UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

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MEETING WITH ADVISORY COMMITTEE ON THE

MEDICAL USES OF ISOTOPES

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TUESDAY,

APRIL 9, 2024

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The Commission met in the Commissioners' Hearing Room, at 10:00 a.m. EDT, Christopher T. Hanson, Chair, presiding.

COMMISSION MEMBERS:

CHRISTOPHER T. HANSON, Chair

DAVID A. WRIGHT, Commissioner

ANNIE CAPUTO, Commissioner

BRADLEY R. CROWELL, Commissioner*

ALSO PRESENT:

CARRIE M. SAFFORD, Secretary of the Commission

BROOKE CLARK, General Counsel

*Present via video teleconference

PANEL:

HOSSEIN JADVAR, ACMUI Chair

RICHARD HARVEY, ACMUI Radiation Safety Officer Representative

MEGAN SHOBER, ACMUI Agreement State Representative

JOSH MAILMAN, ACMUI Patients' Rights Advocate

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

9:57 a.m.

CHAIR HANSON: I will now call to order today's meeting with the Advisory Committee on the Medical Uses of Isotopes since we're all here. I know it's a little before 10:00, but if we're broadcasting on the internet, I think we can probably just go ahead and get started.

Thank you all for being here. This is a routine meeting to hear the views of the Advisory Committee on the Medical Uses of Isotopes on significant issues that have come before them. This last meeting with the committee was in December 2022, so we're just a little overdue and we're glad to have you all with us.

I'll recognize each speaker and we'll hold questions until the end of the speaker presentations, and then we'll hear questions from the commissioners this morning.

Today, I'm pleased to acknowledge the newest members of the committee, Dr. Michael Folkert, brachytherapy radiation oncologist, and Dr. Joanna Fair, diagnostic radiologist, who are both undergoing the onboarding process. Welcome.

Before we start, I'll ask my colleagues if they have any comments they'd like to make? So, with that, Dr. Jadvar, it's nice to see you again, and we'll begin with you.

DR. JADVAR: Thank you very much, Chair Hanson, Commissioners Caputo, Crowell, and Wright. Good morning. This is my first presentation to you as the newly appointed chair of the ACMUI since the

previous chair, Dr. Darlene Metter, completed her term on the committee in February of this year.

I look forward to serving the ACMUI and the NRC the best possible way that I can, and beforehand, I would like to thank all of you, my colleagues on the ACMUI and the entire NRC staff for your support and camaraderie. So, with that, perhaps I can start my presentation. So, I'm going to give an overview of the ACMUI activities. Next slide, please?

On the agenda after my presentation, Dr. Richard Harvey, Radiation Safety Officer Representative, will give the ACMUI's review analysis of the reported medical events from fiscal years 2021 to 2023. Next slide, please?

Then Ms. Megan Shober, the ACMUI Agreement State Representative, will comment on the revisions to the Regulatory Guide 8.39, Release of Patients Administered with Radioactive Material. And after that, it will be Mr. Josh Mailman, ACMUI Patients' Rights Advocate, who will present perspectives on the Regulatory Guide 8.39 and also on the reporting of nuclear medicine injection extravasations. Next slide, please?

This is the agenda for today, the ACMUI role, membership, the 2022 through 2024 topics, the current subcommittees that we have at the ACMUI, and the future activities. Next slide, please?

Just to remind us, the role of the ACMUI is to advise the U.S. Nuclear Regulatory Commission staff on policy and technical issues that arise in the regulation of the medical use of radioactive material in diagnosis and therapy, comment on changes to NRC regulations and guidance, evaluate

certain non-routine uses of radioactive material, provide technical assistance in licensing, inspection, and enforcement cases, and also bring key issues to the attention of the commission for the appropriate action. Next slide, please?

ACMUI membership currently have 13 members. The nuclear medicine physician is represented by me, who is serving as the chair. The nuclear pharmacist who is also the vice chair of the committee is Mr. Richard Green. The nuclear cardiologist is Dr. Andrew Einstein.

We have two radiation oncologists on the panel, Dr. Mike Folkert and Dr. Harvey Wolkov. The diagnostic radiologist, as was mentioned, is Dr. Joanna Fair, who is undergoing the onboarding process, and then the FDA representative is Dr. Michael O'Hara. Next slide, please?

We have two medical physicists on the panel, for nuclear medicine, Ms. Melissa Martin, and for radiation therapy is Mr. Zoubir Ouhib. The patients' rights advocate is Mr. Josh Mailman. The agreement state representative is Ms. Megan Shober. The healthcare administrator is Ms. Rebecca Allen, and the radiation safety officer is Dr. Richard Harvey. Next slide, please?

We also continue to benefit from the expertise and knowledge of our consultant, Dr. John Angle, who is the interventional radiologist. Next slide, please?

These are the ACMUI topics for December 2022 to April 2024, decommissioning financial assurance for sealed and unsealed radioactive materials. The ACMUI subcommittee presented its recommendations on the staff's draft proposed rule that seeks to amend the

regulations for decommissioning financial assurance and funding for sealed and unsealed radioactive material in 10 CFR Part 30.

The impact of ABR's termination request and review of the NRC's process for recognition of specialty boards, the ACMUI subcommittee presented its assessment of the impacts of the American Board of Radiology's request to terminate NRC recognition of its board certification processes and its review of the NRC's process for recognizing medical specialty boards.

Under medical events, the ACMUI reviewed medical events from fiscal years 2021 through 2023 and provided its recommendations to staff. A review of prescription error reduction methods was also discussed.

The ACMUI nuclear pharmacist provided an overview of the published articles on error reduction methodologies for administrations of byproduct material for medical use and the relative success and value of these error reduction methods. Next slide, please?

We also discussed the Akesis Galaxy RTi Unit licensing guidance. The ACMUI reviewed and commented on the NRC's staff draft licensing guidance for the Akesis Galaxy RTi device. This is a new gamma stereotactic radiosurgery device that the staff is recommending to be licensed as an emerging medical technology under 10 CFR 35.1000.

Eye90 Microsphere device licensing guidance, the ACMUI reviewed and commented on the NRC's staff draft licensing guidance for the Eye90 Microsphere device, which is a new Y-90 microsphere device under an investigational device exemption by the FDA, and which staff is recommending to be licensed as an emerging medical technology under 10

CFR 35.1000.

The Liberty Vision Y-90 episcleral brachytherapy source licensing guidance, the ACMUI reviewed and commented on the NRC's staff draft licensing guidance for the Liberty Vision Y-90 episcleral brachytherapy source. The staff is recommending that this source be licensed under 10 CFR 35.1000 because current NRC regulations only cover the ophthalmic use of the Strontium-90 sources. Next slide, please?

Overview of ICRP Publication 153, Radiological Protection in Veterinary Practice, the ACMUI heard an overview of the ICRP Publication 153 from one of the authors of this publication. The ACMUI is interested in how the veterinary use of radioactive material continues to evolve beyond radioiodine I-131. Next slide, please?

These are the staff presentations to the ACMUI during 2022 through 2024. Medical events, the staff has presented overview of medical events, including root causes and corrective actions for recent fiscal years. Limited revisions to the NRC's abnormal occurrence criteria, the staff provided an overview of the changes to the abnormal occurrence criteria that were approved by the commission in the SRM-SECY-22-0009.

Reporting of nuclear medicine injection extravasations, the staff provided an update to the ACMUI on the efforts related to the rulemaking that would codify reporting requirements for certain nuclear medicine extravasations. An ACMUI subcommittee is currently reviewing the staff's draft proposed rule and associated implementation guidance.

Overview of the NRC requirements and guidance for

release of animals administered with radioactive material, the staff presented to the ACMUI an overview of the NRC's regulatory framework, including regulations and guidance for licensing the use of byproduct material in veterinary medicine.

Financial assurance for disposition of category one and two byproduct material radioactive sealed sources, the staff provided the ACMUI with an overview of the rulemaking effort that will revise the regulations that require financial assurance for the disposition of category one and two byproduct material sealed sources, including costs of end of life and timely disposition. Next slide, please?

Recent medical events related to radiopharmaceutical administrations, the staff discussed regulations for written directive and medical event reporting, and provided examples of different types of medical events related to the use of radiopharmaceuticals and their root causes and corrective actions. ACMUI reporting structure, the staff provides the ACMUI with its reporting structure on an annual basis. In fact, we had that yesterday.

Medical team updates, the medical team provides the ACMUI an update related to the ongoing rulemaking and guidance development efforts as well as discusses medical issues of interest with the ACMUI. INFOSEC, ethics, and allegations training, the ACMUI continues to receive training from the NRC staff on these and other topics. Next slide, please?

