

UNITED STATES

NUCLEAR REGULATORY COMMISSION

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MEETING WITH THE ADVISORY COMMITTEE ON THE MEDICAL USES

OF ISOTOPES

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TUESDAY,

OCTOBER 5, 2021

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The Commission met via Video Teleconference, at 10:00
a.m. EDT, Christopher T. Hanson, Chairman, presiding.

COMMISSION MEMBERS:

CHRISTOPHER T. HANSON, Chairman

JEFF BARAN, Commissioner

DAVID A. WRIGHT, Commissioner

ACMUI MEMBERS:

DARLENE METTER, MD, Chair; Diagnostic Radiologist

RONALD D. ENNIS, MD, Radiation Oncologist (Brachytherapy)

HOSSEIN JADVAR, MD, Nuclear Medicine Physician

JOSH MAILMAN, Patients' Rights Advocate

MELISSA MARTIN, Medical Physicist, Nuclear Medicine

VASKEN DILSIZIAN, MD, Nuclear Cardiologist

P R O C E E D I N G S

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10:01 a.m.

CHAIR HANSON: Good morning, everyone. I convene the Commission's public meeting with our Advisory Committee on the Medical Use of Isotopes, or ACMUI. This is a routine meeting to hear views of the Committee members on significant issues that have come before them. The last meeting with the Committee was in November of 2020.

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

Today, I'd like to welcome the two newest members of the Committee, Mr. Josh Mailman, Patients' Rights Advocate, and Ms. Rebecca Allen, Healthcare Administrator.

Before we start, I'll ask first if my colleagues have any remarks they'd like to make.

No? Okay. So, with that, we will begin with ACMUI Chair, Dr. Darlene Metter.

Dr. Metter?

DR. METTER: Thank you, Chairman Hanson, and good morning to Chairman Hanson and Commissioners Baran and Wright. I'm Darlene Metter, ACMUI Chair and Diagnostic Radiologist.

In the realm of the ongoing COVID pandemic, 2020 and 2021 have been particularly challenging to us. And therefore, I would like to thank the Commission for agreeing to meet with representative members of the ACMUI, who will be updating the Commission on several key ACMUI topics discussed in 2021.

1 So today's agenda will be as follows.

2 Next slide.

3 I will be giving an overview of the ACMUI activities in 2021.

4 I will then be followed by the ACMUI Radiation Oncologist, Dr. Ronald
5 Ennis, who will be presenting two topics. The first will be a review and
6 analysis of reported medical events from fiscal year 2020. His second
7 presentation will be on abnormal occurrence criteria.

8 Next slide.

9 Dr. Ennis will be followed by Dr. Hossein Jadvar, ACMUI
10 Nuclear Medicine Physician, and he will be presenting on emerging
11 radiopharmaceutical knowledge requirements and theranostics. Our final
12 presenter will be Mr. Josh Mailman, ACMUI Patient Advocate, who will be
13 giving his perspective on the role of a Patient Advocate on the ACMUI.

14 Next slide.

15 So, for my presentation of an overview of the ACMUI, I will
16 follow the following format. I will discuss the role of the ACMUI, the current
17 ACMUI membership, the topics covered by the ACMUI in 2021, our current
18 Subcommittees, and a comment about the future.

19 Next slide.

20 The role of the ACMUI is to advise the U.S. NRC on issues
21 and policies and technical issues that arise in the regulation of the medical
22 use of radioactive material in diagnosis and therapy. The ACMUI is also
23 able to comment on changes to NRC regulation and guidance, and NRC is
24 asked to have ACMUI evaluate certain non-routine uses of radioactive
25 material.

26 Next slide.

1 The ACMUI is also able to provide technical assistance in
2 licensing, inspection, and enforcement cases, and finally bring key issues to
3 the attention of the Commission for appropriate action.

4 Next slide.

5 The ACMUI has 13 member positions. The current
6 membership is as follows. Our Nuclear Medicine Physician is Dr. Hossein
7 Jadvar. The ACMUI has two Radiation Oncologists, Dr. Ronald Ennis and
8 Dr. Harvey Wolkov. Our Nuclear Cardiologist is Dr. Vasken Dilsizian, who
9 is also the ACMUI Vice Chair.

