

UNITED STATES

NUCLEAR REGULATORY COMMISSION

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MEETING WITH THE ADVISORY COMMITTEE ON THE

MEDICAL USES OF ISOTOPES

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WEDNESDAY,

NOVEMBER 18, 2020

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The Commission met in the Commissioners' Hearing Room at the Nuclear Regulatory Commission, One White Flint North, 11555 Rockville Pike, at 10:00 a.m., Kristine L. Svinicki, Chairman, presiding.

COMMISSION MEMBERS:

KRISTINE L. SVINICKI, Chairman

JEFF BARAN, Commissioner

ANNIE CAPUTO, Commissioner

DAVID A. WRIGHT, Commissioner

CHRISTOPHER T. HANSON, Commissioner

ALSO PRESENT:

ANNETTE VIETTI-COOK, Secretary of the Commission

MARIAN ZOBLER, General Counsel

ACMUI MEMBERS: (attending via video conference)

DARLENE METTER, M.D., Chair, Diagnostic Radiologist

A. ROBERT SCHLEIPMAN, Ph.D., Vice-Chair

HOSSEIN JADVAR, M.D., Ph.D., Nuclear Medicine

Physician

MELISSA MARTIN, Nuclear Medicine Physicist

MICHAEL SHEETZ, Radiation Safety Officer

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

10:05 a.m.

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CHAIRMAN SVINICKI: Okay. I think we're ready to go in the booth. Good morning everyone. I convene the Commission's public session this morning to conduct a meeting with our Advisory Committee on the Medical Uses of Isotopes.

This is a routine meeting of our Commission to hear from this important Advisory Committee, which advises the NRC staff, not the Commission. But, I think that this, at least annual Commission engagement, is important since they are taking on a lot of very complex topics, and in some ways talking to us about things that fall more squarely in the NRC's regulatory domain, and those that have some sort of impact to the practice of medicine.

So, that is something that it is of a great utility, at least to me, and I think other members of the Commission to hear from medical practitioners and other specialists on these complex topics.

So again, I will recognize each speaker that we hear from, from the Advisory Committee. And then after that, Commissioners will be recognized for a round of questions.

But, before we get started, would any member of the Commission like to make any opening remarks?

(No response)

CHAIRMAN SVINICKI: Okay. Hearing none, then we will begin with the current ACMUI Chair, Dr. Metter.

And Dr. Metter will be giving us an overview of ACMUI activities. And so the booth will now pull up the remote feed of Dr. Metter.

1 DR. METTER: Good morning Chairman Svinicki and  
2 Commissioners Baran, Caputo, Wright, and Hanson. I'm Darlene Metter, the  
3 ACMUI Chair and Diagnostic Radiologist.

4 Thank you for taking the time to meet with representative  
5 members of the ACMUI, who will be reporting on certain major issues  
6 addressed by the Committee in 2019 and 2020.

7 As the ACMUI Chair, I will be presenting an overview of the  
8 2019/2020 ACMUI activities. Are my slides up?

9 CHAIRMAN SVINICKI: Yes. Your slides are viewable here in  
10 the room. I think remotely as well.

11 DR. METTER: Okay. Next slide, please. I really don't have a  
12 remote view of the slides that are being presented.

13 But, today's Agenda, Dr. Robert Schleipman will follow me as  
14 the ACMUI Vice Chair. And he will be presenting the ACMUI comments on the  
15 staff's evaluation of training and experience for radiopharmaceuticals requiring  
16 a written directive.

17 Ms. Melissa Martin is our ACMUI Nuclear Medicine Medical  
18 Physicist. And she will be presenting the ACMUI comments on extravasations.  
19 Next slide.

20 Following Ms. Martin is Mr. Michael Sheetz, our ACMUI  
21 Radiation Safety Officer. And he will be presenting his comments on patient  
22 intervention and other actions exclusive of medical events.

23 Following Mr. Sheetz will be our Nuclear Medicine Physician,  
24 Dr. Hossein Jadvar, who is presenting a very interesting topic on trending  
25 radiopharmaceuticals. Next slide.

1                   So, my presentation as Chairman Svinicki stated, will be an  
2 overview of the ACMUI activities. The format will be reviewing the role of the  
3 ACMUI; looking at the current membership of the ACMUI; review the many  
4 topics presented at the ACMUI meetings in 2019 and 2020.

5                   We'll look at the current subcommittees. And lastly, I'll give a  
6 final comment about the future. Next slide.

7                   So, the role of the ACMUI is to advise the U.S. NRC staff on  
8 policies and technical issues that arise in the regulation of the medical use of  
9 radioactive material in diagnosis and therapy.

10                  The ACMUI at times is also asked to comment on changes to  
11 NRC regulations and guidance. And to evaluate certain non-routine uses of  
12 radioactive material. Next slide.

13                  Furthermore, the role of the ACMUI also is to provide  
14 technical assistance in licensing, inspection, and enforcement cases. And to  
15 bring key issues to the attention of the Commission for appropriate action. Next  
16 slide.

17                  The current ACMUI membership consists of 12 members.  
18 The Healthcare Administrator is Dr. Arthur Schleipman. Our Nuclear Medicine  
19 Physician is Dr. Hossein Jadvar.

20                  We have two Radiation Oncologists, Dr. Ronald Ennis and Dr.  
21 Harvey Wolkov. Our Nuclear Cardiologist is Dr. Vasken Dilsizian.

22                  I am the Diagnostic Radiologist, Dr. Darlene Metter. And our  
23 Nuclear Pharmacist is Mr. Richard Green. Next slide.

24                  The ACMUI membership also consists of two Medical  
25 Physicists, with a specialty in Nuclear Medicine, is Ms. Melissa Martin, a

1 specialty in Radiation Therapy, is Mr. Zoubir Ouhib.

2 Our Radiation Safety Officer is Mr. Michael Sheetz. Our  
3 Patient's Rights Advocate was Mr. Gary Bloom, but he recently resigned from  
4 the ACMUI and the NRC staff is currently addressing this vacancy.

5 Our FDA Representative is Dr. Michael O'Hara. And our  
6 Agreement State Representative is Ms. Megan Shoher. Next slide.

7 There are many ACMUI topics presented at the ACMUI  
8 meeting in 2019 and 2020. These include training and experience  
9 requirements for all modalities; training and experience requirements for  
10 administration of radiopharmaceuticals requiring a written directive; Y-90  
11 microspheres brachytherapy licensing guidance; Germanium-68/Gallium-68  
12 pharmacy grade generator licensing guidance. Next slide.

13 Other topics included Xcision GammaPod licensing guidance;  
14 evaluation of infiltrations and extravasations; Regulatory Guide 8.39, Release of  
15 Patients Administered Radioactive Material, Revision 1, Phase 1; an analysis of  
16 the 2018 medical events and appropriateness of medical events reporting; and  
17 a very interesting topic on status of emerging technologies licensed under 10  
18 CFR 35.1000. Next slide.

19 Other topics addressed in the 2019 and 2020 ACMUI  
20 meetings were U.S. Pharmacopeia General Chapter 825. A very interesting  
21 presentation was made on trends in radiopharmaceuticals.

22 And because of the COVID pandemic, the NRC and ACMUI  
23 created a subcommittee with recommendations for NRC COVID-19 regulatory  
24 relief options.

25 We have several ACMUI subcommittees, and they reported

1 during these meetings on the Interventional Radiologists, bylaws, institutional  
2 memory, and there was a discussion on external communications with the  
3 ACMUI with other professional societies. Next slide.

4                   During the 2019/2020 ACMUI meetings, we had eight staff  
5 presentations. These include summary of changes of 10 CFR Part 35, medical  
6 events update; medical event abnormal occurrence criteria; the NRC staff  
7 evaluation of training and experience requirements; past ACMUI  
8 recommendations and NRC response; NRC regulatory process and other tools;  
9 ACMUI reporting structure, membership composition and balance; and an  
10 NMED overview. Next slide.

11                   There are nine current ACMUI Subcommittees. These  
12 include Training and Experience for all Modalities, infiltrations and  
13 extravasations, medical events, bylaws, institutional memory, patient  
14 intervention, the interventional radiologist, the COVID-19 impact on the medical  
15 community, and abnormal occurrence. Next slide.

16                   So what about the future? Well, the ACMUI will continue to  
17 provide assistance to the NRC staff in providing advice and technical  
18 assistance; comment on NRC regulations and guidance as requested; evaluate  
19 uses of radioactive material; and bring key issues to the attention of the  
20 Commission. Next slide.

21                   And these are my acronyms. Thank you for your attention.  
22 This concludes my presentation. And I thank you for your attention.

23                   I turn it back to Dr. -- Chairman Svinicki.

24                   CHAIRMAN SVINICKI: Thank you very much Dr. Metter for  
25 that overview. Next, the Commission will hear from Dr. Robert Schleipman,

1 who is the current Committee Vice Chair, on the topic of ACMUI's comments on  
2 the staff's evaluation of training and experience requirements for  
3 radiopharmaceuticals requiring a directive.

4 Dr. Schleipman, please proceed.

5 DR. SCHLEIPMAN: Good morning. I was invited, as you  
6 said, to discuss the ACMUI T&E's Subcommittee's report, in which we  
7 evaluated the NRC staff presented draft paper for with options for T&E  
8 requirements.

9 Admittedly, much has transpired since then, including a rule  
10 making proposal from NRC staff to the Commission, which I would also like to  
11 briefly address. Next slide, please.

12 At the time of this report, our members included the following,  
13 since then Dr. Hossein Jadvar has joined the Subcommittee, and Mr. Gary  
14 Bloom very recently left the ACMUI. Next slide.

15 As you know, NRC staff were asked to consider the following:  
16 whether it made sense to establish tailored T&E requirements for different  
17 categories of radiopharmaceuticals, how those categories might be determined,  
18 what would be the appropriate T&E requirements for each category, and  
19 whether those should be based on hours of T&E, or focused more on  
20 competency. Next slide.

21 So, we reported on the draft paper in October of last year.  
22 Next slide, please.

23 Several points stood out in the draft's report, the staff's draft  
24 report. Number one that access issues maybe somewhat outside the scope of  
25 NRC regulations. And two, the likely complexity of emerging therapeutic



1 radiopharmaceuticals. Next slide.

2                   The staff envisioned two regulatory approaches. The first,  
3 removing prescriptive NRC requirements and review, represents a significant  
4 departure from past and current practice. Next slide.

5                   This new framework included multiple options. The first  
6 proposed that physicians could be certified by any specialty board.

7                   The Subcommittee cautioned that this would require other  
8 boards to locate, provide, and develop expertise for curriculum and training  
9 programs. Next slide.

10                   And that this approach presented a potential for dilution of  
11 T&E requirements. Furthermore, the alternate pathway was not addressed  
12 there. Next slide.

13                   The next option proposed that licensees would develop their  
14 own process for determining adequacy of T&E. This would likely introduce  
15 widely disparate criteria, did not address -- next slide, please.

16                   Did not address transfer of the AU to other locations, nor how  
17 this might be operationalized in smaller institutions with fewer resources. Next  
18 slide.

19                   The next option reflects the first, refines the first rather. And  
20 that other specialty boards could confer AU status, but with a caveat that those  
21 boards would be recognized by the NRC.

22                   The Subcommittee again expressed concern that appropriate  
23 comprehensive training and experience would need to be realized and affirmed.

24 This option also removed the alternate pathway, which potentially could  
25 adversely impact access to procedures. Next slide.

