which is an x-ray source, and the cesium-137 and interpolate between them to 397 keV. Use a build-up cap with it, of course.

Next slide. And this is -- well a number of papers have come out. This is how you determine the iridium-192 air kerma strength. That's 1/(N sub K) with iridium-192 and your average between these two sources. This is the determined endpoint of how the interpolation should be done. And then you calibrate the source at a number of distances. I'll show you the apparatus for that in a few minutes.

Next slide. And this is the apparatus. The HDR afterloader connects the source on the top, that upper part there. I don't know if I can -- let me see, yes. Here's that point and then there's a number of lasers here for the ion chamber. And you

can move it to different distances. Usually, we use distances between 10 and 40 centimeters and then average.

It gives you three unknowns. The scatter is an unknown. The value for the source is an unknown. And the error in distance is an unknown. And when you do these 7-distances you over determine all three unknowns, and you can determine the calibration very precisely.

Next slide. So all primary labs, whether it's in the UK or otherwise, do a 7-distance technique. PTB does also. MPL has a non-volume chamber so that they at least have a calibration for the energy. And others determine their factor by interpolation. And some of them do four coordinate directions. They spin it around the four different directions around the source.

Next slide. So the 5 HDR sources on the market, Monte Carlo moderately chose that there's a difference between them. And we investigated, measured all the sources using a 7-distance technique. This is published, and we compared it to our original calibration, which was with the classic Nucletron HDR source.

Next slide. So for 21 years, we've been

doing these measurements and looking at them versus the classic Nucletron source. And we compared each individual source that we measured with three well chambers. And they're always within half a percent with the 7-distance technique.

Next slide. This is the table of the various sources and a difference from the working standard. That's the standard determined 21 years prior. And you will notice probably the worst one is the bearer source. It's -1.13. But if you average all of the sources, it's within .01 percent of the working standard.

So for this reason, in the United States we decided that we're going to just use one value for all HDR sources no matter what the manufacturer.

The UK has determined they're going to make energy responsive changes here, like a 1 percent difference if you're using the bearer source. But that depends how you calibrate it and so on.

So there is a question going on here. And at present there's a protocol being developed by the IAEA in Vienna. And they're looking at KQ type values, in other words taking into account the different sources.

This is something that the United States

will have to consider and the brachytherapy subcommittee will have to consider in the future. Right now, it's all one value.

Next slide. When all the source models are averaged, of course, it's .01 percent. And this just compared -- we compare it with all the other labs within a half a percent basically. So we certainly have -- our sources may be statistically different, but they're all within 1 percent of the mean.

Next slide. So the half-life of iridium is short. It's three to four months. Cobalt-60 has been introduced as having a half-life of five years but then maintenance becomes very essential. There have been problems like in Africa where the dust enters in. The source sticks out or in. And there are problems that way.

So you really need to maintain the unit, the afterloader, certainly within -- probably every year anyway. And the calibration is done as HDR for the cobalt being 7-distances but using cobalt energies, of course, instead. And there's a need to develop consensus values for cobalt as well.

So at the moment, the United States doesn't have a cobalt afterloader. Like I say, there are manufacturers who may try to introduce it. There may

be a few in places. But they do not have a tradeable calibration.

Next slide. So one of the things about well chambers, I forgot to mention and I should mention here, they are air communicating. But then one of the things because of the way they're made, there is a difference with pressure.

So if you're measuring in Colorado and Denver versus, like, down to sea level in Washington, D.C., there can be up to a 10 percent difference for palladium sources. This can be corrected for, and this has been published what the correction values are.

I forgot to mention that earlier when I was talking about well chambers. So pardon me for that.

The future, targeted radionuclide therapy, targeted radiopharmaceutical therapy, alphas and betas are the major sources here. Radium-224, technetium, polonium -- oh, you know what I mean. I'm sorry. The present calibration of these sources from the manufacturers is in terms of activity.