10 I am the Diagnostic Radiologist and the ACMUI Chair.
11 Our Nuclear Pharmacist is Mr. Richard Green, and our FDA Representative
12 is Dr. Michael O'Hara.

13 Next slide.

14 The ACMUI has two Medical Physicists. Expertise in
15 nuclear medicine is Ms. Melissa Martin, and expertise in therapy is Mr.
16 Zoubir Ouhib. Our Patients' Rights Advocate is Mr. Josh Mailman. Our
17 Agreement State Representative is Ms. Megan Shober. And our Healthcare
18 Administrator is Ms. Rebecca Allen.

19 Currently, our Radiation Safety Officer position is vacant,
20 and the NRC staff is in the process of filling that position.

21 Next slide.

22 The topics addressed by the ACMUI during our meetings
23 in 2021 are the following. We had an excellent presentation from the
24 Netherlands on extravasations in nuclear medicine by Dr. Jan van der Pol
25 from Maastrich University Medical Center. We also had a topic that was
26 presented that was very interesting by Dr. DeWard from the University of

1 Wisconsin on calibration procedures for brachytherapy sources.

2 Other presentations included revised abnormal occurrence
3 criteria and extravasations and medical event reporting.

4 Next slide.

5 More recent topics that were covered were the following:
6 emerging radiopharmaceutical knowledge requirements and theranostics,
7 radionuclide generators, knowledge and practice requirements, production
8 challenges for therapeutic radiopharmaceuticals, and a very insightful
9 presentation on the feature of personalized dosimetry.

10 Next slide.

11 We had four staff presentations in 2021. These were
12 patient release evaluation of emerging brachytherapy sources, ACMUI
13 reporting structure, medical-related events, and our annual INFOSEC,
14 ethics, and allegations training.

15 Next slide.

16 The ACMUI currently has eight active Subcommittees.
17 The first is Training and Experience for All Modalities; Medical Events;
18 Infiltrations, Extravasations, and Medical Event Reporting; Abnormal
19 Occurrence; and Regulatory Guide 8.39, Release of Patients Administered
20 Radioactive Material.

21 Next slide.

22 Our new Committees are Emerging Radiopharmaceutical
23 Knowledge Requirements and Theranostics, Radionuclide Generator
24 Knowledge and Practice Requirements, and our newest Committee is
25 Diffusing Alpha-emitter Radiation Therapy, or DART Manual Brachytherapy
26 Sources Licensing Guidance.

1 Next slide.

2 So what about the future? The ACMUI will continue to
3 provide advice and technical assistance to the NRC staff and NRC, will
4 comment on NRC regulations and guidance as requested, and the ACMUI
5 will continue to evaluate issues, uses of the radioactive material, and bring
6 key issues to the attention of the Commission.

7 Next slide.

8 And these are my acronyms.

9 So that concludes my presentation, and I'll turn it back to
10 Chairman Hanson.

11 CHAIR HANSON: Thank you, Dr. Metter.

12 Next, we'll hear from Dr. Ronald Ennis, ACMUI Radiation
13 Oncologist. And he'll talk about the review and analysis of reported medical
14 events. Dr. Ennis?

15 DR. ENNIS: Good morning, everyone. And thank you,
16 Commissioner Hanson, and thank you to the other Commissioners as well.
17 It's an honor to be able to present to you today.

18 As stated, I'll be presenting two presentations from two
19 Subcommittees. First, will be a review of medical events, and second will
20 be on abnormal occurrences. So we'll start with the medical events
21 presentation.

22 First slide, please.

23 Okay. There we go. Okay. So medical events for the
24 last year -- so the Subcommittee on Medical Events reviews medical events
25 on an every-one-to-two-year basis with a goal of developing perspective and
26 advice for the NRC about the regulation of medical events.

1 Our Subcommittee includes the people listed here -- next
2 slide, please -- it includes myself, Richard Green, Dr. Metter, Mr. Ouhib, Dr.
3 O'Hara, Mr. Sheetz -- who was the Radiation Safety Officer; his term just
4 concluded -- and Dr. Wolkov.