1                   Now, turning to the second regulatory framework, essentially  
2 the prescriptive options. The Subcommittee, and I would add, many key  
3 stakeholders, endorsed the status quo.

4                   That was established on the record of safety under these  
5 requirements, as well as the familiarity of these by training programs,  
6 regulators, and inspectors. Furthermore, clinician members of the  
7 Subcommittee also saw no intrusion on their scope of practice from these  
8 regulations. Next slide.

9                   The proposal to tailor T&E requirements to specific categories  
10 of radiopharmaceuticals was not endorsed by the Subcommittee.

11                   Members pointed out that unit dose delivery does not remove  
12 many safety concerns such as spills, infusion errors, patient events, all of which  
13 would require expertise in dosimetry, radiation protection, and risk mitigation.  
14 Next slide.

15                   Tailored requirements not for each category, but rather for  
16 every radio -- new radiopharmaceutical was also deemed inadequate by the  
17 Subcommittee. Next slide.

18                   They felt that this would delay introduction of new therapies,  
19 and require multiple reauthorization of authorized users. Next slide.

20                   Finally, a team-based partnership approach was proposed,  
21 also deemed problematic as it potentially relocates, if you will, the  
22 comprehensive expertise requirements away from the authorized user to  
23 others. Next slide.

24                   And while less prevalent than in years past, hierarchies still  
25 exist in the hospital setting, with asymmetric scopes of practice and authority,

1 which may make safety calls by subordinates more difficult.

2 So, I'm going to skip, if you don't mind, the next several  
3 slides, because they just repeat what I just said. I think we need to land on  
4 slide 35.

5 Our Subcommittee recommendations were to maintain the  
6 status quo under 10 CFR 35.390. But we did recognize that specific  
7 requirements could be critically reassessed. Particularly the requirement of 700  
8 hours for training. Next slide, please.

9 There was one minority opinion, which recommended a  
10 hybrid approach that did not list the authorized user on the license. Next slide.

11 So, the next several slides discuss recent factors related to  
12 training and evaluation. I will caution that these were not discussed by the  
13 convened Subcommittee.

14 So, as you know, in January of this year, NRC staff submitted  
15 a rule making plan for training and experience requirements similar to the draft  
16 report the Subcommittee evaluated.

17 The rule making plan considered vary options -- varied  
18 options for T&E, ranging from retention of the status quo, tailored T&E  
19 requirements by specific classes of radiopharmaceuticals, and so forth.

20 Staff ended up landing on, and endorsed Option 3. Whereas  
21 a performance-based approach would remove, review and approval of T&E for  
22 authorized users by the NRC and Agreement States.

23 And would instead recognize certification by a medical  
24 specialty board recognized by the NRC or an Agreement State. Next slide.

25 Again, we have not, as a Subcommittee nor ACMUI, formally

1 reviewed this proposal. Though I point out that Option 3 within the rule making  
2 proposal is quite congruent with Option 1c of the previously discussed draft  
3 paper.

4 We did not endorse this. We endorsed the status quo.  
5 However, we did state that Option 1c might be feasible if, and only if, the  
6 appropriate level of training and experiences required, and that the NRC would  
7 apply sufficient rigor in evaluating radiation related content and competencies  
8 as we discussed.

9 Furthermore, Option 1c did not provide an alternate pathway,  
10 which we do recognize as being a flexible and valuable addition. Next slide,  
11 please.

12 As you know, there was a public broadcast by the  
13 Commissioners in January of this year. Among other items, the staff's rule  
14 making proposal was discussed.

15 And some insightful comments and related questions followed  
16 that discussion, such as what sort of access issues might occur with the  
17 removal of the alternate pathway?

18 A question of, what if no new boards would be developed by  
19 other specialties either through not having enough expertise, or the prohibitive  
20 cost involved in this?

21 What sort of post-board certification competency  
22 requirements might be needed? And then also, is there a way to move forward  
23 in the regulations without listing the authorized user on the license? Next slide.

24 Then as evidenced by our remote meeting, the novel Corona  
25 virus pandemic continues to disrupt and alter the landscape, especially the

1 healthcare delivery and education workspace.

2                   Several NRC authorized specialty boards have adjusted their  
3 experiential requirements, here from the American Board of Nuclear Medicine.

4 Next slide, please.

5                   The ABR as well, American Board of Radiology. Though they  
6 did stress that the accreditation council for graduate medical education has  
7 made it clear that case log numbers are suggested targets and not absolute  
8 requirements.

9                   And that the attestation of clinical competency was in, was the  
10 major milestone needed. Next slide, please.

11                   Similarly, they regulate medical physics education programs.  
12 And said the same thing. Next slide.

13                   The American Board of Radiology also noted that either they  
14 nor the ACGME had authority to waive any NRC requirements for training.  
15 Next slide.

16                   In addressing COVID-19 precautions, the NRC has been  
17 proactive in issuing temporary regulatory relief. Unfortunately, I couldn't hear  
18 yesterday's presentation.

19                   But, until these slides -- up until these slides were made,  
20 these initiatives had not specifically revised T&E requirements.

21                   I would say that some pandemic era change, such as remote  
22 learning and remote working, will likely persist for economic and logistical  
23 reasons in the post-recovery phase.

24                   And there may be an opportunity through the regulations or  
25 rule making to incorporate some of these into T&E requirements. Next slide.

1                   So, in conclusion, the Subcommittee looks forward to not so  
2 much continue its review, but returning to its review. Which may be a more apt  
3 description, as we have held off following and waiting for sort of a signal of  
4 where the NRC is headed from a regulatory approach of T&E requirements.

5                   So, I thank you very much for this opportunity. And I look  
6 forward to our discussions this day.

7                   I would like too next send it back to Chairman Svinicki.

8                   CHAIRMAN SVINICKI: Thank you very much, Dr.  
9 Schleipman. For our next presentation, we will hear from Ms. Melissa Martin,  
10 who is the ACMUI Nuclear Medicine Physicist representative on the topic of  
11 ACMUI's comments on extravasations.

12                   Ms. Martin?

13                   MS. MARTIN: Thank you very much, Chairman Svinicki and  
14 other Commissioners. I'd like to give a report of our Subcom -- the ACMUI  
15 Subcommittee on the evaluation of extravasations. Next slide, please.

16                   I have no financial disclosures. Our Subcommittee members  
17 consisted of Dr. Dilsizian, Mr. Richard Green, myself as Chairman, Mr. Michael  
18 Sheetz, Ms. Megan Shober, and at the time, our patient advocate, Laura Weil.  
19 Our resources from the NRC were Maryann Ayoade and Said Daibes.

20                   What our Subcommittee charge was, was to reevaluate and  
21 provide recommendations on the NRC decision on infiltrations and  
22 extravasations, which was originally published in the Federal Register in 1980.

23                   The purpose of the Subcommittee -- oh, next slide, please.  
24 The purpose of the Subcommittee was to evaluate and review the NRC's  
25 current decision on infiltrations and extravasations when radionuclides are

1 injected into patients. Next slide, please.

2                   The criteria for misadministration from the 1980 Federal  
3 Register consisted of basically the following: either the administration of the  
4 wrong source, the wrong patient, the wrong route of administration, diagnostic  
5 doses differing by more than 50 percent from the prescription, or therapeutic  
6 doses differing by more than 10 percent from the prescription. Next slide,  
7 please.

8                   There was an exclusion of extravasation from the  
9 misadministration definition. And this was as follows: extravasation is the  
10 infiltration of injected fluid into the tissue surrounding a vein or artery.

11                   Extravasation frequently occurs in otherwise normal  
12 intravenous or intra-arterial injections. It is virtually impossible to avoid.

13                   And therefore, the Commission does not consider  
14 extravasation to be a misadministration. This was from the 1980 decision.  
15 Next slide, please.

16                   In 2002, the definition was changed. Basically we went from  
17 calling a misadministration to defining a medical event.

18                   And the medical event is defined as a discrepancy of a total  
19 dosage of plus or minus 20 percent of the delivered dose. Next slide, please.

20                   The prior discussions of extravasations of  
21 radiopharmaceuticals consisted of a reconsideration of the -- by the ACMUI at  
22 both the December 2008 and the May 2009 meetings.

23                   Decisions at both of these meetings were that extravasation  
24 of radiopharmaceuticals not be considered to be a medical event at that time.

25                   The tech -- in April 2019, the ACMUI was presented with a

1 technology that identifies the following: extravasations of PET  
2 radiopharmaceutical injection sites early in the process, and the effect on the  
3 SUV or Standardized Uptake Value of tumors or organs when extravasation  
4 occurs. Next slide, please.

5                   The clinical evaluations of extravasation. The main point of  
6 discussion of extravasation of radiopharmaceuticals is that the denominator for  
7 this problem is several million injections per year of all radiopharmaceuticals  
8 injected.

9                   Extravasation problems are not limited to PET isotopes only.  
10 Prevention of extravasation is a medical training issue for the authorized user  
11 physician and the technologist under the supervision of the AU, which is  
12 considered medical practice. Next slide, please.

13                   So, relative to the SUV of the F-18 PET isotopes. Currently,  
14 there are 48 radiopharmaceuticals approved by the FDA, including five IV  
15 therapeutic drugs.

16                   Extravasation of the six fluorinated compounds, including the  
17 F-18 PET drugs, can bring about discrepancies in the SUV. That is true.

18                   We are all very aware of that. SUV value is not relied on  
19 solely by the physician making the decision as to whether the study was  
20 adequate.

21                   What about isotopes other than F-18? Next -- this is the next  
22 slide, sorry. For isotopes other the FDG isotopes, which are used for the PET  
23 scans, it is difficult to quantify non-F-18 drugs left at the injection site. And  
24 difficult to assign the radiation dosage attributable to it.

25                   When extravasation of radiopharmaceuticals occurs, there is



1 a variable delay in the biodistribution of the isotope after injection. More  
2 importantly, none of the total doses in these extravasations, meet the NRC's  
3 medical event criteria.

4 So, what about extravasation occurrences? This  
5 Subcommittee does not consider extravasation a de facto medical event.

6 Extravasation frequently occurs in otherwise normal  
7 intravenous or intra-arterial injections, and is virtually impossible to avoid.  
8 Many of these patients have had lots of chemotherapy, and their veins or  
9 arteries are just not in good shape.

10 Not all nuclear medicine cameras in use today for PET or for  
11 SPECT can quantify the amount of radiopharmaceutical localized in the  
12 extravasation site. It is not necessarily the case that all - the extravasation sites  
13 would not necessarily be imaged during a normal procedure.

14 Subcommittee members are unaware of any cases of  
15 documented patient harm due to extravasation as of today.

16 Extravasation is a practice of medicine issue in our opinion,  
17 and not an item that needs to be regulated by the NRC. Next slide, please.

18 So, it is the recommendation of the Subcommittee that there  
19 is no evidence at this time for this Subcommittee to recommend a  
20 reclassification of extravasation at the injection site for radiopharmaceuticals to  
21 be considered as a medical event.

22 This Subcommittee recommends that extravasations that lead  
23 to unintended permanent function damage be reportable as a medical event  
24 under 10 CFR 35.3045(b). Next slide, please.

25 This Subcommittee recommends that extravasations be

1 considered a type of passive patient intervention similar to the  
2 recommendations from the ACMUI Subcommittee, which was presented during  
3 the ACMUI public meeting in October 2015, and referenced in the Patient  
4 Intervention Subcommittee report dated April 2017.

5 And should be captured in the NRC's current definition of  
6 patient intervention under 10 CFR 35.2. Next slide, please.