But if you're going to treat, therapy treating, you prefer absorbed dose to water, I think as Zoubir mentioned earlier, there is a new subcommittee being formed for considering these

sources.

And also the alpha tau source, that's in alpha as well. It's a different configuration. More like a brachytherapy source. But there again, it's alphas.

So alphas and betas, oh, how much do you get for the specific area, specific organ? These are all questions that will be determined in the future I'm sure.

Next slide. So betas are calibrated obviously with an extrapolation chamber. And for eye plaque, curved eye plaque, we just published a paper that shows sight calibrated using a windowless extrapolation chamber for curved data eye plaques. And I have a graduate student now I'm trying to do calibration in terms of dose, absorbed dose to water for alphas and betas, with a windowless extrapolation chamber. It's a PhD thesis, and he's just beginning.

So hopefully some day we can get absorbed dose to water that could be delivered from the amount of activity deposited in the tissue of interest. And then it could be, again, the same thing. We know the dose to the tissue.

Next slide. So I want to thank all these folks, my graduate students and staff. I provoke them

with my thoughts all the time. And if there are any questions, I would be happy to take them.

DR. METTER: Thank you very much, Dr. DeWerd. And are there any questions from the ACMUI Committee?

DR. DeWERD: That either means I completely swamped them or -- I'm sorry if I did.

DR. METTER: Any questions from the NRC staff?

MR. OUHIB: This is Zoubir. I have a question for Dr. DeWerd if I may.

DR. METTER: Yes, please.

DR. DeWERD: Zoubir, what are you doing?

MR. OUHIB: This is in regard to let's say -- and I'm just picking this as an example. Let's say the CivaDerm, you know, that basically come into some sort of sheet basic, you know. What are your thoughts about the calibration for those? I understand that there is a jig that could be used to do those. But what's the accuracy on those? I'm just curious.

DR. DeWERD: So it's a palladium source. And basically there's a couple papers written on this that we calibrate it. And we calibrate each dot, if you want, each Civa dot. And you can put it in a well chamber, and you get a calibration, a traceable

calibration. And then a clinical physicist can therefore measure in his well chamber one of the dots. And they will send you extra dots that are supposedly the same as the rest of the sheet.

And therefore you can use each dot and, you know, put in how many dots you have and that kind of thing so that you end up with -- well, basically, you're calibrating each individual dot and measuring what the dose is there.

MR. OUHIB: Okay.

DR. METTER: Thank you. Any other questions?

DR. TAPP: This is Dr. Tapp from the NRC. Thank you so much for this presentation. It was very helpful.

I didn't know if you had any experience yet with the alpha darts and the radium-224 seed that has -- you know, with the gases for the diffusion decay and any suggestions for those.

DR. DeWERD: Actually, that's another PhD thesis that I'm working on. He's just starting. And we have some ideas of using the extrapolation chamber so measure the dose from those as well, just like I mentioned. And so right now I have nothing more to say about that.

But one of the things I've been wondering. And I don't know of this for a fact, but this is just a question. Here's one of my thoughts that I'm provoking you with.

So that alpha tau, it's a deposit on the surface. You insert that in a patient and the patient's tissue and so on, is any of that source lost inside the patient? You know, is it diffusing off the source? It's a good question. I don't expect an answer.

DR. TAPP: Okay. It's a very good question. It is something I know we would have to look at.

DR. DeWERD: Yes. I think that's something that needs to be looked at. Not that I will or maybe my student will. But right now what we're trying to do as far as the calibration of absorb goes to water is to look at a calibration extrapolation chamber and then we would calibrate to a primary value and therefore give what the alpha, again, per activity kind of thing or in this case alpha perceived kind of thing.

DR. TAPP: Thank you.

DR. METTER: Any other questions from the ACMUI or the NRC staff?

MR. EINBERG: No more questions from the NRC staff. Chris Einberg here.

DR. METTER: Thank you very much. Well, thank you, Dr. DeWerd, for your presentation and your expertise. And we may be wanting to hear a follow-up on your PhD research there.