These are the current ACMUI subcommittees, Eye90 microspheres, Akesis Galaxy RTi Unit, Liberty Vision Y-90 brachytherapy

source. Training and experience for all modality subcommittee, the ACMUI is reviewing the staff's draft training and experience implementation guidance.

Extravasations and medical reporting, the ACMUI is currently reviewing the staff's draft proposed rule and associated implementation guidance for the reporting of nuclear medicine injection extravasations. The implementation guidance is a draft regulatory guide for the evaluation and reporting of all medical events, including extravasation medical events. Next slide, please?

And these are the future activities. ACMUI will continue to provide advice and technical assistance, comment on the NRC regulations and guidance, evaluate uses of radioactive material, and also bring key issues to the attention of the commission. And with that, the next slide, I believe, is just my acronyms, and thank you very much for your time.

CHAIR HANSON: Thank you, Dr. Jadvar. Next, we'll hear from Dr. Richard Harvey. He's the radiation safety officer representative. Dr. Harvey?

DR. HARVEY: Good morning, commissioners, and thank you for allowing me to present the subcommittee's report on medical events. Next slide, please?

Our subcommittee members are Dr. Folkert, Mr. Green, Dr. Metter, who has finished her term, Mr. Ouhib, and Dr. Wolkov. Our consultant is Dr. Angle, who serves the committee very well, and our NRC staff resource is Mr. DiMarco. Next slide, please?

The subcommittee's charge is to review medical events to

advise the Advisory Committee on the Medical Use of Isotopes and the United States Nuclear Regulatory Commission about emerging trends that may need regulatory attention. Next slide, please?

Background, the NRC and ACMUI review these medical events that occur throughout the country on a regular basis. Medical events occur when radioactive material used in healthcare results in unexpected radiation dose to patients. Please refer to 10 CFR 35, Subpart M, reports, and more specifically, 10 CFR 35.3045, report and notification of a medical event for more information.

The Medical Events Subcommittee of the ACMUI reviews the data to analyze the nature of medical events, identify emerging trends, and provide recommendations to the ACMUI and NRC. Next slide, please? As Dr. Jadvar mentioned, the fiscal years reviewed were FY21, '22, and '23. Next slide, please?

There's two overarching themes that seem to remain. There seem to be human errors, medical events caused by human errors, as well as inexperience, human errors resulting from failure to have good communication and feedback, and failure to work in teams.

With regards to inexperience, it's presumed that because of the rapidly evolving use of radiopharmaceuticals, there is some inexperience for new users, and there is some dissemination of the radiopharmaceutical therapy use to small institutions that may perform these radiopharmaceutical or theranostics procedures with a lower frequency.

There is no real data to quantity this with 100 percent, so we

are making an assumption here. There may be infrequent users that do this very well, but the assumption has been made that infrequent users, there might be some increased risk of medical events. Next slide, please?

So, some specific issues, again new and increasing use of therapeutic radiopharmaceuticals, we're seeing certainly a boon in the use of some of the lutetium agents and others, and some research protocols that are leading to the potential for more medical events in 10 CFR 35.300. The Yttrium-90 Microsphere procedures, which you're probably familiar with, tend to be the most common medical events, and you'll see that in the data coming forward.

The actions by the committee, we've added two specialty-specific subcommittee members, and an ACMUI recommendation, the authorized users should adhere to manufacturers' recommendations to avoid aggregation, and they should use the recommended catheter size and needle gauge. That's specifically for the Yttrium-90 microspheres.

We have seen in some of the medical events, if the manufacturer recommendations were not followed, it led to medical events and residual activity being left in the treatment device, and therefore not all of the activity reaching the patient.

Another important issue is that microspheres need to be agitated to avoid settling or clumping, and this will assist in prevention of aggregation. Users must remain conscientious and adhere to all manufacturer recommendations during delivery of the microspheres. Next slide, please?

So, for 10 CFR 35.200, we have a breakdown for the past seven years of the medical events defined in classifications of wrong drug, wrong dosage, wrong patient, and extravasation, and human error. And what we believe is that a timeout may have prevented all of the medical events in 2021, FY21 and 2023. So, timeouts seem to be a valuable practice that can certainly help prevent medical events going forward.

Currently, extravasations is in guidance process and being developed with SECY, so there is no reporting requirement for extravasations at this point in time. Next slide, please?

10 CFR 35.300, you can see the breakdown for the seven-year period. Again, timeouts were deemed to be valuable for wrong drug, wrong dosage, and wrong patient medical events. For 10 CFR 35.300, a timeout may have prevented 50 percent of the medical events in 2021, 30 percent of the medical events in 2022, and 91 percent of the medical events in 2023. Next slide, please?

Moving to 10 CFR 35.400, manual brachytherapy, you can see the breakdown, and this is on two slides, so there will be a second slide where this continues. Excuse me. So, there were two eye plaque applicator issues, one in 2022 and one in 2023.

Interesting with these ophthalmic brachytherapies, excessive rubbing of the eyes can shift the plaque and change the dose delivered to the patient, and so there can either be a shift or there was even a situation in 2022 where the source was actually dislodged. So, let's move to the next slide so we can see the continuing 10 CFR 35.400, please?

And there is a typographical error on here. Did we -- oh, we may have fixed it. In 2021, there was three. So, it was originally a two, so the typographical error was corrected by the staff. They saved me from that, so thank you.

So, this shows a summary of the manual brachytherapy and where timeouts may have been beneficial. In 2023, or I'm sorry, excuse me, 2021, the three medical events may have benefitted from a timeout, and there were none in 2022 or 2023 that would have benefitted from a timeout. Next slide, please?

So, potentially 23 percent or nine of the 39 medical events from 2017 to 2023 may have been prevented by the use of a timeout. Those again were defined as wrong site, wrong source, and wrong patient. So, a timeout or checklist for 2021 may have prevented 75 percent of the medical events, and again, we didn't see any benefit in 2022 or 2023. Please move to the next slide? Thank you.

10 CFR 35.600, all right, for the last three fiscal years, the most significant causes of medical events have been from human error, those from wrong position, wrong reference length, and wrong dose or source strength, and machine applicator malfunction.

For the human error situation, there's been 37 of 65 medical events or 57 percent during this period that may have benefitted from a timeout, and 12 of 65 medical events or 18 percent from 2017 to 2023. It does show a relatively stable trend, around ten plus or minus medical events in this area. Next slide, please?

The next slide shows a breakdown of the medical events for 10 CFR 35.600 by anatomical location, and predominantly gynecological procedures were the most common site for medical events, and two-thirds or 66 percent of the medical events were from gyn procedures. Next slide, please?

So, in this category, a timeout may have benefitted in eight percent of the time, five of the 65 medical events during this seven-year period. Next slide, please?

Medical events in this area that may have been caused by infrequent users or authorized users that don't do this frequently, or inattention, or lack of conscientiousness during the delivery of the procedure, there's a breakdown by year, but the total is 20 out of 65 of these or 31 percent may have benefitted from users having more experience, more training, and being more conscientious during this, during the procedures.

Again, we have no data to quantify the number of medical events by organization, so we don't really have the total volume that different organizations are doing. Next slide, please?

Now we're moving into 10 CFR 35.1000. The first item that I want to talk about is radioactive seed localizations, and these are relatively rare as you can see. We've tracked these since 2018, and there was one event in 2019, one in 2021, and one in 2023.

So, the one medical event in 2023 was due to a delayed seed removal during a radioactive seed localization procedure. So, the authorized user removed the clip rather than removing the seed, which is

certainly avoidable using a gamma surgical probe in the OR. The next slide if you would, please?

The next area in 10 CFR 35.1000 is intravenous cardiac therapy, again a relatively infrequent type of procedure. We don't see a large number of medical events. It's been fairly stable. And we have one medical event in 2023 where the radioactive source did not reach the intended treatment site because the author failed to verify source location. They had difficulty in the fluoroscopy being able to see where the source was in the heart. Next slide, please?

The next area is the Gamma Knife, and we're talking about Gamma Knife Perfexion, Icon, and Esprit units. All three are in use domestically. As you can see there, Gamma Knife treatments have resulted in very few medical events and they're very stable. Next slide, please?

Maybe where it gets a little bit more interesting is the Yttrium-90 microspheres. We've divided these up into TheraSpheres, which we'll cover first, and then SIR-Spheres from the two different manufacturers. Excuse me.