7 We did have one member of the Committee what wanted her  
8 minority opinion expressed. And presented a different perspective on potential  
9 medical event reporting due to extravasation.

10 This member wanted extravasation occurrences that trigger  
11 medical event criteria of greater than 50 rem tissue dose, or less than 80  
12 percent of the prescribed dose delivery to the patient, to be reported as a  
13 medical event.

14 This would be consistent with all other medical events that  
15 cause no patient harm, and are currently required to be reported.

16 The exclusion of extravasation is inconsistent with other  
17 regulation. And is unwarranted. This was the minority opinion of our member.  
18 Next slide, please.

19 And this is the list of acronyms that I used for a reference.  
20 And I thank you very much for your present -- your opportunity to present this  
21 today.

22 I will now turn it back to Chairman Svinicki.

23 CHAIRMAN SVINICKI: Thank you very much Ms. Martin, for  
24 that presentation. The next topic will be presented by Mr. Michael Sheetz as  
25 ACMUI Radiation Safety Officer Specialist. The topic is ACMUI's comments on

1 patient intervention and other actions exclusive of medical events.

2 Mr. Sheetz, please proceed.

3 MR. SHEETZ: Thank you, Chairman and other  
4 Commissioners for giving me the opportunity to speak with you this morning on  
5 the ACMUI's comments on the term patient intervention and other actions  
6 exclusive of medical events reporting. Next slide, please.

7 These are the Subcommittee members. And the NRC staff  
8 resource. May I have the next slide, please?

9 So, the objective of the Subcommittee was to determine and  
10 evaluate what types of events are intended to be captured by the term patient  
11 intervention, and what should or should not be reported as a medical event.

12 The purpose for this stemmed from the varying views and  
13 interpretations from regulators, licensees, and previous ACMUI Subcommittee  
14 recommendations on the definition of the term patient intervention. Can I have  
15 the next slide, please?

16 In 2002 the regulations in 10 CFR 35 were revised to be more  
17 risk informed and performance-based, and in alignment with the revised 2000  
18 medical use policy statement.

19 The term misadministration was changed to medical event.  
20 And the reporting criteria was revised to require both a type of error in the  
21 administration, and it also required exceeding a certain dose threshold.

22 The errors are wrong dose, wrong radioactive drug, wrong  
23 route of administration, wrong patient, wrong mode of treatment, or wrong  
24 treatment site. And the dose threshold was set at 50 millisieverts effective dose  
25 equivalent of 500 millisieverts to an organ or tissue.

1                   It was again stated at that time that the purpose of reporting  
2 medical events was one, for the NRC to evaluate if there was a breakdown in  
3 the licensee's program for ensuring the byproduct materials administered had  
4 corrected by the authorized user. And also to evaluate the corrective action  
5 taken by the licensee to minimize the chance for recurrence.

6                   And two, if there was a generic issue that should be reported  
7 to other licensees so that they could take appropriate action, and thereby  
8 reduce the likelihood of other similar medical events. May I have the next slide,  
9 please?

10                   It is interesting to note that there were several specific  
11 exclusions to medical event reporting. As we heard in the previous  
12 presentation by Ms. Martin, in the 1980 final rule, the NRC specifically excluded  
13 extravasation as a misadministration.

14                   There are also two specific exclusions to medical event  
15 reporting in the 2002 rule. One is for permanent implant brachytherapy or  
16 sources that were implanted in the correct site but migrated outside the  
17 treatment site.

18                   And the other is when an event that resulted from patient  
19 intervention, where patient intervention was defined as, and I quote, actions by  
20 the patient, whether intentional or unintentional, such as the lodge -- dislodging  
21 or removing treatment devices or prematurely terminating the administration,  
22 end quote.

23                   It should be noted that in the 2018 amended Part 35  
24 Regulations for the reporting and notification requirements for medical event, no  
25 changes were made to the extravasation for patient intervention exclusions.

1 And the next slide, please.

2                   There are also several patient specific events incorporated in  
3 Part 35.1000 licensing guidance, which are exempt from the medical event  
4 reporting requirement.

5                   In the Radioactive Seeds Localization Licensing Guidance,  
6 there's an exemption for medical reporting for cases either the patient failing to  
7 return for those scheduled explant surgery, and a physician determination not  
8 to explant the seed due to various patient conditions, where doing so would  
9 jeopardize the patient's well being.

10                   Here various patient condition is intended to address  
11 situations where either the implanted seed may have migrated close to  
12 sensitive nerves or vessels, where surgical removal may cause significant  
13 patient harm.

14                   Or the patient's medical condition has changed such that the  
15 patient maybe at the high risk to physically tolerate the surgical explant  
16 procedure.

17                   In the Y-90 Microsphere Licensing Guidance, there's an  
18 exemption for medical event reporting if the procedure must be modified due to  
19 emergent patient conditions that prevent administration in accordance with the  
20 written directive, such as arterial spasm or sudden changes in blood pressure.

21                   There is also an exemption if the total administered activity  
22 was less than that prescribed due to stasis, or if a dose to the wrong treatment  
23 site is due to shunting, concerning the evaluated part of the treatment in  
24 accordance with the manufacturer's procedures.

25                   All of these exemptions are intended to address an

1 anatomical or a physiological condition of the patient that may have affected the  
2 administration or of the therapy in accordance with the written directives. And  
3 are out of the control of the AU or licensee.

4           These types of events are purposely excluded from the  
5 medical event reporting requirement, because they cannot be completely  
6 controlled in following the categories of the practice of medicine. May I have  
7 the next slide, please?

8           So, at issue is what type of events are intended to be  
9 captured by the term patient intervention? And what should or should not be  
10 considered a medical event?

11           As noted by the definition of patient intervention, it was  
12 intended to address physical action taken by the patient, intentional or  
13 unintentional, which caused a deviation in the administration of byproduct  
14 material from that which was directed by the AU.

15           It is also assumed that the licensee did everything it could to  
16 prevent patient intervention during the treatment. And that the actions taken by  
17 the patient were practically out of the licensee's control.

18           For example, a patient pulls out an applicator during an HTR  
19 treatment, or a patient refuses completion of the prescribed treatment, these  
20 would be considered intentional or voluntary physical actions taken by the  
21 patient.

22           However, there could be a situation where the patient's  
23 anatomy or physiology -- physiological condition contributes to, or causes a  
24 deviation in administration of byproduct material from that which was prescribed  
25 by the AU, such as extravasation, migration of implanted radioactive seeds,

1 arterial spasms or shunting with Y-90 Microspheres.

2                   Or for example, a patient experiences a cardiac erythema  
3 halfway through a gamma knife treatment, requiring urgent medical care, thus  
4 preventing the completion of the treatment. These would be considered  
5 unintentional or involuntary actions taken by the patient.

6                   In all of these cases, the patient caused the deviation from the  
7 prescribed treatment which would meet the medical event reporting criteria.  
8 And in all of these cases, the events could not have been reasonably prevented  
9 by the licensee.

10                   Therefore, it would seem reasonable for both types of  
11 examples, intentional or voluntary actions, or unintentional or involuntary  
12 actions, to be considered a type of patient intervention.

13                   A reportable medical event is meant to be an event that  
14 occurred due to some treatment error on the part of the licensee. If the medical  
15 event criteria are met due to a patient death, patient choice, or because of a  
16 changing medical condition was out of the control of the licensee, it should not  
17 be reportable as a medical event.

18                   The value of recording such unavoidable patient medical  
19 specific events is questionable, since it will not help to prevent such events in  
20 the future. May I have the next slide, please?

21                   So, since extravasation is currently an issue of the petition of  
22 proposed rule-making and both the ACMUI Extravasation and Patient  
23 Intervention Subcommittee had made recommendations to classify  
24 extravasations a type of patient intervention, I thought that I would try to dive a  
25 little deeper into the rationale for this position.

1                   Performing an intravenous injection requires a certain  
2 technical skill to locate and position the needle in the vein to infuse the  
3 radiopharmaceutical. However, even the most skilled individual will  
4 occasionally not take the needle far enough into the vein, have the vein roll off  
5 to the side, or push the needle through the vein, resulting in some leakage of  
6 the radiopharmaceutical into the surrounding tissue during the injection.

7                   Patient anatomy also plays a large part in obtaining a  
8 successful injection. Factors such as age, body habit, hydration and prior  
9 chemotherapy can all affect the ability to obtain a complete injection without any  
10 leakage or tear in the vein wall.

11                   So, a successful injection is dependent on a combination of  
12 the required technical skills, and the ability to navigate the patient's anatomical  
13 landscape.

14                   Studies have shown that extravasations occur anywhere from  
15 a fraction to several percent. Studies have also shown that it is very rare for an  
16 extravasation to cause any type of patient harm or tissue damage.

17                   Those that do, are mostly from therapeutic  
18 radiopharmaceutical administrations. Because of all these factors, the  
19 performance of an injection of a radiopharmaceutical, is truly a medical practice  
20 issue.

21                   While there should be a quality assurance initiative to monitor  
22 and improve extravasation rates at an institution, this should be conducted as  
23 part of medical practice, and not something that is regulated. Next slide,  
24 please.

25                   The following are the ACMUI Subcommittee positions on



1 medical events and patient intervention. The purpose of the medical event  
2 reporting rules to evaluate if there was an error or problem in the licensee's  
3 program for ensuring the byproduct material or radiation from byproduct  
4 material was administered as directed by the AU.

5 Or, if there was a generic issue, this should be reported to  
6 other licensees, thereby reducing the likelihood of other medical events.

7 If an unanticipated event occurs during a properly performed  
8 clinical procedure, and results from actions taken by the patient which could not  
9 have been reasonably prevented by the licensee, or from the anatomical or  
10 physiological condition of the patient, which falls in the realm of medical  
11 practice, then it should not need to be reported as a medical event.

12 Reporting such unavoidable patient specific medical events  
13 will not help to prevent such events in the future. And doing so could potentially  
14 infringe on the practice of medicine. May I have the next slide, please?

15 So, the ACMUI recommendations are, the current definition  
16 on patient intervention in 10 CFR 35.2 should be interpreted to include both  
17 intentional or voluntary actions taken by the patient, such as removing an  
18 implanted brachytherapy source applicator, or refusing to continue in the  
19 prescribed course of treatment.

20 And also, unintentional or involuntary actions, which would  
21 include medical outcomes resulting from anatomical or physiological conditions  
22 of the patient such as extravasation, migration of implanted radioactive seeds,  
23 arterial spasms, and the onset of other underlying medical diseases and  
24 disorders which interfere with the prescribed treatment.

25 This expansion of the term patient intervention is consistent

1 with the original definition which was developed in 2002.

2 This Subcommittee agrees that medical events resulting from  
3 patient intervention should not need to be reported as it would potentially  
4 infringe in the practice of medicine. And it will not help to prevent such events  
5 in the future.

6 Medical events resulting from patient intervention in which the  
7 administration of byproduct material or radiation from byproduct material results  
8 or will result in unintended permanent functional damage to an organ or tissue  
9 or a physiological system as determined by a physician, should be reported as  
10 required by 10 CFR 35.3045(b). Next slide, please.

11 And my acronyms. And that concludes my presentation. And  
12 I return it to the Chairman.

13 CHAIRMAN SVINICKI: Thank you very much, Mr. Sheetz.  
14 The next presentation will be from Dr. Hossein Jadvar in the capacity of the  
15 ACMUI nuclear medicine physician specialty. The top is the ACMUI  
16 presentation on trending radiopharmaceuticals.