DR. DeWERD: That would be fine as soon as we have it.

DR. METTER: Thank you very much. You have a good afternoon.

DR. DeWERD: Yes. Thank you very much. Bye.

DR. METTER: Bye. Okay. So now we'll go back to our next topic here. We were in the middle of our open forum. We had talked about some of the issues that had been brought up. Any other items that would be available that the Committee would like to bring up for a future discussion for the NRC staff?

MS. DIMMICK: Hi, Dr. Metter. It's Lisa Dimmick. I think I was going to talk about the emerging medical technology SECY paper. So I can go ahead and do that now.

DR. METTER: Thank you. Yes, Lisa. Thank you for doing that.

MS. DIMMICK: Okay. Sure thing. So on

February 24, 2021, the NRC issued SECY-21-0013, Rulemaking Plan to Establish Requirements for Rubidium-82 Generators and Emerging Medical Technologies.

The NRC uses the term emerging medical technology or EMT to describe any medical technology licensed under Title 10 of the Code of Federal Regulations, Part 35, specifically 35.1000, Other Medical Uses of Byproduct Material or Radiation from Byproduct Material.

So based on about 20 years of operational experience with EMT, the staff identified opportunities for improving the regulatory framework for these other medical uses of radioactive material across the National Materials Program.

The staff evaluated the regulatory issues associated with continued licensing of commonly used and well-established EMTs under 10 CFR 35.1000.

The staff also evaluated a separate need to establish calibration and dosage measurement requirements for Rubidium-82 generators because the design of the Rubidium-82 generator means that licensees cannot meet some aspects of the current regulations.

So to address potential compliance issues

under the current regulations with use of the Rubidium-82 generators, the staff developed temporary enforcement guidance until a more appropriate and permanent regulatory resolution was implemented.

So the staff developed the rulemaking plan to give the Commission three rulemaking options to establish calibration and dosage measurement requirements for Rubidium-82 generators and to improve the regulatory framework for well-established EMTs.

So Option 1 is a rulemaking only for Rubidium-82 generators. This rulemaking would solely address the calibration and dosage measurement requirements for Rubidium-82 generators. It would not result in any changes related emerging medical technologies.

Option 2, limited scope rulemaking to establish requirements for Rubidium-82 generators and certain emerging medical technologies. In addition to Rubidium-82 generators, this limited scope rulemaking would address gamma stereotactic radiosurgery units or GSR units and microspheres. These EMTs are well-established and commonly used.

Option 2 would amend 10 CFR Part 35 such that the current and future GSR units could be licensed under 10 CFR 35.600 or Subpart H, and the NRC would

develop a new subpart for current and future microsphere technologies.

Going on to Option 3, Option 3 is a performance based rulemaking to increase regulatory flexibility. So Option 3 is an expanded version of the Option 2 rulemaking. In addition to developing performance-based requirements for Rubidium-82 generators, GSR units and microspheres, the staff would evaluate how to make additional sections of 10 CFR Part 35 more flexible.

Option 3 would enable licensing of all approved EMTs and future updates to currently licensed EMTs and potentially even new hybrid EMTs. 10 CFR 35.1000 would remain available for emerging medical technologies that do not fit under the revised medical use subparts. So Option 3 is similar to Option 2 but on a larger scale.

So the staff is recommending Option 3, a rulemaking that would establish performance based requirements for Rubidium-82 generators and all current well-established EMTs and would also broadly examine Part 35 to determine where outdated reciprocal requirements could be revised to be more performance based.

SECY-21-0013 is currently under review by

the Commission and the staff will not take an action related to the rulemaking plan unless directed by the Commission.

The SECY paper, SECY-21-0013, is available in the NRC's Agency-wide Document Access and Management System, or ADAM, at the Session Number ML-202-61H562, again, ML-202-61H562. And if you have any questions, I'll try to answer them.

DR. METTER: Thank you, Lisa. Are there any questions from the ACMUI?