So, wrong dose medical events are assumed to be preventable by the use of a timeout. A timeout would seem to be very useful in the Yttrium-90 microspheres' delivery and administration, and greater than 20 percent residual activity left in the treatment device is a surrogate for infrequent use of microspheres and authorized user lack of conscientiousness. There's some subjectivity in that. And if you look at the data, a timeout may have prevented 17 percent, nine percent, and

five percent of the medical events in FYs 2021, 2022, and 2023 respectively. Failure to deliver at least 80 percent of the treatment activity has resulted in a significant number of medical events in 2021 and 2023, 43 and 50 percent respectively. Next slide, please?

On the next slide, we're going to be looking at the Yttrium-90 SIR-Spheres. We're using the same surrogates and assumptions for the SIR-Spheres as we did with the TheraSpheres where a timeout benefits for wrong site, and infrequent user inattention is reflective of the 20 percent residual activity being left in the treatment device.

A timeout may have prevented six percent, 11 percent, and 22 percent of the medical events in FY2021, 2022, and 2023 respectively. Failure to deliver at least 80 percent of the treatment activity has resulted in a significant percentage, 67 percent of medical events in 2023.

In 2021 and 2022, 11 percent of the medical events were from 20 percent residual activity remaining in the treatment device. Again, this may be due to infrequent users performing treatments and users not being conscientious during delivery. Next slide, please?

Actions to prevent Yttrium-90 microsphere medical events, ensure the familiarity of the mechanics of the Yttrium microsphere delivery device and setup procedures, confirm all data and calculations in the treatment plan, perform a timeout to ensure all elements of treatment are in accordance with the written directive. Next slide, please?

There's a list here of some possible elements that could be included in a timeout, identifying the patient, the procedure to be performed,

the radioactive device to be used, which is not here on the slide, the radiopharmaceutical, the activity.

For the dose, it's a second check of the dosage calculation, and that the written directive and dosage to be delivered are identical, and then for some of the other treatments, you know, understanding the units of activity, especially for low dose rate prostate, the anatomic location, identifying the treatment plan for the patient correctly, performing second checks, making sure that the reference length for the HDR catheters and the delivery catheters are the right lengths so obviously the source gets to the proper location, and then the implant site for radioactive seed localizations.

And then the next slide is just my acronyms, and I guess I'd be willing to take any questions or if we're doing that at the end, and I just want to thank the commissioners for allowing me to present this today. Thank you.

CHAIR HANSON: Thank you, Dr. Harvey. Yeah, we'll hold questions to the end, and so next we'll hear from Megan Shober. She's the ACMUI agreement state representative. She's appeared before the commission numerous times and this is just her latest role, so Ms. Shober, over to you.

MS. SHOBER: Good morning. This morning, I'm going to be speaking to you on ACMUI's perspective on Regulation Guide 8.39 which deals with the release of patients. Next slide, please?

Our subcommittee members, I guess I should say the current incarnation of the committee, has Dr. Jadvar, Mr. Mailman, Ms. Melissa Martin, and myself. This committee has been in place for a long time,

I want to say maybe about six years or so, so we've had a number of committee alumni as well, but a lot of people have been working on this for a long time, and our staff resource is Dr. Tapp. Next slide, please?

So, just to give a little bit of historical perspective here regarding Regulatory Guide 8.39 and patient release, the commission has been involved with this for quite a long time.

Back in 2011, the former Chairman Jaczko proposed to staff to evaluate gaps, whether there were gaps in available data regarding doses received by the members of the public following patient release of individuals who have been treated with medical isotopes, and this proposal was due to a concern about I-131 patients being released from a hospital and going to a hotel and potentially exposing members of the hotel staff.

So, following commission approval, the staff requirements' memorandum directed NRC staff to evaluate gaps in available data and to consider a recommendation regarding possibly revisiting the dose assessment that was used to support the patient release rulemaking.

So, then in 2012, staff identified two potential gaps in the patient release data, and the commission directed the staff to revisit patient release calculations and also to conduct additional analytical and empirical data collection regarding that, patients traveling to a hotel.

So, after that research was completed and the information provided back to the commission, the commission directed NRC staff to complete four tasks that were associated with I-131 patient instructions. One of those tasks was to update Regulatory Guide 8.39 to specify guidelines for

that patient information and instructions.

So, in 2018, the staff submitted a SECY paper and communicated to the commission that based on the research done in response to those 2012 and 2014 papers, that a more comprehensive update to Regulatory Guide 8.39 was warranted.

The original request from the commission regarding patient release instructions began phase one of the Regulatory Guide 8.39 update, and the more comprehensive dosimetric update became what we now call phase two. So, next slide, please?

So, originally, Regulatory Guide 8.39 was released in April of 1997, and that was following a rule change to 10 CFR 35.75, which allowed the release of patients administered radioactive material on a solely dose-based criteria.

So, since that time, there have been several challenges to the appropriateness of the release criteria and the associated precautions that are required to minimize radiation exposure to other individuals from the released patient.

So, Regulatory Guide 8.39 was being revised in two phases. The first phase of the revision updated the patient release guidance, patient instructions, and instructions and recordkeeping related to breastfeeding for nursing infants.

So, the initial proposed revision one to this regulatory guide was issued in March 2019 and was reviewed by this ACMUI subcommittee. The subcommittee then subsequently provided comments on the final draft

phase one revision which was issued in December of 2019, and the NRC subsequently published revision one in April of 2020.

So, in the phase two revision, the dosimetric equations, the methodologies, and the tables used to calculate dose to members of the public are being updated. So, NRC staff provided the ACMUI with the draft proposed revision two back in August of 2021. Next slide, please?

So, the phase two revision, it overhauled the methodology that was used to calculate bystander dose. It significantly lowered the release thresholds based on administered activity and dose rate by making some more conservative assumptions in certain places, and then again provided additional updates to the breastfeeding interruption times. Next slide, please?

So, again for the timeline for this phase two revision, which is where we still are with this regulatory guide, in August of 2021, the ACMUI subcommittee received the draft proposed revision two, and then we held a public teleconference in December of 2021 and provided recommendations on that draft document, and then the NRC staff formally responded to our comments last summer in July. And I just put up there as a note that this draft proposed revision two was released for public comment last year in April. Next slide, please?

Okay, so the ACMUI subcommittee had a number of comments on the draft proposed revision two. We have strongly encouraged many times over the years that this regulatory guide focus on the external dose contribution to bystanders.

That has been shown in a number of studies to be the

predominant pathway for dose to bystanders from released patients, and so we have also recommended that the regulatory guide consequently de-emphasize contamination concerns associated with released patients as, again, that has been shown to not influence the bystander dose nearly as much as the external dose.

The subcommittee did raise some concerns with the significant reduction in patient specific, the threshold at which patient-specific release calculations are required. Again, this relies on several places where these calculations assume 100 percent occupancy for a number of hours following the patient administration, and of course, 100 percent occupancy is as conservative as you can get with that and not represent -- it doesn't really represent any kind of reasonable occupancy scenario.

One of the other concerns that the subcommittee had with the proposed draft revision two for Regulatory Guide 8.39, there is a series in the appendices, a series of examples that licensees can use to base their patient release calculations on.

However, there isn't an example for the most common release example, and so we did recommend that this appendix be revised to provide a calculation for that most common situation, which is a patient returning directly home. Next slide, please?

One of our, I guess, approach or philosophical concerns with the change to the methodology is that it does require licensees to have an unrealistic knowledge of patient behavior following release and, you know, even in very short time increments.

So, you know, at like this number of hours after treatment, what is the occupancy going to be? And then at this next segment of a couple of hours, what is the occupancy going to be, and kind of repeating on its way out.

And so, ACMUI did recommend that considerations should be given in the development of this model to provide some simplifying assumptions that can be used in common occupancy scenarios. So, for example, if the patient is unable or unwilling to follow instructions, that would have an occupancy value associated with it.

If the patient will be living alone, but will have potential contact, there would be a default value that's associated with it. That would simplify what the licensee needs to know about each of these specific time increments.

And then the ACMUI also recommended eliminating two of the four variables that went into the modeling as they didn't have as much impact on the final, as you do the math, it had much less of an impact. Next slide, please? Oh, wait, one more point about that. We, the ACMUI did not support two sections of the draft regulatory guide, the sections called release of patient after a hold time.

The concept was you hold the patient and allow for some biological elimination and physical decay, and then you start your calculation, you know, like four hours in, and that, the subcommittee felt that this just, this isn't how hospitals operate and they're going to choose another calculation route, so we did not see that section as value added for this calculation

process.

The ACMUI also did not support the section called materials separated from the patient, and that was if radioactive material becomes separated from the patient, the language was written such that that material was then subject to the public dose limits in 10 CFR 20, which has a 100 millirem dose limit, which is, again, 20 percent of the 500 millirem patient release dose limit.