17 Dr. Jadvar, please proceed.

18 DR. JADVAR: Thank you, Chairman, and Commissioners.  
19 Good morning. I'm delighted to be meeting you all virtually.

20 I would mention my topic is on trending radiopharmaceuticals.

21

22 Can I have the next slide, please? Please note that all the  
23 agents that I will cover in this presentation are investigational and not currently  
24 approved for clinical use.

25 Next slide, please? This is my outline. I'm going to talk about

1 some of the recent radiopharmaceutical approvals and then I'll focus on  
2 oncologic and theranostic agents. And I will define theranostic in one of my  
3 upcoming slides. And then I end with a summary.

4 Can I have the next slide, please? So there has been what  
5 can be considered a renaissance with regard to activity in approval of  
6 radiopharmaceuticals, particularly in positron emission tomography, or PET. As  
7 you can see, in 2012 through 2014 we had three radiopharmaceuticals that  
8 were approved under neuropsychiatric domain for imaging evaluation of  
9 patients with cognitive impairment and dementia, particularly Alzheimer's  
10 disease.

11 More recently, in 2019 there was another  
12 radiopharmaceutical, fluorine-18, fluorodopa, that was approved by the FDA for  
13 imaging evaluation of patients with movement disorders including Parkinson's  
14 syndrome.

15 And very recently, just several months ago, a few months ago  
16 there was a radiotracer that was approved called flortaucipir for imaging  
17 evaluation of the tau deposits, which is a pathology in the brain of patients with  
18 Alzheimer's disease.

19 Under the cancer domain or oncology, back in 2012 there  
20 was a tracer, C-11 choline that was approved for imaging evaluation of patients  
21 with biochemical recurrence of prostate cancer after definitive primary  
22 treatment. It was followed by the very first alpha particle radiotherapeutic,  
23 radium-223 dichloride in treatment of patients with metastatic castration-  
24 resistant prostate cancer. This was first-in-class approval for alpha particle  
25 therapy.

1                   This was soon followed in 2016 with a tracer for -- with a  
2 name of fluciclovine for imaging evaluation of patients with biochemical  
3 recurrence of prostate cancer, and two agents, one for imaging; one for  
4 treatment of patients with neuroendocrine tumors. And those are the gallium-  
5 68 dotatate and lutetium-117 dotatate, which is a beta particle.

6                   And very recently, in 2020 there was a copper-64, a longer  
7 half-life, 12-hour half-life dotatate agent for neuroendocrine tumor imaging. And  
8 also very recently the last approval was fluoroestradiol, which is a PET tracer  
9 that targets estrogen receptor in patients with recurrent breast cancer.

10                  May I have the next slide, please? So this is just to show you  
11 the concept of the theranostics. Basically we have a target. This is a biological  
12 target. It could be antigens, receptors, enzymes or transporters. And then the  
13 idea is to design an agent that has affinity for these targets. This could be  
14 antibodies, it could be peptides or other agents that have that affinity for that  
15 particular target. And then those are linked to an isotope. Now the isotope  
16 could be a reporting unit, which is for imaging. And you see some examples  
17 under that. Or it could be cytotoxic, where you can deliver to that target beta or  
18 alpha particles for very localized radiation treatment of that area that this agent  
19 is actuating.

20                  And the idea here is, which is consistent with what's called a  
21 precision medicine or individualized care, is to target tumors that overexpress  
22 these targets for localized treatment and less toxicity. So this called a  
23 theranostic concept.

24                  Next slide, please? I just want to go over some examples of  
25 tracers that are not approved but are being studied in clinical trials. This is one

1 of them. It's the zirconium-89 trastuzumab. This is targeted to the human  
2 epidermal growth factor receptor 2, or HER2, which is an important target in  
3 patients with breast cancer.

4 This image is a PET image of this particular PET tracer just to  
5 show you that if the patient -- for example, in this case a woman with breast  
6 cancer. If the primary tumor is not expressing the HER2, there are sites of the  
7 tumor and metastases may actually express the HER2 receptor. So therefore  
8 one cannot decide on not using an appropriate drug, in this case Herceptin, or  
9 trastuzumab, just based on the histology information from the primary tumor.

10 Cancer is very heterogeneous and therefore with tools like  
11 this we can actually see if there are other sites of this disease in this patient that  
12 may be expressing in this target and therefore the patient may be a candidate  
13 for that particular drug.

14 Next slide, please? This is another very exciting development  
15 for an anti-CD8 minibody. There is a lot of activity going on in the cancer  
16 immunotherapy domain basically using the patient's own immune system to  
17 fight cancer. But to do that the tumors need to have a sufficient number of  
18 inflammatory cells. In this case cytotoxic T cells that express CD8. And to find  
19 out or decide which one of these patients with cancer would be a good  
20 candidate for various types of cancer therapy drugs, this type of PET imaging  
21 with this type of tracer would be very important.

22 Next slide, please? This is another very exciting  
23 development. This is called gallium-68 FAPI, which stands for fibroblast  
24 activation protein inhibitor. This particular radiotracer was designed in  
25 Heidelberg, Germany and has a bright future I think for theranostics, not only

1 for imaging cancer, but also to use it for treatment of cancer.

2                   The idea here is that we are not imaging the tumor directly as  
3 we do with FDG, which is the most common PET radiotracer, but what we are  
4 imaging is actually the microenvironment of the tumor. And you can see in  
5 these particular images that I show here, these are PET scans in various types  
6 of cancers. There are situations where the primary tumor or the tumor sites  
7 may not be very FDG-avid particularly, but the microenvironment of the tumor  
8 actually shows a high signal and therefore we can not only have a good idea of  
9 the extent of the tumor, but also fight cancer on both grounds, both targeting  
10 the tumor itself, but also targeting the microenvironment of the tumor for  
11 synergistic effect and better patient outcome.

12                   Next slide, please? This is another area which is rapidly  
13 developing and very exciting. This is based on prostate-specific membrane  
14 antigen, or PSMA, which is being explored in patients with prostate cancer,  
15 although it is not specific to the prostate and it is not specific to cancer. The  
16 name is a rather misnomer, but it is basically an enzyme which is a  
17 transmembrane enzyme and it's overexpressed in a tumor, especially in  
18 prostate cancer, but also in other tumors. And therefore this is a very good  
19 target for not only imaging prostate cancer, but also for delivering treatment.

20                   Next slide, please? So this shows you just three of the PET  
21 radiotracers that have been designed for targeting the PSMA. The first one,  
22 gallium-68 PSMA-11 is the oldest one, or the grandfather of all of them. And  
23 that was designed in Heidelberg, Germany. And a number of  
24 radiopharmaceutical companies are in process of hopefully getting that FDA-  
25 approved and available to the clinics soon.

1                   The second is F-18 with a longer half-life. And that was  
2 spearheaded from Johns Hopkins University investigators.

3                   And the last one that I showed here in this slide is another F-  
4 18 labeled PET radiotracer targeting PSMA, which is called PSMA-1007. And  
5 that is -- also was designed in Heidelberg, Germany, and is being studied.

6                   Next slide, please? Just to show you some of the exciting  
7 work that has been done in this domain. This is an article that was published  
8 last year in *Lancet Oncology*. This compared the gallium-68 PSMA-11 PET/CT  
9 with Fluciclovine, which is a currently FDA-approved PET agent that I  
10 mentioned in my earlier slide, to show that this particular target, PSMA, and this  
11 tracer, gallium-68 PSMA-11, is substantially more sensitive in detecting a small  
12 site of disease. These are in patient with very low PSA levels where it's very  
13 clinically relevant to see if there any sites of disease. So that if the patient has  
14 metastatic disease, they can be a candidate for systemic therapy. If there is  
15 localized disease, they can be a candidate for salvage radiotherapy.

16                   Next slide, please? This also was shown to -- this study was  
17 also very nice to show that we are missing a lot of sites of disease with PSMA-  
18 11 PET/CT in these patients who were being considered for salvage  
19 radiotherapy, basically just treatment to the prostate bed after radical  
20 prostatectomy their PSMA-11 showed that there are many, many other sites  
21 that we are kind of blinded to and don't know about.

22                   This image that you see on the right-hand side -- the green  
23 area is an area that would have been treated with radiotherapy, but all the  
24 yellow dots are the areas of the disease that would have been missed in this  
25 treatment domain, and therefore the patient would have stayed that type of





1 prostate cancer it was shown that lutetium-177 PSMA-617 is actually quite  
2 useful and can decrease the PSA substantially in a large number of patients.

3                   Next slide, please? And there are a number of clinical trials  
4 going on right now with lutetium-177 PSMA. One of them is VISION trial, which  
5 has already completed. It compares the PSMA treatment versus the supportive  
6 care. This is very much patterned after a single clinical trial that ended up  
7 having the radium-223 dichloride to be approved and we are awaiting for the  
8 results of the VISION trial.

9                   Next slide? Another exciting trial is the TheraP trial which  
10 compares the lutetium-177 PSMA versus a currently approved -- FDA-approved  
11 chemotherapy, cabazitaxel, in patients with metastatic prostate cancer.

12                   Next slide, please? And finally I want to mention that we are  
13 not limited only to beta particles that I showed you, lutetium-177. We can also  
14 have alpha particles. In this case you can see actinium-225 and bismuth-213 is  
15 an alpha particle agent conjugated to PSMA with remarkable responses.  
16 These images are provided here from a study that was done in South Africa.

17                   Next slide, please? And there are other things that are  
18 coming up also. This is another alpha particle-based PSMA agent that uses  
19 thorium-227. The preclinical studies in mice have been very encouraging and  
20 that led to initiation of a phase 1 clinical trial in patients with metastatic  
21 castration-resistant prostate cancer.

22                   Next slide, please? And finally, there are other targets that  
23 we can look at. This is another target. It's called Chemokine Receptor 4. That  
24 is overexpressed in a number of cancers. One of the exciting work that has  
25 been done was in the area of multiple myeloma. And you can see in this case

1 that you can use not only the CXCR4 as an imaging agent. As we can see,  
2 gallium-68 Pentixafor, but also you can conjugate it with lutetium-177 for  
3 delivering beta particle locally and treating these patients in a theranostic  
4 domain.

5                   Next slide, please? And I mentioned that there was a  
6 dotatate agent already approved by the FDA for not only imaging but also for  
7 treatment of patients with neuroendocrine tumors using alpha particles. And  
8 just to show that there is also an -- I'm sorry, using beta particles, but right now  
9 there is also studies going on in using alpha particles for doing -- for delivering  
10 treatment to patients with neuroendocrine tumors. In this case with lead-212.

11                   Next slide, please? So in summary I think theranostics will  
12 continue to grow with the approval and clinical introduction of many agents for  
13 targeted imaging and radioligand therapy of cancer, which fits very well with the  
14 concept of precision medicine.

15                   Next slide? And these are the acronyms related to my slides.  
16 And thank you very much for your time and attention, and I will turn it back over  
17 to Chairman Svinicki. Thank you.

18                   CHAIRMAN SVINICKI: Thank you very much, Dr. Jadvar. I  
19 know that while it's encouraging that there are so many promising results, that it  
20 was difficult for us to go through even some of the most promising ones in the  
21 time available, but thank you. That was very comprehensive.

22                   And my thanks to all of the presenters from the ACMUI, but  
23 also those who supported the work of the subcommittees and the Committee  
24 overall. Again, you've laid down a number of topics that I'm certain my  
25 colleagues and I will want to pursue.

1                   And we do rotate the order of recognition in our meetings.  
2                   Today we will begin with Commissioner Baran.