DR. ENNIS: This is Ron. Hi, Lisa. Yes. It seems like there may be two things going on simultaneously if I'm understanding correctly in what's being considered.

One is the currents are relatable. But one is maybe a presumption that having things in 35.1000 is less good than having them in the .100 series. And then if that's the case, I would be interested in hearing why the staff feels like 35.1000 is less good.

And then related to that though is the thought that 35.100 series might be too prescriptive and should be modified. So I guess I'm just -- am I hearing correctly that those are really the two kind of interrelated issues that these proposals are trying to get at?

MS. DIMMICK: Yes. That's probably an okay way to say it. So let's just briefly talk about GSR units and microspheres. Currently a number of the regulations in 35.600, specifically some of the calibration requirements, describe specific components that are no longer used in the current generation of gamma knife units.

So in that sense there is probably -- the last one I looked at it may be 20 units installed in the U.S. that meet the 35.600 requirements. Everything else is under the gamma knife licensing guidance under 35.1000.

So when we developed those licensing guidance documents, they are vendor specific. So every time there is a new vendor of a new gamma knife, it needs a -- we develop a vendor specific licensing guidance for its use. And that can be time consuming to build that specific guidance.

So staff is envisioning that we could develop perhaps for 35.600 for the calibration requirement, the requirement is more based on function because these units have similar functions and not necessarily specifically identify the component and regulate that component. So that was where we were looking at that.

With regard to microspheres -- oh, and by the way we have a couple of new manufacturers of GSR units that we haven't started the guidance yet for. So there was a little bit of a delay in staff developing the guidance for these new GSR units. And right now these guidance documents take, you know, a year to make or a year to develop.

For microspheres, microspheres have been around for a long time. We're on Revision 10 to the licensing guidance. We have more vendors of microspheres. So within, again, each microsphere vendor, there are -- it's a new guidance that needs to be developed to accommodate that new vendor's own technology.

So it's just we now have operational experience with some of these emerging technologies or what we call emerging technologies. They're really no longer new or novel or emerging. They've been around. So it was an opportunity to think if we could gain some efficiencies by putting them into the regulations.

DR. ENNIS: Understood. That's very helpful. I understood that. So is the idea, though, that for some brand new emerging technology, it would sit in 35.1000 for a period of time and then move into

a series (audio interference) experience?

MS. DIMMICK: So we would definitely -- we're not going to change the flexibility that we have with 35.1000 to that. That requirement would stay. So if we have an emerging technology that needs to be authorized under 35.1000, we would continue with that.

And, again, we last updated Part 20 -- well, we did the update in 2018 but that had a different scope and charge. But back in 2002 when Part 35 was updated, a number of technologies were codified at that time for the reasons why we see that we might need to codify some of our emerging technologies that have been around for 20 years or so.

So we might think that any time something is a 35.1000 technology that it will eventually be codified, that may or may not happen. We're trying to, again, like I said, we have lots of experience with microspheres, operational experience and also with newer generation gamma knife units that it's an opportunity to go ahead and put them into regulation.

DR. ENNIS: Great, great. And just one last question for my understanding. Would it not be possible perhaps from a regulation point of view to have a 35.1000 approval that was not vendor specific

and more generic and then leave things in 35.1000 but just be generic?

MS. DIMMICK: Ron, I'm sorry. But some of your question was breaking up. I didn't quite hear it all the way.

DR. ENNIS: I'll try it again. Is there a reason why one could not create a 35.1000 guidance that was generic enough that would cover all of the units of different types of different manufacturers or does 35.1000 require vendors specificity for some reason?

MS. DIMMICK: So the generic requirements that you're mentioning is a rule. That's basically the rule. That's a regulation. If you were to develop generic requirements for all types of vendors of a type of technology, that's really what's happening in a rulemaking space.

DR. ENNIS: Okay. Thank you.