And so, in our discussions, how does this release the patient with the radioactive material, and now at some point in the future, that separated material would then be subject to a lower dose rate, and how does the licensee know about this? It didn't appear under their control to be able to manage that and the patient's already been released. So, as just like a structure for, a regulatory structure for that, we struggled to see how that could actually be implemented by licensees. Next slide, please?

So, at this point, the NRC staff continued to be working on what we assume will be a draft final version of this phase two of Regulatory Guide 8.39. When the staff has that document ready, the ACMUI subcommittee will, of course, take a look at that draft revision two and provide recommendations on that document.

So, we thank the staff for the time that they are putting into this. We know that the impact of patient release guidance is, it's much more widespread than perhaps some of the NRC's guidance documents, and so we do appreciate the effort that is being put into this. And with that, I will turn it back to you, Chairman Hanson.

CHAIR HANSON: Thank you, Ms. Shober, very much for your presentation. And last, we'll hear from Mr. Josh Mailman. He's the patients' rights advocate on the committee. Mr. Mailman?

MR. MAILMAN: Thank you. Thank you, commissioners, for your time. Thank Megan for giving us such a great history of Reg 8.39. I know I joined into the committee about 2022, and so looking at all of the back history going back to 2011 has really been quite impressive and quite a reminder of what we've gone through to get there. The first slide or next slide, whichever?

So, that's me. We know what I'm talking about. Next slide? This is the agenda. We'll talk about the extravasation work that we've been doing over time, as well as a little bit more on Reg Guide 8.39 from a patient's perspective. Next slide?

Okay, so we're going to talk about extravasations. Next slide, please? So, what's changed since the last time we sat here in December of 2022? Really, we haven't had much of an update since the last meeting or the last vote.

The current proposed guidance is to have patients be part of the solution by learning how to report these as well. One of the things that I've found in talking in patient forums widely is that most of them don't know what an extravasation is, so we're going to be educating from ground zero because there just isn't that knowledge.

In public and private forums, I've probably talked to over 1,000 patients who've had either gallium, some type of gallium or copper scan,

or their FDG scans, or the current available FDA-approved therapies. So, education needs to be done.

This was driven home to me by Mr. Einberg when I came visiting earlier, sorry about that, earlier in March where how do we educate patients? What do we tell them? How do we keep them from being fearful of a nuclear medicine procedure, but still educate them so they can report correctly?

When I think about the education, I think we need to be able to be precise about what the impact to safety and efficacy is, and that's where I feel that there's other data that we haven't used as a resource to get there, and I will discuss that in a second as well, that will, I think, help us with the educational aspect. Next slide, please?

All right, so are patients discussing this? Clearly, some patient groups are. For me, I'm a neuroendocrine tumor as I said. I've worked and talked to thousands of patients on this topic. The issue has rarely, if ever, come up in a patient forum that I've been a part of.

But these are the types of things that come up in a patient forum. How does this imaging work? How long do I need to be off my long-acting therapies before I can do this type of imaging or this type of therapy? How do I deal with side effects? And this pertains mostly with the therapy.

I re-looked at the FDA label for Lu-177 dotatate. There is no mention of extravasation and injection site issues on the label at all, figuring the FDA also had phase three data to look at which included dosimetry. We'll get into that as well.

Pertaining to Reg 8.39, how do I travel home safely? Big questions about sitting across each other in a car and taking public transportation, and again, other things that pertain to 8.39. How do I stay around loved ones, partners? And yes, animals, but one day we'll get to animals. Next slide, please?

And I should say while I said I've been in neuroendocrine tumor meetings and various places where radioligand therapy has been discussed, I understand that there are multiple viewpoints to this. So, two things that I have done in both public and private forums, medical meetings, patient meetings, is encourage those who have an opinion or those who want to make, you know, at least comment on the topic to use the available public comment periods to actually inform staff.

When people talk to me about what their concerns are, I'm somewhat, well, I am in listen-only mode, and I've said that the only way that we can make this transparent to both the staff, the ACMUI, and the commissioners is to actually use the public comment period and to make sure that their feelings are relegated into that. Even when we were at a patient meeting, I had a representative of the NRC talk about how to make public comments because I think it's that important that people do.

I also feel it's important to listen to different views, so I have actually attended webinars by groups that certainly support the petitioners' comments, so I've attended webinars as well. Can I see what slide we're on, please?

Okay, so we have a lot of conflicting data here, right? We

have one piece of data that says, from the petitioner, and then I've looked at some of the websites in the last few days again that this happens one out of every 30 times that there's a medical event or a significant extravasation that could lead to a medical event one out of every 30 times.

We've seen articles published in the JNM that will go to one in 36,000 or three in 36,000, about one in every 12,000 of imaging, and there's a, sorry about that, there's a large difference between one in 30 and one in 12,000, and if we've giving education and trying to give education to patients, giving the education on one side versus the other would be problematic.

We have had three different phase three trials that have been completed in the United States since the time this has happened. That would be NETTER-1, NETTER-2, the Vision Trial that all included dosimetry that might have and should have picked up this as part of the FDA process for approving a drug, and if anything rose above two percent, it should be on the label.

I also have a belief in the free market, and I think if any of the pharmaceutical companies that were doing these things, especially in competitive spaces like prostate cancer, if it was happening at a rate of one of 30, it would be in their best interest to figure out how to make sure that it doesn't happen so the efficacy of their drug could be higher than whatever drug is coming after them, and as of yet, I have not seen any of the pharmaceuticals use this or submit data to use this with the FDA.

And the last point I wanted to make is many centers since both PSMA, Lu-177, and dotatate Lu-177 are doing three, four, or three to

four-hour post-therapy scans, and these are images with the arms in place, where you can actually see if there's an extravasation and what the rate is.

There are several centers that are doing this. Since the time, early March, when I had the discussion, I've contacted seven centers around the world that do this routinely, so I know there's data there.

And while I won't say it's one in 30 because it's not, it's not one in 12,000 either. Extravasations do happen. They mostly clear very quickly and there would fall way below what the reporting rate is to be on the label for an FDA, but I think I'm not the one to do that trial.

I'm not the one to do the prospective trial, but I believe there are many centers around the country that would do that, that would be able to do that. So, I would implore staff to work on that so we have the right number to educate patients with on what the likelihood is because patients in general like transparency, like to know what they're facing.

We're facing a lot of -- you know, either Pluvicto or Lu-177 dotatate, sorry for mentioning brand names, you know, there's a lot of side effects that can lead to -- there's a two percent chance in using dotatate that you could end up with MDS. These are serious concerns.

We're used to seeing serious concerns, but we need to know what the likelihood is, what we can do about -- not what we can do about it, but what to prepare for, and having something between a three percent and a one-tenth of a percent is hugely important. Next slide, please?

Yeah, so that was the end of my comments on the extravasation issues. I do believe there is education that can be done, but I

think we also need to have proper data that we base this off of, and I think we can do prospective studies certainly on the therapy side that would better guide our education.

All right, on this slide that we're on right now, which next slide, please? I think Megan has given us a wonderful overview of all the activity that has gone on with 8.39. Sorry.

In general, the patient community has been somewhat hard to engage in this even though we have discussions or we try to have discussions about this, but they don't know about Reg 8.39, but they do know about things that are in Reg 8.39, and I'll go on to explain that. Next slide?

So, yes, for the most part, patients and referring oncologists have really very little insight on what Reg 8.39 is. This is much more of something that the nuclear medicine community can cite verse, or chapter and verse, but in general, actually everything we discuss is included in Reg 8.39, whether or not patients know what it's called or where it came from.

You know, the big issues which I mentioned before in the extravasation conversation for patients is how do I travel home safely? What precautions do I take around partners, children, and animals? This is what patients talk about.

The other big thing that they talk about is why do centers across the country and across the world, in forums that, we'll talk about this, across the world, have different center instructions? And this is very confusing to what now is a global conversation.

You know, do the examples that we do take into account

the different isotopes that we use and potentially even the different ligands that we use? I don't know how that will affect any of this. I did, in my brief viewings with extravasation, notes that at some centers, the same isotope had different issues with extravasations whether it was coupled with a different radioligand, and so it's not just the radioligand, I mean just the isotope. Lu-177 might behave differently depending on what you bind it with, and so is this is a per-drug or is this a per-isotope consideration? Can you show the slides again?

So, for instance, we're going to see, and we've had conversations by Dr. Jadvar before on the new isotopes that are coming down the pike that are under clinical trials, do they behave the same way? Can you sweat out radioactivity with an alpha particle, a PSMA alpha particle, or does it only appear in urine?

That would change how that release criteria goes for that particular combination of a radioisotope. And I think, next slide? And with that, we have three minutes left to give back to the commission. Thank you.