3                   COMMISSIONER BARAN: Thanks, Chairman.

4                   Well, thank you all for your presentations. I'd like to ask some  
5                   questions on the topic of whether extravasations should be reported as medical  
6                   events.

7                   The NRC is currently evaluating this issue. In 1980 the  
8                   Commission established a policy that extravasation should not be considered  
9                   misadministrations. This decision was based on NRC's understanding that  
10                  extravasations occurred frequently in otherwise normal injections and were  
11                  virtually impossible to avoid. That was 40 years ago though and obviously  
12                  medical practices and technologies have advanced quite a bit.

13                  I'll direct these questions I guess to Ms. Martin since she  
14                  presented on the topic, although I know Mr. Sheetz also talked about it a little  
15                  bit, but others should feel free to chime in.

16                  What is the current understanding of how frequently  
17                  extravasations occur and is there reliable data around that?

18                  MS. MARTIN: Thank you for the opportunity to respond. One  
19                  study we looked at; and actually Dr. Jadvar provided some of this data, in  
20                  diagnostic administrations the percentage of extravasations was approximately  
21                  0.1 percent. And for therapeutic is about 0.2 percent. So it's not a common  
22                  occurrence. It does happen.

23                  Since 1980 patients' veins really haven't changed. So the  
24                  problem of having an extravasation due to a patient having a problem with the  
25                  condition of their veins, particularly if they're a chemotherapy patient, really

1 hasn't changed. I don't think anyone would say that extravasations are  
2 common. They do happen. They happen routinely whether it's with  
3 radiopharmaceuticals, with chemotherapy drugs, with any other type of drugs  
4 administered IV.

5                   So we do have extravasations. Most every facility and every  
6 practitioner goes through training to try to avoid this. We have not seen a  
7 significant difference between the percent of extravasations that occur where  
8 the nuclear medicine technologist or authorized users are administering  
9 radiopharmaceuticals from anyone administering say chemotherapy drugs or  
10 administering other IVs. So it is not unique to radiopharmaceuticals that  
11 extravasations occur.

12                   And I would certainly turn the floor over to our physicians if  
13 they would like to add anything to these comments.

14                   DR. JADVAR: This is Dr. Hossein Jadvar. I second what Ms.  
15 Martin just mentioned. And she was referring to a study that was published in  
16 the *European Journal of Nuclear Medicine and Molecular Imaging* in 2017. It  
17 was basically a systematic review of publications on this particular topic of  
18 extravasation. And these authors basically found that 37 publications were  
19 relevant and in these 37 publications there were 3,016 cases of extravasation  
20 that folks reported. And these are all diagnostic in this group of publications.

21                   And as Ms. Martin already mentioned the incidence of  
22 extravasation was very small, 0.1 percent. And essentially only three patients  
23 were reported to have some mild itching, or pruritus as we call it, and redness  
24 at the site of the extravasation.

25                   With regard to therapeutic agents, which potentially could be

1 more problematic, there were eight publications that were looked at. And in  
2 those eight publications again the incidence was very low and none of them  
3 had permanent functional damage with regard to the patients who actually  
4 ended up having some extravasation of the radiotherapeutic drug.

5                   But also I reemphasize, as Ms. Martin mentioned, that the  
6 extravasation is not just for radioisotopes. It can happen with chemotherapy.  
7 And so there is nothing particular to radioisotopes. Chemotherapies also are  
8 irritant and if they are deposited through extravasation, they can also cause  
9 local issues. But again, there is evidence published out there that this is not a  
10 huge or major problem. Thank you.

11                   COMMISSIONER BARAN: Thank you. That's very helpful.  
12 And one of the other questions the NRC staff is trying to determine is whether  
13 the dose consequences of extravasations are significant. You touched on that  
14 a little bit. Is there anything else you'd want to add on the current state of  
15 knowledge on that question of the dose consequences?

16                   MS. MARTIN: Yes, this is Melissa Martin responding from the  
17 physicists' perspective.

18                   The actual dose calculations are fairly complicated to do an  
19 accurate dose assessment for a extravasation. Thankfully the body has a lot of  
20 physiological functions going on to clear out the extravasation, and so you have  
21 a physiological component to the calculation.

22                   The other problem that we've run into is to try to get an  
23 estimate of the actual amount of dosage that has been extravasated. Many of  
24 the gamma cameras that are used today are of a vintage that do not give  
25 accurate uptakes. They can localize the extravasation. They can show what it

1 is, but they don't give you the uptake values.

2                   And to replace that equipment you're talking a very significant  
3 amount of money to replace a camera that is perfectly functional except for the  
4 fact that it doesn't give a quantitative information on doing dose calculations.  
5 So the physicist really would not have the information needed to do an accurate  
6 calculation of the dose.

7                   COMMISSIONER BARAN: So that's interesting. So part of  
8 what you're saying there I take it is that if we were to change the policy here  
9 and the medical event dose criterion were to apply for example of a dose to an  
10 organ or tissue that exceeds the prescribed amount by more than 50 rem, there  
11 may just be a challenge in ascertaining whether that's occurred in any particular  
12 instance?

13                   MS. MARTIN: And the fact that basically that organ would be  
14 the skin. That's what we're looking at is the dose to the skin. That would be  
15 from an extravasation. And yes, we don't have the data right now from -- every  
16 facility that performs these examinations does not have the ability to provide the  
17 information that would be required for a nuclear medicine physicist to do a dose  
18 calculation. We could to an estimate, but it's very much of a raw estimate. It is  
19 not going to be accurate due to the limitations of the equipment that is out  
20 there.

21                   COMMISSIONER BARAN: So at this stage would you say  
22 we have a sense, or really not, about whether or not the 50 rem dose criterion  
23 would be  
24 met --

25                   MS. MARTIN: No, it would be --

1 COMMISSIONER BARAN: -- pretty frequently or not?

2 MS. MARTIN: Excuse me.

3 COMMISSIONER BARAN: No. Please go ahead.

4 MS. MARTIN: It would be hard to reach the 50 dose limit  
5 unless you had an extravasation of a very small area with a very high uptake.  
6 The larger the area the dose is spread out, so the actual skin dose in any one  
7 area is diminished. So the 50 rem would be -- it is possible to reach that,  
8 particularly with a therapeutic administration. It is -- again, it depends on how  
9 large an area that the radiopharmaceutical is infused into.

10 COMMISSIONER BARAN: Okay. And recognizing the  
11 challenges you've been discussing about making a determination on the dose,  
12 one of the things I'm trying to figure out is whether the medical event reporting  
13 exclusion for extravasations is actually impacting the amount of reporting. If we  
14 applied the medical event reporting criteria to extravasations, as ACMUI's prior  
15 patient advocate member suggested -- trying to figure out would that actually  
16 result in many extravasation-related medical events being reported if in fact it  
17 would be pretty rare that the 50 rem threshold would be met?

18 MS. MARTIN: In our opinion it would still be a rare event. I  
19 think Mr. Sheetz might have more information on that to help fill in that  
20 information, but we did not feel it would be a routine certainly occurrence.

21 MR. SHEETZ: Thank you. I'd like to comment. The  
22 challenges, as Ms. Martin alluded to, is trying to do the dosimetry calculation  
23 because of all the variables on the clearance rate of the radiopharmaceutical  
24 from the extravasated tissue the volume and shape of the extravasated tissue.  
25 And this becomes very complex. And if you consider all that, it probably clears

1 out and would not exceed the 50 rem tissue dose.

2 But if one assumes a very simply model where you assume  
3 it's one cc of the cylinder of tissue and the activity stays there until physical  
4 decay, it would only take 150 microcuries of technetium-99m or 30 microcuries  
5 of F-18 to reach the 50 rem dose. So if you do a very simplistic model, a  
6 conservative model, you will have a lot of reported medical events from this.

7 If you take the time to look at the clearance rate, then most  
8 likely the tissue dose would not exceed this 50 rem. So it really would create a  
9 large burden if this rule were to address extravasation as a potential medical  
10 event. Won't it would require every administration to be evaluated whether any  
11 extravasation? So that would require either an image over the site or some  
12 radiation detection system to monitor the injection site.

13 And then once you detect it or monitored or identified any  
14 extravasation, you would have to do the dose calculation, which would be again  
15 very complex, very time-consuming. And so yes, it would result in probably a  
16 significant number of medical event reports just because of trying to do it  
17 simplistically and not spend a lot of time on it.

18 COMMISSIONER BARAN: Well, this is very helpful. Thank  
19 you so much for your perspectives on this and I'm looking forward to reviewing  
20 what the staff finds and recommends this spring. Thanks.

21 CHAIRMAN SVINICKI: Thank you, Commissioner Baran.

22 Next we will recognize Commissioner Caputo.

23 COMMISSIONER CAPUTO: Good morning. Thank you all  
24 for coming and speaking with us this morning.

25 I would like to start with a few questions to Dr. Schleipman.



1                   As I understand it there's been a misunderstanding of the  
2 NRC's training and experience proposal by some external stakeholders. I'm  
3 referring to apparently the American Medical Association has been quoted as  
4 stating that the NRC is proposing that non-physicians could become authorized  
5 users, and I think that article, quoting the AMA, was in Medpagetoday.com.

6                   Dr. Schleipman, can you just confirm that only physicians can  
7 be qualified to be trained as authorized users?

8                   DR. SCHLEIPMAN: Yes, that is a misunderstanding that you  
9 just mentioned.

10                  COMMISSIONER CAPUTO: Okay. Thank you.

11 Dr. Schleipman, again another question for you: The Certification Board of  
12 Nuclear Cardiology was established in 1996 and the NRC then recognized  
13 those physicians whose credentials had been verified by that board a few years  
14 later. Isn't the staff's current proposal to revise the training and experience  
15 regulations similar to how nuclear cardiologists became authorized in the past?

16                  DR. SCHLEIPMAN: Can you expand that a little further?

17                  COMMISSIONER CAPUTO: Well, it was my understanding  
18 that they were credentialed by their board prior to the establishment of our 700-  
19 hour requirement, I think.

20                  DR. SCHLEIPMAN: I'm not sure of that. I was not a part of  
21 this group then. I do think that the nuclear cardiology -- nuclear cardiologists  
22 that I have worked with have definitely exhibited a facile understanding and  
23 training regarding radiation safety.

24                  The NRC did recognize that board, did it not?

25                  COMMISSIONER CAPUTO: That was my understanding, but

1 it also predates my own time here at the Agency.

2 All right. I think the issue that I wanted to highlight was just  
3 that you have on slide 36 acknowledged the training and experience  
4 requirement of 700 hours is somewhat arbitrary, so I'm just questioning whether  
5 a continuing reluctance to support a more risk-informed performance-based  
6 similar to what was used in the past with the nuclear cardiologists might be a  
7 reasonable approach considering it's been done in the past.

8 DR. SCHLEIPMAN: The subcommittee felt -- was concerned  
9 of dilution of training programs, but also recognized that it was hard to find a  
10 provenance of that 700 hour. That is, it was actually a greater number in years  
11 past and that it would be quite reasonable to evaluate that carefully, and as the  
12 subcommittee is willing to look at that.

13 COMMISSIONER CAPUTO: So given that our medical use  
14 policy statements states NRC will not intrude into medical judgments affecting  
15 patients except as necessary to provide for the radiation safety of workers and  
16 the general public, isn't it more appropriate to have physician credentialing left  
17 to the medical specialty boards such as the American Board of Internal  
18 Medicine's Oncology Board and the American Board of Urology or other expert  
19 boards within the practice of medicine?