DR. DILSIZIAN: Vasken Dilsizian. Lisa, thanks for the presentation. As a Rubidium generator user, we lived through the issues of the Bracco generator approximately 8, 9 years ago. And it was my understanding that they went through the FDA approval process and maybe Michael O'Hara can clarify it for me. They had just come up with a new generator

and, as you know, the other company, Jubilant DraxImage, they both have a current renewed FDA approved generators.

I guess my question is, are we talking about these new generators that are FDA approved do not meet the compliance issues for calibration dose measurements?

MS. DIMMICK: So the Rubidium generators, because of their design, because of the short half-life, they're not able to assay the doses just prior to administration. And that's one of the requirements in Part 35. And it's because of the short half-life.

The other part is the calibration of the system itself. Equipment used to measure dosages needs to be calibrated by national standards or you can apply national standards for the calibration. And given the closed system design, it doesn't quite meet the intent of the regulation.

There were requirements for licensees using Rubidium generators that were included in the guidance by NRC. So, again, it's just the design of the system likely aren't able to comply with the calibration of the unit itself and the measuring the dosages.

DR. DILSIZIAN: So, Lisa, so I guess my question is, since they were updating and going through the update approval process, is it not possible? Is that why they couldn't do it? I mean, you would think that they would try to meet the NRC requirements when they were updating it. Is it just not possible because of the short half-life of Rubidium and the way it's administered?

MS. DIMMICK: I'm not certain of the new design or the update to the new system if they failed to meet the requirement in Part 35 or not.

DR. DILSIZIAN: Okay. Dr. O'Hara, do you know?

DR. O'HARA: This is Michael O'Hara. While the generator is a medical device, it's considered a production, an isotope production device. So it's regulated by the drug side of the FDA.

There have been changes to the generators. And I think some of these incremental changes is what the NRC is reacting to.

DR. DILSIZIAN: Okay. Thank you.

DR. METTER: Thank you. Any other questions from the ACMUI?

MR. SHEETZ: Hi. This is Mike Sheetz.

DR. METTER: Yes.

MR. SHEETZ: Thank you, Lisa, for the explanation. My questions come -- one is I'm curious why the ACMUI is not brought in to comment on this initiative before going to Commission. And then, two, can you explain the NRC staff's reason for choosing the third option to revise Part 35 to accommodate all the new emerging technologies.

I can understand the second option where you wanted to formalize the rulemaking for the well-established ones, gamma knife and Y-90 microspheres. But to try to change 35 to accommodate all emerging technologies coming down the pike, seems to be a huge paradigm shift and a complete rewrite to what was done in 2002.

Do you have any details on how that would be accomplished or is that more of a concept of what you would like to have? Thank you.

MS. DIMMICK: Okay. So a couple of things. This is a rulemaking plan. It's not any -- there's no rule text yet developed or anything. So at that point when there is rule text developed, the ACMUI would have an opportunity to comment and provide input and be very much a part of the rule development stage.

So with the rulemaking plan, we're

developing considerations for the Commission to change regulations. So the ACMUI would be very much involved once we -- depending on the options and when the Commission does make a determination that we would move forward and develop proposed rules, the ACMUI would be a part of that.

As far as going with Option 3, we were identifying that based on our experience with emerging medical technology that there are some similarities from what has been authorized under 35.1000 in the past for maybe what's coming down the pike.

So if there was an opportunity to look at the rule to make some things a little bit more generic that might accommodate some of the types of technologies that we see coming, it's an opportunity if the rule is open.

We identified that the resources to do the Option 3 rule were not that much greater than the Option 2 rule. So it's an opportunity to try to make things a little bit more flexible in Part 35. That's what we were trying to achieve.

We know that we can't envision all emerging technologies and what they're going to look like because they're not out there yet. But if there is a way to -- brachytherapy is a good one. We have a

lot of hybrid technologies.

We have with brachytherapy things that are unsealed sources that are used like sealed sources so if there's a way that we can accommodate that in 35.400 a little better than what we currently have.