CHAIR HANSON: Thank you, Mr. Mailman. Thank you all for your presentations. We'll begin questions this morning with Commissioner Wright.

COMMISSIONER WRIGHT: Thank you, Chair. And again, good morning. It's good to see some of you again, and hope everybody's doing well. And I really do appreciate your presentations this morning.

I look forward to this. I wish we did it a little more often, but we get there. And then when I go to the CRCP meetings, and things like that

that are out there, even the agreement state meetings you do here, presentations on some of this too, so I'm trying to do my best to keep up. Right? This is a fast changing area.

And thank each of you for what you do outside of this Committee, because your work is very important to patients and to families, and just people in general. So, thank you for that.

I'm going to go ahead and dive in, in the ten minutes that I've got here.

Dr. Jadvar, since you've been a member here at ACMUI, what, several years now, right? I'd like to hear your thoughts maybe on the future of the Committee.

I mean, all of you, you continue to bring to the Commission issues that are important and that need our attention, which we thank you for, but having said that, do you see any issues or challenges on the horizon that are going to require NRC attention?

And if you do, what can we do to, as a Commission, get better prepared, or help the Committee get better prepared?

DR. JADVAR: Thank you very much for that great question.

So, as you mention, I've been on this panel since four-and-a-half years ago. And I must say, during this time I learned so much from the regulation kind of side of things, and I also learn from my colleagues on the ACMUI panel, and many, many things from the NRC staff. So, it's been a wonderfully illuminating experience.

And I have also seen evolution over these past four years of how the fields, both in nuclear medicine and radiation oncology, have evolved. Tremendously.

And as already been mentioned in the previous meetings and also today, there are many new emerging technologies that are coming up and they will be important to be discussed in this Committee, with the NRC staff, some of these may pose new issues for the patients, or perhaps issues for the regulation. And I think Josh very nicely mentioned some of those.

For example, we don't have an offer in between for PSMA-based treatment yet, but I think that will come at some point. And already the patients are asking, is PSMA going to go into my sweat.

And this is very interesting that even the patients are thinking ahead of what's going on. So, these are the kind of things that this Committee can discuss, with all the feedback that is brought back from different perspectives, the patients' perspective, the states, and from our radiation safety officer representative and others, so that we are kind of a little ahead of the game of what to think about and what the issues and challenges may be.

Some of the challenges are known, some of it unknown. So, we'll kind of have to deal with it as they come in.

But I think we're up to it, and definitely NRC staff is up to it. They have done a great job educating us, working with us, and we have enjoyed really this working relationship, discussing issues with each other, learning from each other, and really trying to do the best we can for the

community and for our patients.

And in that sense, for example, with the emerging technologies, which I spoke about twice before in this commission meeting, for example, NRC took the initiative to hire new staff members in their medical team to increase the knowledge base that they need to accommodate for that, which is excellent.

I was wondering if at some point, for example, they may need a physician on their medical team to kind of bring in this clinical context perhaps, if that's useful. But that may be something in the future that may be considered.

And so, in any case, I'm not sure if I answered your question, but we have to see as it goes.

And I encourage all the members of this Committee, and also the NRC staff, to bring to this Committee, to our Committee, anything that they hear, so that we are kind of try to be ahead of the game. And of course, you are trying to keep the pulse of what's going in the field.

COMMISSIONER WRIGHT: Sure. Thank you for that. And most of you know, myself, I'm the beneficiary of the safe and secure use of nuclear medicine and nuclear technology. So, I have an interest in this.

And Dr. Harvey, I want to focus a little bit on the timeout stuff. And I don't know, maybe it's hitting me a little wrong, but I got a little bit concerned about something.

I want to be sure that I understand what it is you were saying. Because if it's not already happening, I've got some concern too.

As a patient, when I went through what I went through, and my daughter after me, we were very aware of what the procedure was, how it was going to be done, who was doing it, that we knew the doctors that were doing it.

We knew what we were supposed to expect, and then we knew what we were supposed to do after, as a patient and as a caregiver, right? I knew what I had to do to be responsible.

I had to protect my daughter, myself, and my family. Right? Because some of them were small. When you talk about the timeout stuff and this fast changing area, people are new and possibly it's always evolving. So, training is huge, right? And you mentioned some of these procedures are not done that often, right? And then people are coming back and forth. They may do it today and somebody else may do it tomorrow. Right? Which speaks to training. Right?

And on page 39 you listed a bunch of things that you thought -- possible elements of the timeout. And I was going down the list of them and I'm like, are these lists not there now?

I mean, if it's a procedure that is not done that often, is there not written guidance on how to go about it from the authorized user, or from the doctor himself who's the one responsible for making sure his patient gets a dose the right way.

I mean, was I hearing you right about that? Can you explain a little bit more to me, or allay my fears of what I think I heard?

DR. HARVEY: Thank you very much, Commissioner

Wright.

Those elements and those things are managed, and managed effectively, by most organizations.

The use of a timeout is another practice that can be employed or used in addition to what is -- those aspects are already covered. But taking another timeout or a pause, another time to re-look at all those issues right before you're about to administer the radiopharmaceutical, as another cross-check, or double-check, or triple-check, depending on how many you do, can be an effective way in some of the procedures, to help prevent some of the medical events.

Some organizations may do all that stuff very effectively without a timeout. But when we see medical events occur, we think that a timeout could be a useful avenue, a useful thing that somebody can do to help.

And I applaud you and your family for being excellent stewards of your own care. And I think that's very, very important. And certainly, not everybody is quite as good a steward as you and your family have been.

COMMISSIONER WRIGHT: So, to address that, is this something that needs to be more deeply addressed within the NRC, or is it something that the medical industry has to take a deeper dive into themselves, or is it a combination? And I see Ms. Shober's hand going up too, so I'm going to let her speak too.

DR. HARVEY: Yes, I can't wait to hear what Ms. Shober has to share with us because she is so insightful.

I think the use of a timeout is something that is very useful. I don't think it should be regulatory mandated, because it's not always needed by organizations, but I think it's a tool that can be very useful, that can be added in certain situations.

If you look at the Yttrium-90 Microsphere, which is relatively complicated with the delivery device and all the things that go into that, it's a really nice opportunity.

And as we see, some of the modalities, some of the areas, they're relatively flat. And the numbers of measurements are relatively low.

But at least to me, the Microsphere procedures are a little bit high. And I think there's a real opportunity there to maybe use a timeout.

I would hate to mandate it for everything, because many people are doing this effectively.

COMMISSIONER WRIGHT: A generic communication of some kind, maybe?

DR. HARVEY: Yeah, there's a number of communications, checklists, there's a written directive, of course, which outlines route of administration, the activity, your two-method identification, the authorized users verifying all this, your routes of administration, the prescribed dose, the actual dose.

So, these things are being covered and being taken into account to protect the patient and deliver high-quality care.

But the use of a timeout can be that second cross-check, or another cross-check, to maybe help enhance that process if someone's

having trouble, and maybe having some medical events.

COMMISSIONER WRIGHT: Thank you. And if you would allow for Ms. Shober.

MS. SHOBER: I just wanted to add that the NRC did issue an information notice on these timeouts.

I want to say with 2020 or 2021, that was coming out of some of this original work that ACMUI Medical Events Subcommittee put forth. So, we have done that recently.

COMMISSIONER WRIGHT: Okay, thank you so much.

MS. SHOBER: You, the NRC, has done recently.

COMMISSIONER WRIGHT: I didn't do it. And thank you so much.

CHAIR HANSON: Yeah, thank you, Commissioner Wright. Commissioner Caputo.

COMMISSIONER CAPUTO: Thank you for presenting to us today, thank you for being here, and thank you for your dedication work on the Committee in service to the Agency and the public. We very much appreciate the value of your expertise and your remarks here today.

I'm going to continue on from my colleague's line of questioning, to just say Dr. Harvey, you just rattled off a lot of options of actions. Are those being taken by licensees and doctors that are administering, or are those other tools that the Agency is using to address the situation?

DR. HARVEY: Thank you, Commissioner Caputo. So,

timeout is a well-known practice that is in the medical community in healthcare. And it's something that's used quite often throughout healthcare.

So, it's more driven by the organizations themselves. There have been notices, as Ms. Shober pointed out, encouraging that as a possible tool that can help prevent medical events and be useful in the effective redelivering quality healthcare.

COMMISSIONER CAPUTO: Right. So, I'm familiar with the fact that we did an information notice. I guess my question is, you're suggesting that a timeout would be effective in further reducing. Does that mean we need to send another information notice because timeouts aren't being used enough? Or is there some other, more effective tool that we could apply here?