5 Next slide, please.

6 So two overarching themes have been identified by the
7 Subcommittee over the last couple of years, and those continue to be seen
8 in the current review as well. One of those issues is the possibility of a
9 time-out or a use of a checklist immediately prior to the administration of
10 byproduct material, as is done commonly now in medicine, particularly in
11 surgery and other procedures, could have prevented some of the medical
12 events.

13 And next slide.

14 The second overarching issue that remains is a sense
15 from review of the medical events that there's an issue of lack of recent or
16 frequent performance of the particular administration, or possibly more of an
17 issue of inattention during the performance, of the particular treatment
18 appeared to be contributing factors.

19 These interpretations are based on information that we
20 have available to us, which is through the NMED system. And that
21 obviously is a little bit difficult to interpret such subjective things, as
22 particularly of this category.

23 In previous years, we really focused more on our thinking
24 that it had to do with frequency of performance, but in this year's
25 Subcommittee discussion, it was suggested appropriately that many of those
26 may actually be more about the issue of inattention as opposed to a lack of

1 frequency of performance, and really hard to go beyond that in terms of
2 attribution based on information that we have in front of us.

3 These issues, as I said, have been already recognized by
4 this Committee in years past, and in 2019, as to our suggestion, the NRC did
5 issue an information notice to users alerting them of these issues, obviously
6 with the goal of trying to decrease the number of events.

7 So it would be hard to say at this point whether that has an
8 impact, as it's only been a couple years. But about the same proportion of
9 events for each category that we attributed to these two criteria, these two
10 categories, occurred again in this year's review.

11 Next slide.

12 There was a concern that we raised last year of increased
13 complexity of unsealed sources as potentially unsealed source
14 administration potentially relating to contributing to a higher number of
15 medical events in the coming years. Take Lutathera, for example, is much
16 more complex than, for example, Xofigo.

17 That remains a concern of the Subcommittee, although to
18 date we have not seen this play out. We think we need a few more years
19 before we can feel comfortable that this will not become an issue.

20 Next slide, please.

21 For this year, our main message is that the number of
22 medical events of Y90 administrations continue to be the most common
23 medical event. Important to note that it is still an extremely small fraction of
24 the number of Y90 administrations across the country. For all medical
25 events across the board, they represent a tiny fraction of all administrations,
26 both on diagnostic and therapeutic side.

1 Nevertheless, of course, we do want to try and decrease
2 these two as well as possible. And Y90 administrations continue to be
3 stubbornly high and stable, as you will see. Therefore, the Subcommittee is
4 recommending to the wider ACMUI that we create a subcommittee to go and
5 look into this in more depth in connection with users and vendors and
6 propose solutions for starting to make an impact on the number of Y90
7 medical events.

8 Next slide.

9 The next series of slides will show the actual data of the
10 number of medical events by each of the criteria that we regulate. I won't
11 belabor these, really. I'll move through them relatively quickly in the interest
12 of time and highlight important issues. But as I said, the number of events
13 in each category is really relatively small, and there are no trends in any
14 category that we observed over the last several years that are worth
15 highlighting.

16 You will see on the slides an estimation of the proportion of
17 events in each category that may have been impacted by the use of a
18 time-out or checklist and the number of events that may have been impacted
19 by this concern for either infrequency or unfamiliarity with the administration
20 of the byproduct material, or due to possibly just inattention, as was
21 mentioned briefly.

22 So, for § 35.200, Use of Unsealed Byproduct Materials for
23 Imaging and Localization, there are actually no events in the last fiscal year,
24 and there have been very few in each year.

25 Next slide.

26 In § 35.300, Unsealed Byproduct Material Needing a

1 Written Directive, there were only two events in the past year.

2 Next slide.

3 And § 35.400, Manual Brachytherapy, there were six
4 events, and again, a relatively small number of events considering the
5 number of procedures done. Worth noting for Commissioners, just to
6 highlight, there was a rule change that redefined medical event for manual
7 brachytherapy for prostrate, I'm sure you recall. And the motivation for that
8 was a sense that more events than should be were considered medical
9 events because of the nature of the definition. The definition was changed
10 from a dose-based definition to an activity-based definition. And we can say
11 that from 2018, '19, and '20 that indeed the number of true medical events
12 now has gone down to a very small number. And so the rulemaking seems
13 to have the desired effect.