20 DR. SCHLEIPMAN: The currently recognized boards: the  
21 American Board of Nuclear Medicine, the American Board of Radiology, provide  
22 those core elements of necessary training: radiobiology, shielding, dosimetry.  
23 Those are naturally imbedded in existing programs that have been approved or  
24 vetted by the NRC. So again, if a new board would be developed, they would  
25 need to have that expertise, not only to provide the training, but to assess its

1 effectiveness.

2 COMMISSIONER CAPUTO: Okay.

3 DR. SCHLEIPMAN: But those are medical boards, yes.

4 COMMISSIONER CAPUTO: Okay.

5 DR. SCHLEIPMAN: Are you referring to the alternate  
6 pathway?

7 COMMISSIONER CAPUTO: I believe so.

8 We have received several letters from medical oncologists  
9 that treat patients for prostate cancer who state that patients need to travel  
10 significant distances to receive their treatment. Are you familiar with any of  
11 these letters that we've received? Have they been shared with the board, or  
12 the subcommittee?

13 DR. SCHLEIPMAN: Oh, absolutely.

14 CHAIRMAN SVINICKI: Okay.

15 DR. SCHLEIPMAN: Absolutely. The letter from the  
16 manufacturer of radium-223, XOFIGO -- we're familiar with that -- we did note  
17 that most stakeholders felt that there were no access issues overall.

18 I think Dr. Metter is asking to be recognized to contribute to  
19 this, if she may.

20 DR. METTER: Yes. Thank you, Dr. Schleipman. I just would  
21 like to make a comment on a previous discussion point regarding the nuclear  
22 cardiologists. And the point that you did make about the training and  
23 experience of 700 hours was actually addressed many years by the cardiology  
24 training and they put the required 35.290, the Imaging Localization, as part their  
25 training requirements for their ACGME program. And so they do have that

1 imbedded in their training programs, because it would come to our department  
2 in nuclear medicine and we would be helping to educate them and train them  
3 for the nuclear cardiology program.

4 COMMISSIONER CAPUTO: So doesn't it make more sense  
5 for them to be setting the number of hours than for the NRC? Isn't there a  
6 certain argument to be made for us to defer to those boards?

7 DR. METTER: The thing is that I think for that, the diagnosis  
8 and imaging for the 35.290 for imaging localization is something that I think is  
9 very pertinent. And I think the current requirements are adequate for the safe  
10 use of these radiopharmaceuticals for diagnosis.

11 COMMISSIONER CAPUTO: Okay. I've got one last question  
12 for either of you. Has the subcommittee reached out to other boards such as  
13 the Medical Oncology Board with the American Board of Internal Medicine or  
14 the American Board of Urology to determine if they see a shortage in authorized  
15 users?

16 DR. SCHLEIPMAN: This is Robert Schleipman. The  
17 subcommittee has not reached out to those boards. We have seen their  
18 comments.

19 COMMISSIONER CAPUTO: Okay. So what is the  
20 subcommittee's basis for saying there is no shortage?

21 DR. SCHLEIPMAN: We raised the potential concern in an  
22 early report in February 2018. At a subsequent meeting in February 2019 after  
23 reviewing the pipeline, if you will, of training programs and certifications, we've  
24 determined that there were no objective data to confirm a shortage. We also  
25 recognize that many agreement states also made that same conclusion.

1                   COMMISSIONER CAPUTO: Okay. One last question. I'm  
2 going to go back to what Commissioner Baran was asking about  
3 extravasations.

4                   So, Ms. Martin, the subcommittee more or less reaffirmed that  
5 the committee does not consider extravasation to be a medical event, that it's  
6 virtually impossible to avoid, and that the subcommittee is unaware of any  
7 cases of documented patient harm. As a practice of medicine issue, the NRC  
8 need not regulate it.

9                   However, the subcommittee recommended that  
10 extravasations that lead to, quote, unintended permanent functional damage  
11 should be reported as medical events.

12                  If the subcommittee members are unaware of any cases of  
13 documented potential patient harm, what scenarios do you envision or have the  
14 members postulated that could cause permanent functional damage thereby  
15 requiring reporting of medical events?

16                  MS. MARTIN: We put that in there basically to cover the  
17 potential in the future of these new drugs that are being developed.

18                  We just don't know what would happen in the future. But if  
19 there's a possibility of one of these therapeutic agents causing a permanent  
20 damage, we are agreeable that that would be reported as a medical event.

21                  The worst reactions we've seen to date is I think there's a few  
22 documented cases of some ulceration that have occurred. And those have  
23 been cured. They have not been permanent.

24                  But if there is something in the future, we just wanted to  
25 make, agree that if it was a permanent damage, that should be considered a

1 medical event.

2 COMMISSIONER CAPUTO: Okay. Thank you.

3 MS. MARTIN: Dr. --

4 COMMISSIONER CAPUTO: Oh, sorry.

5 MS. MARTIN: Michael Sheetz has a comment if that's okay  
6 with you.

7 COMMISSIONER CAPUTO: Sure, absolutely.

8 MR. SHEETZ: Thank you. If I could just comment on that, is  
9 that if we consider extravasation a type of patient intervention, then it is  
10 consistent with the Part 35 regulations that even those events caused by  
11 patient intervention, if they result in permanent functional damage, they will be  
12 reportable as a medical event. So it's consistent with extravasation being  
13 considered a type of patient intervention. Thank you.

14 COMMISSIONER CAPUTO: Okay. Thank you.

15 CHAIRMAN SVINICKI: Thank you, Commissioner Caputo.  
16 Next we will hear from Commissioner Wright.

17 COMMISSIONER WRIGHT: Thank you, Chair. So good  
18 morning. I'd like to start first by just recognizing the work that you do outside of  
19 this committee as medical professionals. And I want to thank you for the  
20 sacrifices that you make each day and especially during this pandemic. You  
21 know, as a cancer survivor myself, I can personally tell you that the work that  
22 you do is very much appreciated.

23 And I know that your commitment to what you're doing on this  
24 committee, as well as what you're doing every day to care for your patients,  
25 keeps you up late at night, away from your family, and keeps you very busy. So

1 thank you for what you do.

2 Dr. Schleipman, as I was preparing for this meeting today, I  
3 was thinking about, again, as usual, the proposed changes to the training and  
4 experience requirements that are before us.

5 There's still a few issues that I'm kind of still trying to get my  
6 head around, which you summed up I think, if I remember it was like slide 41.  
7 You don't have to pull it up, but I think that was the slide.

8 So we've had a lot of discussion about whether there is a  
9 shortage, as Commissioner Caputo was talking about, in this country overall  
10 and in certain geographic areas.

11 In our SECY-20-0005, the staff recommends requiring  
12 authorized users to be certified by a medical specialty board recognized by the  
13 NRC or an agreement state and removing the alternate pathway. So I got  
14 some questions about how this may affect the number of authorized users.

15 My understanding is that individuals currently using the  
16 alternate pathway have a number of board certifications. Is there any indication  
17 that the boards issuing these certifications would be interested in being  
18 recognized by the NRC or an agreement state? And if not, would removing the  
19 alternate pathway close a route for certain medical professionals wishing to  
20 become authorized users?

21 DR. SCHLEIPMAN: Thank you, Commissioner. The  
22 subcommittee felt that it may be difficult for these boards to develop the  
23 expertise to administer training. We did not want to see the alternate pathway  
24 disappear.

25 Some radiation oncology and diagnostic radiology trainees

1 have to wait up to 15 months between completing their requirements and  
2 achieving the board certification so that granting AU status through the  
3 alternate pathway provides an additional input to the pool of authorized users  
4 and can continue to promote the access to procedures requiring an authorized  
5 user.

6 COMMISSIONER WRIGHT: So did I understand you to say  
7 that you did not see any issues with maybe keeping both things going, keeping  
8 the alternate pathway as well?

9 DR. SCHLEIPMAN: Yes, we saw value in the alternate  
10 pathway.

11 COMMISSIONER WRIGHT: Okay. Thank you. And I'm  
12 going to stay with you. And, obviously, anybody else can chime in if they wish.

13 But I want to talk a little bit about the minority opinion on T&E  
14 regarding shifting the T&E framework to focus on individuals who handle or  
15 administer radiopharmaceuticals.

16 So we had a commission meeting last month with OAS. And  
17 we received similar feedback, that some states feel strongly that we, at the  
18 NRC, need to shift our focus from the physicians and instead look more to  
19 those actually handling and administering the materials.

20 So what are your thoughts on such a shift? And I guess first  
21 would be the first question.

22 DR. SCHLEIPMAN: I will point out that it was a minority  
23 opinion.

24 I think it's, what the subcommittee had thought was that any  
25 sort of coworking, sort of team approach to administering radiopharmaceuticals



1 requiring a written directive would still require an authorized user understanding  
2 all of the radiation safety issues and being able to address them, particularly in  
3 the cases of infusions, infusion errors, extravasations, patient events that might  
4 occur that would require complex dosimetry and so forth, and that relegating  
5 that to others would not necessarily promote safety.

6 COMMISSIONER WRIGHT: So does the medical event  
7 reporting data support the assertion that authorized users are often not present  
8 or supervising at the time of these events?

9 DR. SCHLEIPMAN: I would defer to Ms. Martin or Mr. Sheetz  
10 on that.

11 MS. MARTIN: This is Melissa Martin. I would just say I've  
12 been radiation safety officer now at five major medical centers for about the  
13 past 25 years. I have never been at one of these procedures when the  
14 authorized user was not there to administer the radioactive material. It is their  
15 responsibility.

16 COMMISSIONER WRIGHT: Okay. Thank you. So, Ms.  
17 Martin, I'm going to stay with you --

18 MS. MARTIN: Uh-oh.

19 (Laughter.)

20 COMMISSIONER WRIGHT: So thank you for the  
21 presentations today from each of you. But the extravasations in patient  
22 interventions, a lot of this, especially the extravasations part, has gotten a lot of  
23 external attention.

24 And, you know, one thing we keep circling back to is where  
25 do we draw the line between radiation safety and the practice of medicine. So,

1 along those lines, I got a couple of questions. And, Michael, if you want to jump  
2 in, you can, too.

3 So, with the current practice and standards of care, how  
4 would a medical professional know that an extravasation happened for a  
5 diagnostic dose? And how, if at all, would that be different for a therapeutic  
6 dose?

7 MS. MARTIN: Well, obviously, you can, it's visual for one  
8 thing. You could also image the injection site with the camera if it was a large  
9 enough extravasation that you think it's going to affect the study that the patient  
10 is having done.

11 You can image it. You can document that it happened. But  
12 it's basically a visual perception.

13 COMMISSIONER WRIGHT: Okay. So ACMUI is proposing  
14 that extravasations be treated as a passive patient intervention.

15 And given current diagnostic and therapeutic doses, could  
16 you have -- and I think this piggybacks on Commissioner Caputo's question.  
17 Could you have an extravasation that met the threshold for reporting as a  
18 patient intervention and resulted in unintended permanent functional damage to  
19 an organ or a physiological system?

20 And I know you mentioned the new drugs, future stuff. I know  
21 you mentioned that, but under, currently.

22 MS. MARTIN: You can certainly reach the point of 50 rem or  
23 .5 sieverts. But what you don't reach is the level to cause permanent functional  
24 damage. That is a discrepancy. Fifty rem does not cause permanent functional  
25 damage.

1                   Having, if you've gone through radiation oncology, you were  
2 probably given at least 180 to 200 rem or rads on a daily basis. That does not  
3 cause permanent functional damage.

4                   So just because you reach that 50 rem dose is not going to  
5 cause you permanent functional damage. And I think we need to disassociate  
6 those two, that result from that 50 rem dose.