Also there are other ophthalmic sources being used. There is a yttrium-90 source for ophthalmic treatment. So that's already -- in looking at 35.400, right now that is for strontium-90 sources. So that's different.

So if we can make things a little bit more flexible, that's what we're trying to achieve, you know, with the information we know now of what emerging technology is and what we've licensed in the past if that helps.

MR. SHEETZ: It does. And I guess I understand and I appreciate the flexibility. I just see it as being very challenging even with the gamma knife to try to put it all into 35 with any consistency and the federal regulation requirements between all the gammas and the icon perfection and then the rotating gamma knifes coming out. I don't know how you can write regulations to cover all of them. I just see it as very challenging.

MS. DIMMICK: And that's why we'll be

keeping 35.1000 because we may not be able to -- we know that we can't completely cover everything in this next rule. But we can lean forward and see what is coming and what we can envision for it, but we know that we'll need to keep 35.1000.

MR. SHEETZ: Thank you.

MS. DIMMICK: Mm-hmm.

DR. METTER: Thank you, Lisa. Any other comments or questions from the ACMUI members? Operator, are there any comments from the public or questions from the public regarding what's been discussed today?

OPERATOR: Thank you. To ask a question or make a comment on today's discussion, please press star 1, unmute your phone and record your name to be introduced. One moment while we wait for any questions to come in.

MR. EINBERG: Dr. Metter? Chris Einberg here. While we're waiting for a question to come in, I just, you know, wanted to note that it looks like we discussed many items that are coming down the pike after the ACMUI's review here during the summer time frame, at least in the next six months.

So it looks like it's been a bit of a lull right now as far as the work. But it certainly seems

that there are quite a few things that are coming down the pike. And I just jotted down a list of them that, you know, Katie, Dr. Tapp, mentioned the Alpha DaRT, 35.1000 licensing guidance that's coming down, the Reg Guide 8.39 Phase 2, patient release guidance.

The AO Commission paper will be provided to the ACMUI to review as well. The NRC's independent of extravasation and whether they should be medical events. We will be reporting out on medical events, again and then lastly CivaDerm.

So I guess I just wanted to kind of say thank you ahead of time. It looks like it may be a busy summer for the ACMUI members.

DR. METTER: Thank you, Chris, for the heads-up. And I do have a similar list and thank you very much. We'll go offline and discuss further on this. Thank you.

OPERATOR: I do have a question.

DR. METTER: Yes, please.

OPERATOR: Paul Wallner, you may go ahead.

DR. WALLNER: Thank you very much. It's actually not a question. It's several comments. My name is Dr. Paul Wallner. I'm a radiation oncologist. I've been in practice for now 49 years and much of that time has been devoted to a clinical and research

interest in the use of radiopharmaceuticals and that included my time as a branch chief at the National Cancer Institute.

I had hoped to comment and speak with Dr. van der Pol earlier but was unable to do that. I wanted to compliment him on his lecture, which I thought was excellent, and his meta-analysis, which I think is terrific for educating and informing residents and practitioners in nuclear medicine and technologists but not for development of public policy because I think the conclusions that he drew were actually not correct based on the material he researched.

First of all, I think his comments, his meta-analysis was really demonstrative of the weaknesses of meta-analysis. He sub-selected from 4,000 plus manuscripts that did not include anything about extravasations and clearly were not related to extravasations, 44 publications of which 37 were diagnostic and 8 therapeutic.

In the United States, peer reviewed editors and reviewers will require that complications be listed very clearly. So the complications related to extravasation are clearly not a problem in the United States and not a problem worldwide based on his own analysis.

He commented in one of his conclusions that extravasation is common despite the fact that his own data suggests that's not the case.

In his diagnostic evaluation, he reported 3,000 cases, of which only three demonstrated radiation injury. Twelve of the reports that he cited, six of those reports, or 50 percent had three or fewer cases that were included. So you can see even in these individual reports, they are essentially anecdotal because they are so rare. Of the eight publications that listed therapeutic complications, all were single case reports except one, which, again, reported three cases.