14 In terms of these categories here, there's a fair proportion,
15 a modest proportion, of manual brachytherapy events that may have been
16 prevented as a time-out or may have been attributable to either lack of
17 experience or inattention.

18 Next slide.

19 § 35.600, which has to do with HDR afterloader units and
20 the older stereotactic units. There were 13 events, a relatively stable
21 number, slight higher, but certainly nothing of any statistical or trend
22 significance at this point. With the typical distribution, a variety of different
23 things can go wrong in these procedures and these are those medical
24 events categories.

25 Next slide.

26 By disease, the bulk of them are in GYN. And our sense

1 is that's proportional to the use of HDR. The brain is obviously about to
2 (inaudible). But the rest are essentially HDR treatments, and
3 overwhelmingly, those procedures are gynecological.

4 Next slide.

5 And for this category, the number of events that may have
6 been done, affected by time-out, are reflected here, slight uptick in the last
7 year. Some may be a trend we would have to watch out for. Some may be
8 just slightly different. There was a different membership to the
9 Subcommittee and may have been somewhat differences.

10 And these are all attributing the medical events, as I
11 alluded to earlier, as based on information we have in NMED, which is not
12 perfect for making these judgments. So there's some subjectivity, and
13 variability in the number attributed to time-out may be somewhat subjective,
14 a reflection of the subjectivity of this assignment.

15 Next slide.

16 And similarly, for the issue about inattention or infrequent
17 users, a higher attribution this year, somewhat. And again, that may be
18 somewhat subjective. Personally, that is my impression, having been a
19 leader of the Committee for a few years, is this isn't really a trend,
20 necessarily, but more of just a subjective difference of interpretation. As we
21 keep talking about this topic, perhaps we're more attuned to it. Time will
22 tell, I think.

23 Going into -- next slide, please -- § 35.1000 for radioactive
24 seed localization, one event.

25 Next slide.

26 In cardiac brachytherapy, two events. One may be what

1 would be considered a patient intervention issue, which is, again, a topic of
2 other Subcommittees in the last few years. So I won't go into that further.

3 Next slide.

4 For Gamma Knife and Perfexion and Icon -- Gamma Knife
5 Perfexion Icon, excuse me -- number of events, again, just two.

6 Next slide, please.

7 For Y90 -- so we present by both of the Y90 producers.
8 So the Therasphere product had 15 events, about the same as it's had the
9 last four years, with the exact issues below, again residual activity of the
10 device being the number one. And some thought that infrequent or
11 inattention may be a significant contributing factor.

12 Next slide, please.

13 For SirSpheres, the absolute number is lower. Not clear if
14 that's a reflection of a difference in the process of delivery, if these are real
15 differences or just statistically different. The belief, as I understand it, the
16 market share of each product is about 50/50, but that's not been formally
17 investigated by the Subcommittee.

18 Next slide, please.

19 So this is prior things that we know about microspheres
20 that are important to make sure things go well. This has been promulgated
21 already by the manufacturers and the specialty societies, et cetera. But we
22 are still seeing these number of events.

23 Next slide.

24 That concludes this part of my presentations. These are
25 my acronyms.

26 CHAIR HANSON: Thank you, Dr. Ennis. I understand

1 now we'll hear from you about the Abnormal Occurrence Subcommittee
2 report.

3 DR. ENNIS: That is correct. And we'll move into that
4 presentation and can we show my slides, please. Again, an honor to
5 present this topic.

6 Next slide, please.

7 This will be the outline of what we'll be covering on the
8 next several slides.

9 Next slide, please.

10 So the Subcommittee was chaired by Michael Sheetz,
11 listed here on the fourth line as former. He was our Radiation Safety
12 Officer. His term just expired. But because he's technically not on ACMUI
13 anymore, I was asked to present for our Subcommittee. The other
14 members of the Subcommittee were Dr. Jadvar, Mr. Ouhib, Ms. Shober, and
15 Donna-Beth Howe. Dr. Donna-Beth Howe was our resource.