7                   COMMISSIONER WRIGHT: All right. So let's stay with the  
8 50 rem and go to less than 80 percent of the prescribed dose delivered to the  
9 patient being I guess reported as a medical event.

10                  Can you discuss with me, maybe expand a little bit more on  
11 how a licensee would go about making that determination for an extravasation?

12                  MS. MARTIN: Well, that's why right now that's only referred  
13 to pretty much on the PET isotopes, because the SUV values would be  
14 affected.

15                  COMMISSIONER WRIGHT: Right.

16                  MS. MARTIN: But what happens in most of the time is the  
17 study is repeated within a day or so. And then you start from scratch. The  
18 numbers are fine. But that number is usually picked up pretty much for the PET  
19 isotopes at this point.

20                  I am not the physician. So certainly if Dr. Jadvar has, or Mike  
21 has other information on this, I would be glad to have them add information to  
22 that.

23                  DR. JADVAVAR: Well, all I can say as a physician, you know,  
24 extravasation can occur. And as Ms. Martin already mentioned, that's usually  
25 visual. You can see that there is a little bit of, you know, a bump or swelling

1 maybe even forming.

2                   And then when we do the image on the PET camera, you will  
3 see that that area is hot on the image. And, in fact, if sometimes we know for a  
4 fact that some of the tracer has been extravasated, you may want to exclude  
5 that area from image so that it doesn't damage the image processing of the rest  
6 of the scan, because it can do that.

7                   But, you know, this comment that there is, that the, for  
8 example, warm the area, you know, using hypothermia to make sure that the  
9 clearance is made more radically. We have the patient's arm elevated. So  
10 there are interventions that we do, like massaging the area, just to make sure  
11 that the clearance is improved. And then, of course, you ask the patient if they  
12 have any symptoms of any sort in relation to that.

13                   I have not, you know, to my experience at least, it has not  
14 been a major problem. Even the images are not that bad, you know, and then  
15 the diagnostic quality. And we are able to make our determination of what is  
16 going on with the patient.

17                   But if there is a large amount for some reason that gets  
18 extravasated, because of the, some of these patients officially who have  
19 received many, many chemotherapies. Their veins are fragile. And that can  
20 happen. And it turns out that it may be a difficult re-do of the procedure.

21                   We actually have, you know, our hospital and I'm sure in  
22 many other places, nurse practitioners or other folks from, typically from  
23 oncology, in our case, from our cancer center, who are very good at, you know,  
24 accessing the veins, even in these difficult cases.

25                   So we can do that, or if nothing works, some of these patients

1 have what we call PICC lines or central lines. So we don't even have to worry  
2 about injecting the tracer through our own access, but the access has been  
3 provided to us. And we use that access for delivering the radio tracer.

4 COMMISSIONER WRIGHT: So, and one last quick question  
5 because I was -- you're hitting right where I wanted to go. So, as a patient  
6 myself, I had a port.

7 What is the percentage of ports for people that are getting  
8 the, you know, the real wicked stuff versus, you know, PET scans or, you know,  
9 MRIs or CAT scans or whatever? How many are going through veins versus  
10 with a port?

11 I would think that, I mean, just intuitively, I would think if  
12 somebody's been sick for a while, they're going to go through a PICC line or a  
13 port. Can you give me some idea what the percentage is there?

14 DR. JADVAR: I can't tell you the percentage. But we  
15 generally don't use the port, because that's an area that is used for delivery of  
16 chemotherapeutic drugs. And we, you know, typically we don't want to, you  
17 know, interfere with the function of that port.

18 But PICC lines has been used. I can't tell you the percentage  
19 for PICC lines, you know, peripherally access lines.

20 And again, even in patients with port and PICC lines, well, not  
21 PICC lines. PICC lines we use it. But if there is a port, there is still a way.  
22 Most of the time we are able to access the peripheral vein. And that's not a  
23 problem.

24 We try not to use the ports. And sometimes they tell us not to  
25 use the ports --

1 COMMISSIONER WRIGHT: Right.

2 DR. JADVAR: -- you know, the oncologists.

3 COMMISSIONER WRIGHT: Thank you so much. All right.

4 CHAIRMAN SVINICKI: Thank you, Commissioner Wright.

5 Next we will hear from Commissioner Hanson.

6 COMMISSIONER HANSON: Thank you, Chairman Svinicki.

7 I think the -- and thank you all for being here today and for what you do.

8 I want to kind of dive into the language on some of these  
9 slides because I think it's very interesting. And I want to probe just a couple of  
10 things here.

11 And I guess I'll start off with Ms. Martin. At the top of page 65,  
12 the subcommittee recommends that extravasations should be considered a  
13 type of passive patient intervention. Is that always a type of passive patient  
14 intervention, so it's never a misadministration, for example?

15 MS. MARTIN: As far as I'm aware and as far as this  
16 committee is aware, I would certainly say that is it. I don't think anyone in the  
17 medical field is going to purposely misadminister or cause an extravasation.

18 As far as I'm aware, that is a patient intervention from a  
19 problem with the patient's physiological status.

20 COMMISSIONER HANSON: So there is never a medical  
21 error, of course, not --

22 MS. MARTIN: I am not aware of a medical error when it  
23 comes to extravasations. I'm sure -- like I said, I don't know of anyone that  
24 would certainly do it on purpose.

25 COMMISSIONER HANSON: Of course.

1 MS. MARTIN: I'm sure they -- all extravasations, I mean, you  
2 can -- you know, when you're trying to make those injections would depend on  
3 whether you say, yes, there is some people that are just hard to hit the vein  
4 correctly would be how you would define that. But I don't think it is a purposely  
5 caused medical error.

6 COMMISSIONER HANSON: Right, no, of course not  
7 purposely caused or intentional, right. I'm not trying to --

8 MS. MARTIN: Correct.

9 COMMISSIONER HANSON: -- ascribe intention. And yet,  
10 errors happen. Sometimes you don't sink the putt or hit the ball or --

11 MS. MARTIN: Correct.

12 COMMISSIONER HANSON: -- whatever, score the  
13 touchdown. I don't know. Sometimes you fumble or there's an interception. It  
14 happens.

15 Okay. Well, I guess I have kind of a similar question on page  
16 75.

17 MS. MARTIN: Well, wait --

18 COMMISSIONER HANSON: Go ahead.

19 MS. MARTIN: -- I think some -- go ahead --

20 MR. SHEETZ: This is Mike Sheetz. May I comment on that --

21 MS. MARTIN: Yeah.

22 MR. SHEETZ: -- Commissioner Hanson? I think the  
23 performance of injection is a combination of technical skill and navigating the  
24 patient's anatomy.

25 Prior to going into radiation and taking health physics, I was a

1 practicing nuclear medicine technologist a number of years ago. I performed  
2 thousands of intravenous injections. Some of those resulted in extravasation.  
3 Sometimes I realized it. Other times I didn't, and it appeared on the image.

4 It's very difficult to tease out whether it was an error on the  
5 part of the person performing the injection or the patient's anatomy such that it  
6 was very challenging or difficult to get a needle into the vein or the vein tore or  
7 in removing the needle there was some leakage out.

8 So there are so many different variables and factors. I think it  
9 would be very difficult or, again, as I keep going back to, this is a practice of  
10 medicine issue. And it really should not rise to a medical event reporting unless  
11 it results in permanent functional damage. Thank you.

12 COMMISSIONER HANSON: Thank you, Mr. Sheetz. I think  
13 that's a really interesting point. And I want to just kind of drill down on that even  
14 just a little further, because I think we have kind of similar language on page 75  
15 where exceeding the medical event dose threshold doesn't indicate error or  
16 harm.

17 Does it not -- again, is that a never or is that a never  
18 statement or a not necessarily statement, so exceeding the ME dose threshold  
19 doesn't necessarily indicate error or harm, or does it not ever exceed error or  
20 harm?

21 MS. MARTIN: Well, I'll take a first answer at this. I think it's  
22 a, it is not a never, because, like we said, if you, particularly with some of these  
23 more potent therapeutic agents in a very small area, you can get the dose up to  
24 a level that you could potentially cause at least ulceration or something.

25 But most of the time, that is a not necessarily comment. In



1 other words, exceeding the 50 rem does not necessarily mean permanent  
2 functional damage.

3 MR. SHEETZ: This is Mike.

4 COMMISSIONER HANSON: Yeah, thank you. Go ahead --

5 MR. SHEETZ: May I comment also?

6 COMMISSIONER HANSON: Yeah.

7 MS. MARTIN: Yeah.

8 MR. SHEETZ: Exceeding 50 rem or at 50 rem, it will not  
9 cause any tissue damage no matter where it is.

10 MS. MARTIN: Yeah.

11 MR. SHEETZ: So you can exceed the dose threshold for  
12 reporting the medical event, and there will be no harm to the patient.

13 There will be harm if the dose gets great enough. And I  
14 would say that would almost be exclusive to the therapeutic  
15 radiopharmaceuticals and would be very, very rare for a diagnostic  
16 radiopharmaceutical to reach the level of patient harm or tissue damage.  
17 Thank you.

18 COMMISSIONER HANSON: Thank you. Thank you both  
19 very much for that.

20 I think I want to follow up on that, because I think some of the  
21 language here that we're kind of talking about is the language of medical  
22 liability. And I think that's kind of bleeding into regulatory and practice of  
23 medicine type of language.

24 And I think that's, at least for me, part of what's confusing and  
25 difficult to tease out in this issue. So, whenever we talk about errors, there's

1 often talk about, well, who made the error and whose fault is it and was there  
2 any damage and so forth.

3 And I'm concerned that, for instance, by not, say, reporting --  
4 you know, there's kind of a categorical statement on page 77 about, you know,  
5 that medical events resulting from patient intervention, which I think is kind of  
6 the bucket where all of these things are falling into, would not improve the  
7 practice of medicine.

8 And I'm finding that, and would not, it would potentially  
9 infringe and wouldn't actually help prevent the occurrence of these events in the  
10 future. That seems confusing to me.

11 If we had information about how these events are occurring,  
12 whether on the patient side or the administration side, whether they rise  
13 specifically to the level of medical events or not, how could that not improve the  
14 practice of medicine and not prevent them from occurring in the future, at least  
15 in some way, even on the margins?

16 MR. SHEETZ: If I could respond to that, again, the causes for  
17 extravasation are, you know, varied, and again, depending on technical ability  
18 and patient anatomy.

19 I'm not sure you would get a medical event report, the actual  
20 root cause analysis, of what the reason was and would just get it extravasated  
21 and it exceeded the dose threshold. So I don't see that information coming  
22 back to the licensees and providing any benefit.

23 MS. MARTIN: I would support that answer, too. You can say  
24 you had an extravasation. But that's not necessarily going to cause.  
25 There's not a transference from one patient to the other. So, in other words,

1 just because it happened on patient 1, you're really not going to prevent it from  
2 happening on patient 2, if you happen to have two patients with problem veins.

3 COMMISSIONER HANSON: Okay. Well, let me kind of take  
4 a different angle on that slightly.

5 In the 2019 report on the subcommittee on extravasations, it  
6 said the prevention of extravasation is a medical training issue. So, if it's a  
7 medical training issue, why do we call it a passive patient intervention?

8 MS. MARTIN: Well, Mike is actually the one that's been  
9 through the training. But I've been on the teaching end of it but not doing the  
10 actual needle training.

11 My understanding is whether you're a nursing student or  
12 whether you're a nuclear medicine technologist, they all go through the basic  
13 training on how to do injections. Mike probably has more information than I do  
14 on that.