DR. HARVEY: I think the timeouts are being used effectively, and if you look at some of the areas, the number of medical events are low. So, I think they're being used well.

I think the area that we may want to be a little bit stronger with to push something out would be for the microspheres.

That's where we're seeing a higher number of medical events. And I think that might be a valuable tool that could be used.

COMMISSIONER CAPUTO: Okay. Well -- and I should have made a note of this when you were speaking -- but you rattled off how you believe timeouts have reduced the medical events by various percentages. And if the percentage is 50 percent, then I guess my question is, why wasn't it useful in that remaining 50 percent? And is it just that the

numbers are so low that it's not really distinguishable?

DR. HARVEY: So, the timeouts I believe have been effective. And the -- trying to figure out how the best way to answer this is -- could you restate your question for me so I don't make a mistake, please?

COMMISSIONER CAPUTO: You're saying that the timeouts are effective, and that they are reducing a significant percentage of the medical events. But they aren't reducing it by 90 percent.

DR. HARVEY: So, the medical events may have been a useful tool in the percentages cited.

COMMISSIONER CAPUTO: Right.

DR. HARVEY: So, we don't know if timeouts were used in those situations or not, because we don't know all the practices and all the organizations.

So, the methodology that we're using comes from Dr. Ennis. And so, we've continued and carried that forward thus far. And those certain classifications are areas where we feel -- the subcommittee feels -- that a timeout could benefit, possibly benefit, in those types of situations, and help reduce a percentage.

COMMISSIONER CAPUTO: So then my question is, do we need to emphasize timeouts again through another information notice, which would seem a little redundant, or is there different way for us to communicate or get at this?

DR. HARVEY: I think timeouts, again, are very well-known and well-used within the organization. If the NRC would think that would be

valuable, or if there's other comments from other people, I don't think it would hurt to push something out and continue that -- promote maybe that use or that tool going forward.

COMMISSIONER CAPUTO: Okay.

DR. HARVEY: And then some of the other medical events were for other reasons that a timeout may have not benefitted. That's why there was the percentage that we felt would have benefitted from a timeout.

COMMISSIONER CAPUTO: Okay. All right, thank you.

DR. HARVEY: So, I hope I answered all your questions. Thank you.

COMMISSIONER CAPUTO: Thank you. Dr. Jadvar, obviously there have been concerns raised about the draft guidance started shifting gear to Reg. Guide 8.39.

Concerns with the draft guidance requiring a medical practitioner to perform an unrealistic and complex patient-specific calculations for patient release.

So, letters also express that the revised draft guidance could potentially curtail access to valuable treatments. Do you have a perspective on that? Is there really a risk of curtailing patient access based on the nature of this Reg. Guide?

DR. JADVAR: I think Ms. Shober presented very nicely on that account. But I think yes, if this has to be done on a patient basis in a very complex manner using mathematical models, and the potential whole time for patients and complicated procedures, that may affect the workflow in the

hospitals or clinics that cater to these patients, may in fact make the whole process more confusing, both for the people who are applying these treatments to the patients, and also to the patients who are going to follow them.

There may be additional resources needed to do all of that. Not every place has a medical physicist, for example, or the tools needed to do these complex model calculations.

And I'm not sure even if the benefit is there for doing all of that. And in an indirect way, it may cause an issue with availability and access to these treatments. That's what concern I think you're bringing up.

COMMISSIONER CAPUTO: All right, well, I'm going to keep going here. Did the subcommittee review data indicating members of the public are being exposed to external dose by patients that have been treated?

So, do we have data that can validate that this is a significant safety concern, or is it a postulated safety concern that we are modeling?

DR. JADVAR: To my knowledge, it's postulation, not actual data. But Ms. Shober may know better on that.

MS. SHOBER: I believe in one of the original asks from the Commission in 2012, asked NRC staff to do a study that included collection of data in some limited cases for a really silent 31 patients, but I don't know if anyone on the staff can speak to that. But I do believe there was --

COMMISSIONER CAPUTO: But was that data on patient

behavior, or --

MS. SHOBER: It was specific to the hotel situation, with patients released to the hotel.

COMMISSIONER CAPUTO: Oh. Okay.

MS. SHOBER: Like a subset of patient behavior.

COMMISSIONER CAPUTO: Okay. We have a document here that says the staff concluded that a hotel cleaning staff person would need to clean approximately 670 rooms of newly released thyroid cancer patients, to exceed the 100 millirem standard.

MS. SHOBER: Right. So, there was a claim, and then I believe that they did that assessment and came up with that number. The 670 patient number. I believe that was part of what the Commission had asked the staff to do.

COMMISSIONER CAPUTO: Okay. So, since we're talking about personal experience, having been a hotel cleaning staff person, if every single room that was cleaned was a newly released thyroid patient, it would take at least two years to clean that many rooms, to trigger that dose.

So, that seems overly conservative, if that's the kind of data that we're using to base the Reg. Guide on. Which, I guess, gives me a concern of the costs and burden associated with this revision of the Reg. Guide actually justified, compared to the safety benefits.

MS. SHOBER: I agree with your statement. And I also believe that subsequent to that initial research, that it was identified that the greatest potential for exposure to bystandard would have happened in the

public transportation part of the patient going to whatever destination they were going to.

So, I believe that that public transit situation came on the heels of -- the original request was for hotels. And then the public transit situation came on the heels of that, and that's where the possible -- that was the situation where possibly the existing methodology was in some situations underestimating dose.

COMMISSIONER CAPUTO: Okay. If the Commission would humor me one last bit, Dr. Jadvar, do you believe the staff is responding adequately to the concerns that ACMUI is raising on this topic?

DR. JADVAR: I believe so. And I think that's why we're in the revision and trying to work with them.

As Megan already mentioned, some of the appendices were quite complex and complicated, and not really addressing, we felt, not really addressing the comments and areas that we face in our practice.

And I think it's going to back and revamped and looked at again. And I think that they are definitely listening, and we are communicating very well with each other.

COMMISSIONER CAPUTO: Okay. Because from my read of the response back to the Committee from July of 2023, it looks like the bulk of ACMUI's comments were not accepted. So, I guess if you are comfortable with where things are headed, then that gives me a source of comfort. Thank you.

DR. JADVAR: Thank you.

CHAIR HANSON: Thank you, Commissioner Caputo. Commissioner Crowell, are you still out there with us?

COMMISSIONER CROWELL: I think I am. Can you hear me and see me okay?

CHAIR HANSON: Yes, we can. Thank you.

COMMISSIONER CROWELL: Okay, great. Thank you, Mr. Chair. Thank you to all the panelists as well for being here today and providing the information. Always informative.

And thank you to the Commission for indulging me joining remotely today. My family and I went to Ohio to see the solar eclipse and we're slowly making our way back.

So, I'm joining you from a hotel outside of Columbus, Ohio, and it's just me and my dog in the room.

So, I'm going to start with a question related to veterinary practice, and then I'm going to move to some of the other topics that my colleagues raised.

So, for starters -- this is a new element of this topic that I hadn't thought about before -- but are there similar things in the patient-release requirements that are anticipated to be applied to veterinary practices? There didn't appear to be so previously, but sure, a pet could have some sort of procedure using radiological and liquid medicine, and if they're coming back to a home with a vulnerable family member or a young child, or a pregnant or breastfeeding mother, I supposed that could be a problem.

So, just give for a second, either Dr. Jadvar or Ms. Shober,

just tell me what you're thinking of with that narrow space on this.

MS. SHOBER: So, I'll start by saying that yes, that question has definitely come up.

When veterinary patients are released, there is no veterinary equivalent of 10 C.F.R. 35.75. So, those released animal patients are limited to a 100 millirem dose to people and their household. So, veterinary patients are subject to a lower dose from 10 C.F.R. 20.

COMMISSIONER CROWELL: And that's because the risk to humans that share a home with a pet is less through a veterinary vector? Or why is that? I don't know if a dose, an animal would receive is so much -- a typical household animal -- is so much less that it's not as much of a concern at the home. Is that the idea here? Is that what you're saying?

MS. SHOBER: So, the release limit in 10 C.F.R. 35.75 is specific to human medical ESA material. So, they are given a higher threshold. But the veterinary animals are subject to a lower dose limit, 100 millirem. And that's the same for any other, like, dose from any licensed activities -- 100 millirem.

COMMISSIONER CROWELL: I think I follow you.

MR. MAILMAN: We had a presentation at our last ACMUI meeting on veterinary release and how it was different than, or regulated differently than -- and not necessarily this group, I can't remember who gave the presentation.

MS. SHOBER: And part of the issue is that we can argue about how well or not humans will follow release instructions. But pets are

less able to follow release instructions.