He also reported that there were no National Registries looking at this issue and that's absolutely incorrect. The Australian government has an Australian Registry, which has been reported in peer reviewed literature in the Medical Journal of Australia. Several years ago they reported 2.5 million procedures, that's 2.5 million diagnostic and therapeutic procedures, of which there were 7 extravasations that were reported.

I think that extravasation issues are best handled in the clinic the way they are now using practice guidelines. I see no clinical or public

health reason why there should be any change in those guidelines or regulations. Thank you very much.

DR. METTER: Thank you very much for your comments. And I do apologize. Dr. van der Pol was on a short timeframe, so we had very limited time on answering questions. But I really appreciate your insight and your expertise and thank you for your comments. Very valuable. Any other questions or comments from the public?

OPERATOR: Currently, there are no other questions or comments. However, if you would like to make one, please press star 1, unmute your phone and record your name so you may do so. There are no additional questions or comments at this time.

DR. METTER: Thank you. So it looks like we're on the final item of our meeting unless there's other items? Chris or anybody from the NRC before we go to the administrative closing?

MR. EINBERG: I think we can move forward.

DR. METTER: Thank you. So right now Ms. Kellee Jamerson will provide a meeting summary and proposed dates for the fall 2021 meeting. Ms. Jamerson?

MS. JAMERSON: Good afternoon. This is Kellee Jamerson. For our ACMUI members, I recently

provided a set of dates to propose for our fall meeting. The dates that I have highlighted on the September calendar, as you see on the screen, are the dates that I provided for September. And I'll show October as well.

So beginning with September 13 and 14 or September 17 and 28 and the other two October dates are October 4 and 5 and also for 18th and 19th. I received the most response for October 4th and 5th as a first option and September 27th and 28th as the second option. Is there any discussion as far as these two recommended dates that I received the most feedback for?

MS. SHOBER: Kellee, this is Megan Shober. I'm wondering if these dates are going to be depending on the Commission schedule or is the Commission briefing going to be offset like it was last year?

MS. JAMERSON: So that's one thing that I will have to find out after we select our first and second option. I will provide those dates to the Commission staff and hopefully they will be able to align with our proposed date for our fall meeting. If not, it will be a separate meeting from our ACMUI meeting in the fall.

DR. METTER: This is Darlene.

MR. OUHIB: Go ahead, Darlene, go ahead.

DR. METTER: No, go ahead, Zoubir. I was going to ask if there were any people that had problems with these two dates.

MR. OUHIB: Yes. Just curious, Kellee, is there any conflict with the ASTRO meeting at all. I don't know what the dates are. But in case, it's a live meeting I just wanted to --

MS. MARTIN: ASTRO is the end of October, Zoubir.

MR. OUHIB: Okay.

MS. MARTIN: The week of the 25th of October.

MR. OUHIB: Okay. So there's no conflict there. Okay.

MS. MARTIN: Either one of those two dates work for me. I just can't do the one at the end of October -- the 18th and 19th don't work. But either one of the ones that you're listing now work fine for me.

DR. METTER: Okay. So this is --

(Simultaneous speaking.)

DR. ENNIS: Go ahead. The options are the 4th and 5th or 18th and 19th?

MS. MARTIN: Mm-hmm. The 4th and 5th or

September 27th and 28th.

DR. ENNIS: Oh, I see. September 27th and 28th, I would not be able to attend.

MS. JAMERSON: Okay. Thanks, Dr. Ennis.

DR. METTER: Dr. Ennis, could attend October 4th and 5th?

DR. ENNIS: Yes.

DR. METTER: Okay. So is there anybody on the ACMUI cannot attend October 4th and 5th? Okay. That looks like our first date. And so Dr. Ennis is unable to attend on the 27th and 28th. What other one was also up?

MS. JAMERSON: 13th and 14th.

DR. METTER: The 13th and 14th. Did someone -- Kellee, were there individuals that were unable to attend on the 13th and 14th of September?