15 COMMISSIONER HANSON: Presumably even on people  
16 with bad veins, right? I mean --

17 MS. MARTIN: Correct.

18 COMMISSIONER HANSON: -- there are probably different  
19 approaches and techniques and so forth, right?

20 MS. MARTIN: Yes. I happen to have a nurse, a niece that's  
21 an RN. And, I mean, we've gotten into this discussion fairly often. And that  
22 was when I learned a little bit about what all training they went through.

23 And I know the nuclear medicine technologists in the  
24 programs I've been involved with do basically the same training. In fact, they're  
25 trained on patients with difficult veins because they know that many of their

1 patients are going to have the difficult veins.

2 Mike, do you have any, as a nuclear medicine tech, do you  
3 have anything to add to that?

4 MR. SHEETZ: Not really. Training components, certainly you  
5 have to learn how to perform injections.

6 MS. MARTIN: Yeah.

7 MR. SHEETZ: And then the skill level increases with the  
8 more you perform and the more different types of challenging veins that you  
9 encounter.

10 So, again, that's why we caution this is not something to try to  
11 regulate, you know. And now you're regulating the person's skill level.

12 So certainly there should be the basic instruction and training  
13 on how to perform injections. All nuclear medicine technologists receive that,  
14 physicians receive that. And then you acquire more skill the more  
15 administrations you do.

16 COMMISSIONER HANSON: Okay. Thank you. Thank you  
17 both very much.

18 CHAIRMAN SVINICKI: Thank you, Commissioner Hanson.

19 Well, my colleagues' questions have been very illuminating.  
20 And I'm struck by that old saying of everything's been said but not everybody's  
21 said it.

22 I could return to some of my questions. But maybe I'll just  
23 kind of elevate this in the sense that I'm not a medical practitioner. I'm not a  
24 medical expert.

25 And yet, things that we've been talking about today that fall

1 within the domain of, and, again, I think Commissioner Caputo quoted it  
2 directly, but, you know, radiation safety around occupational things for medical  
3 workers and looking at that, of course, we do get into the area of medical event  
4 reporting.

5                   So, ironically I'm sure to many, our medical event reporting is  
6 not necessarily linked to patient harm or overall negative patient outcomes.  
7 But, again, that was explained.

8                   It might have been Commissioner Caputo or others who  
9 talked about the fact that what we're trying to do is bring to light things that are  
10 systematically, programmatically maybe deficient. And, therefore, our  
11 regulations are meant to bring those forward or identify if it's occurring either  
12 with individual practitioners or maybe the program of a large medical facility.

13                   And then our regulations would, once bringing those out into  
14 the daylight, hopefully get the examination so that corrective actions or training  
15 or things could be taken.

16                   But a lot of the focus at least in this particular meeting with the  
17 ACMUI has been on some of these things that really get very, very close to  
18 patient care.

19                   If I begin with Dr. Jadvar's presentation, which was the final  
20 presentation, and we looked a bit over the horizon, I mentioned that it seemed  
21 that many of these trials were having very promising results.

22                   Frankly, as he was delivering the presentation, I was looking  
23 at some of the scans and the patient response, and I thought -- I don't know.  
24 The word that comes to mind is borderline miraculous in some of these cases.  
25 And I understand that there are very rigorous trials that need to be completed.

1                   But the public policy objective, or one of many, that's broader  
2 than the NRC would be to make these promising things, if they prove out  
3 affordable, available, you know, kind of in settings where the right amount of  
4 medical care and radiation safety was put around them, but not excessive  
5 elements that made them less available, less affordable, and, therefore, their  
6 promising results, you know, are not available to as many patients who could  
7 benefit.

8                   So I think what we are trying to do with trying training and  
9 experience, you know, is look at kind of the right set and have a routine or, you  
10 know, a periodic reevaluation of that.

11                  And when I think about all the things that Dr. Jadvar  
12 presented, if those things proved out, it looks like to me as a person, not an  
13 expert in the area, that there could be growing applications in both the  
14 diagnostic and therapeutic area, which in a perfect world would be able to be  
15 administered not just in major medical, you know, centers in the United States  
16 but maybe in communities at least of medium size.

17                  And we've talked a lot about this issue of shortages of  
18 authorized users. And, you know, if I reflect on all my years on the Commission  
19 I think about how -- this may sound a little bit unfair, but we keep coming back  
20 to, it's like, well, we don't have data of where it's not available and our  
21 authorized users. It's like this proving of a negative.

22                  And if we, again, return to that public health objective of  
23 having the right set of regulations that allow these things that are promising or  
24 prove out to be administered and available to the broadest possible set of  
25 patients with the least, you know, amount -- and I don't mean that least like

1 we're cutting corners. I just mean the appropriate amount of training and  
2 experience or requirement.

3                   And I did take note, in one of the reports, there was a  
4 discussion that like even unit dosing is not really a reason. You still need the  
5 full complement of medical and radiation safety training around everything.

6                   You know, as we look at this pandemic and we have  
7 promising, we hope, vaccines on the horizon, one of the things that the logistics  
8 of deployment is about is, you know, how could we get the largest number of  
9 authorized pharmacists and people that can administer the vaccine. Once it's  
10 ready it can be distributed amongst the population as quickly as possible. So  
11 there's some parallels there.

12                   And I was going to ask about the minority opinion on training  
13 and experience. But I think the question was already posed.

14                   But there's a kind of intuitive allure a little bit of moving away  
15 from tracking the specific physician authorizations. If this is such an area of  
16 promise for medicine, then does that just become such a cumbersome  
17 regulatory orientation that you would somehow want to?

18                   So I don't know enough to know. And the committee didn't  
19 maybe spend a lot of time on the minority opinion, other than to note that it was  
20 a minority, so it obviously was not embraced by the subcommittee as a whole.

21                   But that being said, it also I think came a little late and was  
22 not central to what the subcommittee was looking at in the main. So maybe  
23 they didn't spend as much time on it.

24                   I do, as a member of the Commission, support continuing to  
25 look at the 700 hours, to continue looking at training and experience.

1                    Maybe I'll ask this question. And it's borderline philosophical.  
2                    What are the things, given that if this is a promising area of research and  
3                    development in terms of nuclear medicine both for diagnostic and therapeutics,  
4                    what would trigger really looking at different approaches to training and  
5                    experience or how the NRC touches on this area of nuclear and radiation  
6                    safety?

7                    I just -- it seems that we keep returning to it. And maybe in  
8                    the absence of either being compelled to make a change, because although  
9                    there are new modalities, they are, you know, they're growing at a pace where  
10                    we can keep feeding the pipeline of the various physician specialties, and, but if  
11                    there were truly kind of game changer things out there that you would want to  
12                    say we need to make a step change in the availability of getting something out  
13                    there.

14                    We're going to keep returning to it every, you know, five or ten  
15                    years and just saying this is generally the way we should approach this. NRC's  
16                    trying to look at innovation in all areas of its regulatory framework.

17                    And so, if it doesn't really need fundamental changing today,  
18                    what would be signs and indicators that we should begin to look at that? I don't  
19                    know if anyone would like to offer some commentary along those lines.

20                    DR. SCHLEIPMAN: This is Robert Schleipman. Thank you.

21                    I think that the current recognized boards, such as the nuclear  
22                    medicine community, the radiation oncology community, are very much  
23                    champions of the theranostics. And they built this and are building this into  
24                    their training programs. It's part of those 700 hours. But it's with focus on these  
25                    newer technologies so that these are being addressed in the training and



1 competency of trainees.

2 Dr. Jadvar may have additions to that.

3 DR. JADVAR: I second that. Yeah, that's correct. Right now,  
4 for example, with the recent approval of Lutathera, which is basically the, after  
5 radioiodine is the first theranostic after a long time.

6 This is completely incorporated into our training. There are  
7 questions being presented in the boards' examinations by, in the ABNM, ABR,  
8 and also, I believe also for radiation oncologists.

9 So it's being incorporated as they are developed and  
10 available in the clinic. And they are also being taught about some of the future  
11 potential theranostics that I already mentioned in my presentation.

12 So they are definitely on top of this. And they recognize that  
13 they're championing this field and make sure that the training is appropriate for  
14 people who are going to be practicing this in the future.

15 And I think Melissa Martin had also her hand up. Melissa?

16 CHAIRMAN SVINICKI: Oh, I think you might be muted.

17 MS. MARTIN: Thank you very much. I will learn how to  
18 operate the mute button.

19 As one of the people that's been, as one of the physicists on  
20 the ABR's question-writing committee for several years, I would just reiterate  
21 that the current trainees that pass the American Board of Radiology exams  
22 have this inherent training spread out over their entire training period.

23 I think it is very different when you are talking about trying to  
24 take a particular drug and say, oh, we just want limited training.

25 I've had experience with non-radiologists, non-nuclear

1 medicine physicians administering some of these drugs, particularly iodine-131.

2 For a while, there were a fair number of endocrinologists that gave these drugs  
3 without involving the radiation oncologists.

4 It was not uncommon to spend an inordinate amount of time  
5 as the radiation physicist and radiation safety officer answering the patients'  
6 questions trying to clean up some of the things that happened in the room.

7 That basic radiation safety training in radiation physics is just  
8 not part of their curriculum. And I think I would just really support the idea that  
9 that basic training has to stay in the training for whoever is an authorized user.

10 CHAIRMAN SVINICKI: Well, and I appreciate that, Ms.  
11 Martin. And maybe that's really a central point to return to. And please don't  
12 misunderstand me. I'm not looking to cut it close.

13 I mean, patient care is, it isn't just, yeah, someone with an  
14 injectable going in and not understanding what if the patient begins to have an  
15 adverse reaction.

16 Some of the reason that I take comfort in the views you all  
17 have expressed on extravasations is that these are patients that are receiving  
18 medical care. They wouldn't be having these isotopes and things administered  
19 to them.

20 And, therefore, if there can be a visual cue and then there's  
21 follow-up care and everything else, it does kind of seem to draw one to a  
22 conclusion on extravasations that you could have tons of reporting around it. It  
23 is a little bit of an elusive physiology of the patient question. It is skill of the craft  
24 of the person doing the injection.

25 But at the end of the day, what we care most about I think is

1 patient harm. So what we want to do is be able to follow up and know if this  
2 became something that was causing some concern for the patient.

3 And in most cases, it sounds like it would not be, because  
4 there's a lot of physiological processes going on that lead to the ultimate  
5 biodistribution of the isotope after the event occurs.

6 But I think we all want an extremely strong safety net and  
7 safety culture around the practice of nuclear medicine.

8 I think it is important that as a Commission and as a nuclear  
9 regulator we continue to probe the level of requirements that we are putting  
10 around these things and continue to look at them critically, not just is what we're  
11 doing working, but are there recommended changes that need to be made.

12 So it is -- and I'll kind of end with where I started. To me and I  
13 think to members of this Commission, to hear from practitioners and specialists  
14 on this committee is very, very important. We can kind of look at nuclear  
15 phenomenology, but this is people at the end of the day. And it's health care  
16 and medical care.

17 So we do give a lot of substantive weight to the dialogue that  
18 we have with you as a result of this meeting and also the written reports that  
19 you provide that I know all members of the Commission review prior to this  
20 meeting and that informed our questions here today.

21 So I thank you all again. And seeing that no one on the  
22 Commission is trying to give me a sign to be recognized, I will thank you all  
23 again for the work you do. And with that, we are adjourned.

24 (Whereupon, the above-entitled matter went off the record at  
25 12:07 p.m.)