COMMISSIONER CROWELL: Exactly. Okay, well, perhaps a topic for further discussion. Moving on, Dr. Harvey or whomever wants to take this, you mentioned that the increase in medical events associated with new radiopharmaceuticals has been seen.

Can you give me a sense of the trend here? Is it increased in number but the same statistically, or is the statistical trend increasing as well, in terms of medical events? Just want to get a sense what that looks like now, and if you see it going in one direction or the other moving forward?

DR. HARVEY: Yes, Commissioner. So, what we've seen in the absolute number has increased. But we don't really have a good handle on the denominator. We don't know how many procedures are being done.

What was indicated yesterday from NRC staff is because of the increasing number and volume of procedures, the actual incidents or an occurrence is actually decreasing, because the denominator is getting larger.

So, it's flat to a relative decrease, per the information that we were supplied with yesterday.

COMMISSIONER CROWELL: Okay. Understood, thank you. I'm going to delve into some places that we've talked about a bit here, including timeouts.

But before I do that, let me just say I appreciate the delicate balance of all of this that everyone involved in this topic take.

It's important for all of you in the medical field to make sure that as many patients are getting access and benefitting from available care,

at the same time minimizing any impacts on families or others from that care.

And then the NRC has got a balance here too, in terms of its regulatory jurisdiction and making sure that we're putting up appropriate safeguards but not a strain into what we consider the practice of medicine.

And so, there's some balance here that I think we all appreciate. And I think striking that balance comes down to good education and communication on all sides through this process.

And to delve into timeouts a little bit more, can someone just give me a little bit more of a layman's walkthrough of how a timeout works? Is it initiated by the provider? Is the patient aware that a timeout exists, so to speak, and could say, hey, we've taken a timeout, can we look at the checklist again?

Just how does a timeout happen, in practical terms, for the experience?

DR. HARVEY: Thank you for your question. So, usually the provider will take a pause and stop before the procedure moves forward with the administration of the radiopharmaceutical or radioactive treatment.

So, that is initiated typically by the provider. And they will go through the parameters that they feel are very important to the administration of the radioactive procedure.

COMMISSIONER CROWELL: Okay.

DR. HARVEY: Does that sufficiently answer your question? I'm sorry.

COMMISSIONER CROWELL: Yeah, I think so. Is a patient

generally aware of that as part of the process? I guess what I'm getting at is if you see a discrepancy in how well patients are educated -- probably in rural health centers, versus more urban settings that do these practices more often -- is there also a delta in how well patients are educated about what the procedure's going to have, what the impacts could be to themselves afterwards to their friends and families, etc.? Like, how confident are you that patients understand their side of the equation?

DR. HARVEY: Commissioner, Dr. Angle's going to take this question from the podium. Thank you.

COMMISSIONER CROWELL: Sure.

DR. ANGLE: Hi, this is John Angle, a consultant to the ACMUI.

So, I want to differentiate a timeout from a checklist. I think it's important you know a Joint Commission, the accreditation of a hospital, is defined to 30 years ago the concept of a timeout before any type of procedure or operation.

And this is where we make sure doing the right patient, right procedure, right side, these changes have been proven over and over again make a huge difference in all manners of procedures and operations.

And then really about fifteen years ago, along came this concept of doing checklists. And maybe some of Atul Gawande's book, Checklist Manifesto, and this book really shook up our medical field quite a bit. And so, now the concept of checklists I think is very applicable to a lot of procedures.

And so, all of the operative timeout is very well-established. If the patient's awake, it involves making sure they understand the nature of the procedure. That, of course, has happened during the consent process, and also visits beforehand.

But it's for everybody in the room, including the patients, involved in discussion. Are we doing the right procedure, the right time and the right side, etc.?

And then the evolution of these checklists is, I think, very applicable to these procedures that we're talking about here. Because there are a lot of steps where you can't step back. You got to get it right the first time. And so, checklists make a lot of sense for this.

I personally don't think that is the realm of the NRC. I think that this has to come from societies, and has to be led by doctors who are doing the research to find out what steps are key, how do we educate everyone in the room about what steps are important and when to call them out.

So, I think there's a lot of opportunity there, a lot of work to be done. I think for years, of course, physicians all have a very high sense of responsibility, and go through all these steps in their mind.

Or maybe some senders are already doing checklists, and so there's not -- and we hope this will get rolled out in a more general fashion in the future.

But in the meantime, I think it's very much a physician-patient relationship to make sure that patient understands the risks and the

potential side effects. And that has always been true, but I think we've got an opportunity to do more in the future.

COMMISSIONER CROWELL: Thank you.

DR. JADVAR: May I add to also something? Excellent comments by Dr. Angle. I just say as a patient myself, when I was a patient doing the consent form, when I was in the OR I was lying on the bed, and the surgeon comes in.

So, he asks my name again, and then said, this is what we're doing, right? And then said, yes, which side? And I said, the left side. He said, yes, we're going to do the left side.

So, these are kind of things that -- the checklist, or making sure that the patient is involved. And I think that's the best practice, to make sure that they understand what we're doing, and they confirm what's going to happen to them.

MR. MAILMAN: And obviously, this is not just a nuclear medicine issue. I recently had a biopsy, and I was actually surprised. I thought when the word timeout came in whenever I was doing anything, that we were going into some sports performance.

But in fact, this physician said to all of her staff, we're going to do a timeout, and now let's look over what we're doing, and let's go through all of it and make sure.

And I was still awake and they asked me questions on top of making sure all the staff that was in the room understood where they were, what they did, and reported back.

But it was a break. It was, like, a seven-second break until they started the procedures of what they wanted to do a timeout about, and I felt much better now, knowing what a timeout meant in medical world.

We don't get taught that timeouts are something to listen for. So, I may have been ignoring them up to then.

COMMISSIONER CROWELL: And I appreciate all of those comments and examples, because all of us collectively are a relatively sophisticated group and we even learn something through it.

But for an average person, they may easily understand the difference between which leg is going to be operated on, but administering a cancer treatment's a little bit more complicated. And along those lines, I'm wondering if the statistics on reportable events has teethed out at all whether these are happening more in areas that are socioeconomically disadvantaged, versus other areas? Is there any insights into kind of geographically and socioeconomically, where these events are happening most or increasing most?

DR. HARVEY: I have no real comment on that. I have no data or anything I can justify. I don't know. I'd open it up to anyone else in the group that may be able to provide more insights than myself.

DR. JADVAR: Well, I don't have any specific data. But just from my own professional life, when I was a medical student there were situations. I was in centers that they were less-advantaged, socioeconomic patients, and obviously you get the consent form, you tell them what's going to happen.

Sometimes they listen, sometimes they don't. Sometimes they don't understand exactly what is going on. But it's really on the provider or the physician to make sure that they can try to tell them the best they can what is happening to them and what the procedure is, what they're going to do, what they're going to go through, what they're going to experience, all that stuff.

But then at other hospitals or other situations I've been, where there are more educated patients, they really want to be involved. They ask questions -- very good questions, very detailed questions, of what exactly is going to happen to them, and what to expect and all that.

So, it's both ways. But as far as hard data, I don't know.

COMMISSIONER CROWELL: I appreciate that and I understand it may not exist today. And maybe it's something we want to see we can teethed out later.

My gut says that some of these concerns we've discussed today are perhaps more acute or predictable in rural or de-served areas. So, it's something to think about.

And I've been alerted that I'm over my time and I didn't have a clock on my end, so I apologize for that. No more questions. Thank you, Mr. Chair.

CHAIR HANSON: No problem at all, Commissioner Crowell. Thank you all very much. I am, of course, last, and so I'm in the unenviable position of picking up a lot of threads that I think my colleagues have laid. So, I'll start with this one.

Dr. Harvey, just picking up on something Commissioner Crowell had mentioned, trying to get a hold on the denominator, which I think is, as you mentioned, difficult because the number of procedures is increasing.

But can you just kind of give us a rough order of magnitude? I mean, we're talking about medical events here that are -- maybe if I add up all of the kind of reportable medical events, we're talking about 100, or maybe 200.

But what's the scale of the denominator in that equation? Are we talking about 10,000? Are we talking about 100,000? Fifty thousand?

DR. HARVEY: Honestly, I have a good answer for you. We're not really privy to some of that information. We had some conversations about, like, the Yttrium-90 Microsphere yesterday, and, like, the manufacturers knowing how many, like, vials they may have shipped out.

But the NRC knows that. But we can't know that because it's proprietary, as I understand it. I would open it up to any of my colleagues who maybe are more well-versed in the number of medical nuclear medicine procedures, or other procedures --

CHAIR HANSON: Thank you. Mr. Mailman?