MS. JAMERSON: I do not recall specifically who the individuals are. But I would remind you that Dr. Jadvar is not on the call, so I'm not sure about his availability for the 13th and 14th.

MS. MARTIN: That's right in the middle of the Jewish holidays, isn't it, between Rosh Hashanah and Yom Kippur?

MR. ENNIS: It is. It falls in the spot where from my perspective, I could do it then. It's

not optimal for me. But I could --

MS. MARTIN: Okay. You're being very good.

DR. METTER: Well, Kellee, can we do this? Let's make October 4th and 5th our first choice and then we'll look at the 13th and 14th, 27th and 28th as the second choice. We'll have our input from the rest of the Committee and Dr. Jadvar.

MS. JAMERSON: Okay. I want to ask Dr. Ennis, the 20th and 21st isn't an issue? I know it's also a Jewish holiday on the 21st but.

DR. ENNIS: Yes, kind of the holiday that starts the 20th at night. So I wouldn't be available -- in person, I could be here on the 12th. And I would not be able to attend in any way on the 24th. And the same thing is basically for the 20th, (audio interference) begins the second federal holiday. And so I could not be in person on that day.

MS. JAMERSON: Okay.

DR. ENNIS: So I could do remote for the first day of either of those two weeks. But if it's the 27th, that's acceptable. But I would not be able to be in person and could not be there the second day on either of those two weeks.

DR. METTER: Okay. Can you look at the

13th and 14th, Kellee, and see if there was a problem with that when you go back. And then we'll probably just look at maybe sometime during those last three weeks of September as a second option or should we make another option in October?

MS. JAMERSON: The other options in October, could we meet possibly later in the week? The beginning on -- well, October 11 is a national holiday so the NRC staff would be out that day. But it could possibly be Tuesday and Wednesday of that week or Wednesday/Thursday.

DR. METTER: Okay. Can we --

MS. JAMERSON: Also the Astro meeting so.

MS. MARTIN: Can you look at, like, instead of -- if you can't do the 4th and 5th, could we make an option, like the Thursday/Friday or the Wednesday/Thursday of that week?

I'm just gone from the 14th on and I'm going to an international flight on the 14th hopefully. I guess I should rephrase that. Hopefully, this meeting is going to happen otherwise I may be sitting in front of a computer screen.

DR. METTER: Okay. Let's go ahead, Kellee, why don't you get some other dates and send it out a doodle poll. I really think October 4th and

5th looks like our first date. I think Kellee said it was actually our number one choice. And so we'll make that as our first choice. And the second choice will be either later in October or one of the three weeks in September, if you don't mind sending out a poll for that.

MS. MARTIN: I see what you're saying, Kellee, maybe the 12th and 13th would work in October, too. That's a Tuesday/Wednesday after your holiday.

MS. JAMERSON: All right.

DR. METTER: She can put those two days on. Okay. So let's do the poll so everybody can participate and then we'll go from there. But that sounds very good. Thank you, Melissa.

MS. MARTIN: Okay.

MS. JAMERSON: Okay. So other than finalizing or proposing our potential fall 2021 meeting dates, there were no ACMUI recommendations or action items that I captured from today's meeting. So that is all that I have, Dr. Metter.

DR. METTER: Okay. Do I have any final comments from the ACMUI or NRC staff?

MR. EINBERG: This is Chris Einberg, yes. On behalf of the NRC, I wanted to thank all the members of the ACMUI for their continued support and wisdom.

I'd like to also thank the NRC staff who worked diligently behind the scenes to make this meeting happen and then also our outside presenters who made it a very educational and informative meeting and brought the latest information to the Committee and to the NRC staff as well and the comments that we received from members of the public.

DR. METTER: Thank you, Chris. And thank you, again to the NRC staff and ACMUI members for working to make this meeting possible and the meeting is adjourned.

(Whereupon, the above-entitled matter went off the record at 2:39 p.m.)