MR. MAILMAN: Twenty million.

CHAIR HANSON: Oh. Oh, I was missing three zeroes in there.

MR. MAILMAN: There are 20 million procedures done. Now, are all of them with injectables, versus -- but roughly, there's a big number. It's a very big number.

CHAIR HANSON: Okay, thank you.

MR. MAILMAN: And therapy.

CHAIR HANSON: Yeah, diagnostic and therapeutic. Okay.

MR. MAILMAN: And we have certain things that are -- when you have new therapies that are a little bit on a hockey stick, and so they're growing more rapidly. But overall, yeah, we're doing a lot of procedures.

CHAIR HANSON: Okay, thank you. Thank you. If I could, Megan, I want to pick up on something Commissioner Caputo brought up about Reg. Guide 8.39, because I think I share some of her concerns about what this thing does and how it's differed.

I mean, just looking at the occupancy factor, right? The previous, if I understand it correctly -- and I'm not an expert on this by any stretch of the imagination -- but if I understand it correctly, the previous occupancy factor in the old Reg. Guide was 25 percent, and now it's 100 percent.

So, that, just from a layman's perspective, that looks like it's four times more conservative.

And can you maybe just revisit the history a little bit on this. I mean, I think Commissioner Caputo brought it up, because I think it's worth revisiting about what's the basis for that? Or how did that really, a four-fold increase in conservatism, really come about?

MS. SHOBER: So, the initial concern that people who developed that modeling were interested in meeting, was that public transit situation right after release.

And so, what they really want to do is have the default values be very low at which these things are required, and then the licensees then become responsible for modifying those default values using patient-specific information.

So, it's really pushing license facilities to the patient-specific calculations in a greater number of cases.

So, for example, right now if you are receiving I-131 therapy for hyperthyroid administration, that's often ten to fifteen millicuries of I-131.

So, right now that doesn't require patient-specific calculation because Reg. Guide 8.39 has a 33 millicurie limit.

So, what this is going to do in practice is reduce that bar to seven millicuries at which these things are required, and then the patient populations that receive hypertherapy, the license facilities would now need to provide a patient-specific calculation.

Are they going to be able to release those patients? Yeah. But there's an additional evaluation that has to happen for a class of patients which previously didn't require that kind of documentation.

CHAIR HANSON: You raise a really good question though, that was maybe behind some of this. And that is, okay, so we've layered on then this conservatism, right? We basically said, okay, we have a low threshold before. And then if they get more, so if it's like a Lutetium-177 type administration where they're getting a lot more activity, then maybe just Iodine-131, because it's over four doses, rather than a single dose, right?

But then you have this kind of low floor, and then you would

add requirements if they get more. And now, we've got a high requirement and you're kind of modifying then, kind of release requirement somehow from that higher thing based on what you might learn.

But at the bottom of that is really just about patient behavior and patient restriction, right? So, we've added all this conservatism, but what's fundamentally different about what a patient might do or not, in terms of where they can go?

MS. SHOBER: That's a wonderful question. And that is part of the reason why as the subcommittee, we were advocating for reducing the complexity of some of that modeling.

Because we as a subcommittee were questioning the value of some of that granularity. You know it's there. If you've got a full-time medical physicist that really geeks out on that kind of calculation, like they can make something that is very patient-specific.

But I have a math minor. I know how to do math and I can follow equations through, but some of those that are in this draft Reg. Guide are hard to follow. They're very abstract.

And so, that's why our subcommittee was making comments to say, we need better examples. Because I think it's a challenge to apply that model to classes of patients that many facilities will see on a very regular basis.

CHAIR HANSON: Well, I think you raise a good point, right? In all of this stuff there are actual patients doing real things here, right?

If somebody walks out of Columbia-Presbyterian in New

York and they have to get home, in New York City they've got kind of three options, right? They can get a cab, they can get the subway, I supposed they could get a bus, or they can walk.

But if they live in Brooklyn, that's going to be pretty hard. Right? Particularly if they've just had a medical procedure and they're tired, and whatever else.

And so, I understand there's a certain amount of uncertainty around patient behavior, that I think is trying to be accounted for in this change, particularly in the occupancy factor, but -- well, let me step back and kind of ask this then.

Do I have it right, at least on your slides, that the ACMUI is not a big fan then of this change?

MS. SHOBER: So, I guess to paint a very broad brush stroke, the subcommittee does believe that it is too complex.

CHAIR HANSON: For the additional benefit in terms of exposure to other members of the public.

MS. SHOBER: Correct.

CHAIR HANSON: I see. Okay. Okay. Well, thank you. I think I've reached the end of that thread.

Mr. Mailman, I just wanted to touch on one thing, kind of with regard to extravasations. And as you know, there's a lot of external interest in this, and yet you've said maybe you didn't hear as much from external groups.

One of the concerns I think I've heard is the concern about

kind of mis-administrations for extravasations, right? Whether it's diagnostic or therapeutic.

And that through training and timeout and practice, getting to kind of the infrequency, Dr. Harvey, that you were talking about, that mis-administrations can really be significantly reduced, and therefore, extravasations can be significantly reduced.

Is that something you're hearing in your interactions? Can you talk more about how kind of extravasations is playing in Peoria, I guess, as an issue?

MR. MAILMAN: So, one of the reasons that I suggested we actually do prospective studies, is that we can actually have data, as opposed to two opposing views of, it never happens, to, it happens a thousand times a day.

CHAIR HANSON: Right.

MR. MAILMAN: And as far as therapeutic extravasations of target radiotherapies, what I have seen in the data I looked at, let's say at Seven Centers, is that doses hitting the target.

And even if there's a partial extravasation, the dose will get there within, in certain cases, 24 hours, or somewhere between three and 24 hours, and the dose will not stay in the extravasated site. It will move and be therapeutically if effective, and those who have been -- who have had extravasated are then followed. And we can take a look at that.

And I think from that standpoint, I'm actually less worried about -- we've targeted radiotherapies that want to go seek their home, that

things are going to stay somewhere in the arm for a long period of time, because they want to find their target.

As far as imaging, we have two different types of reports. They may be measuring different aspects of this, which I can't tell either. But again, these newer targeted radiotherapies want to find home pretty quick. And honestly, you're used as more of a contrast to background ratio between healthy tissue and tumor tissue.

And it's not that they produce images that will be ineffective or not useful. The contrast between the tumor and healthy tissues will be there. I mean, it isn't that someone gets imaged 20 seconds after they're infused. There's an hour that these things can travel to their site.

And may it defect SUV? I'm not sure. But it should allow someone to see whether therapy is doable or not, especially with these newer radio-likened therapies.

Again, I'm not the physician in the room with a nuclear med doc in the room. I got one over there who's going to stand up.

DR. JADVAR: So, let me just add to excellent points that Josh brought up.

When you puncture a vein, you're going to make a hole. So, there's going to be a little bit of blood that comes out. And you're going to have some mild amount of activity there.

In my practice, I've been doing this for almost 25 years, and once in a while we see imaging extravasations. And in almost all cases, except maybe one I remember, that the image quality was sufficient to be able

to make a diagnosis.

Remember, even as Josh mentioned, if the contrast to background ratio changes a little bit in a patient who has 25 metastatic lesions and you don't see one of them, it doesn't make any difference. There is no clinical significance to that at all.

The management would be exactly the same as what you thought. SUVs is only one part of a semi-quantitative measure that we look at. There are many other things that can have effect on SUV -- the drug effect, the patient's nutritional status, all these kind of things.

So, nobody ever makes a decision if, for example, this treatment is working or not working, comparing baseline to post treatment scan, just based on SUV.

You look at the CT scan, you look at the lesion size, the number of lesions, what's going on with the patient, and if there is any SUV, if you want to include that also, then you can correct it or normalize it to the blood pool background, the whole liver background.

So, basically, you normalize this scan for the same background ratio, the other scan for the same background ratio, and then you compare the ratios. Because then you can compare apples to apples.

So, this can be done. Nobody really makes a decision on SUV going up or down by 20 percent. Oh, did this patient has responded or not responded? It's not like that.

So, if anybody proposes that that's the way we do practice, it's incorrect.

CHAIR HANSON: Okay, thank you. Thank you for both of those perspectives then. Appreciate it very much.

All right, well we've reached the end of our time together. I want to thank you all very much for your presentations. Thank you to the four of you, and also the other members of the Committee, for your service to the Agency and to the country.

Thanks to my colleagues, as always, for their insightful questions, and their thoughtfulness in all of this. And with that, we will wrap it up.

Thank you again very, very much. We're adjourned.

(Whereupon, the above-entitled matter went off the record at 11:48 a.m.)