16 Next slide, please.

17 Okay. So what we attempted to address was considering
18 what is patient harm in a medical abnormal occurrence, look at the current
19 definition of a medical abnormal occurrence, define what the goals were,
20 evaluate whether the current definition was appropriate, and to comment on
21 the NRC staff's proposed changes to that definition.

22 Next slide, please.

23 So, just by way of a little bit of background, I guess -- so
24 the AO criteria, abnormal occurrence is a level of occurrence of an event, of
25 a radiation exposure, to which the NRC is required to report to Congress an
26 annual report. And as written in the regulations, this is supposed to be

1 something that is important to public health and safety that Congress should
2 be made aware of.

3 The definition is different for medical events of the
4 abnormal occurrence type than other abnormal occurrence types, of course,
5 because we are purposely exposing people to more radiation than would
6 normally be allowed. And in that context, there has been changes in the
7 abnormal occurrence criteria for which events should be reported to
8 Congress over the years, and the last update was in 2017.

9 In 2017, the event -- any medical event that met two
10 criteria would then be considered an abnormal occurrence and would be
11 reported to Congress. One part of the event was a dose threshold, and you
12 see that on your slide here, one gray to a large proportion of bone marrow or
13 to the lens, two and a half gray to the gonads, or exceeding by ten gray to
14 any tissue.

15 So you had to have that plus -- next slide, please -- the
16 criteria for the incident itself, which are essentially similar to a medical event,
17 if you will, though slightly higher for the dose, but the concept of, okay, it's
18 not what was intended. And the doses to particular organs were very high.
19 This was a sort of dose-based criteria, essentially, medical event plus a high
20 dose.

21 Next slide, please.

22 In our Subcommittee, we looked over abnormal
23 occurrences that have been reported to Congress over the years and have a
24 strong feeling that this definition is over-conservative and captures events
25 that are not of significance from the standpoint of public health and safety.
26 They certainly are medical events, but they just don't rise to that level of

1 needing Congressional reporting. There will be no impact on public health
2 and safety, they don't represent that type of event.

3 And therefore, our Subcommittee felt that there should be
4 a change in the definition to a higher threshold that would really represent
5 something significant, and felt that the best step forward in that was to focus
6 the definition not on dose but on -- that cause actual patient harm.

7 Next slide, please.

8 So the NRC has proposed changes to medical event along
9 these lines. Attain the current dose threshold, but for the -- the or is now
10 not just a regular medical event criteria but also that there's a medical
11 consequence to this.

12 So, as opposed to just a medical event, the doses have to
13 a) be of a certain level high, and B, that there was some significant medical
14 consequence, so unintended radiation-induced injury causing permanent
15 impairment of bodily function or permanent damage to body structure or
16 surgical intervention needed to preclude such permanent impairment.

17 Next slide.

18 Looking over the abnormal occurrences that were reported
19 and then applying these new criteria, these would indeed decrease the
20 number of events reported to Congress every year from about 12 over the 3
21 years that we looked to about 3 or 4 per year, certainly a much more
22 reasonable number for the goal, again, of highlighting to Congress the
23 important public health and safety issues.

24 Next slide, please.

25 So, as I said, we also feel that the NRC's definition would
26 improve medical event criteria -- medical abnormal occurrence criteria,

1 excuse me -- more appropriate for the goal of abnormal occurrence.

2 Next slide.

3 So, as I stated, we fully support the NRC proposed
4 changes to the abnormal occurrence definition, and we recommend that
5 communication be prepared and distributed to all the NRC agreement state
6 medical licensees to inform them of the best practices for reporting medical
7 events so that important information is provided, root cause analysis on why
8 that occurred, and medical effect on the individual.

9 This subtopic actually is something that we have had a
10 Subcommittee proposed, and NRC is actually preparing advice to be sent
11 out in this regard. This will obviously help both medical event reporting as
12 well as abnormal occurrence reporting.

13 Next slide.

14 Unfortunately, Mr. Sheetz isn't here to present his opinion,
15 but I will do my best to. On one subtopic of this, there was a dissention, and
16 this has to do with the criteria for reporting embryo and fetal events.

17 The dose threshold for these categories is only 60
18 millisieverts. And Mr. Sheetz is of the opinion that, really, there should no
19 be -- should no distinction between embryo/fetal events and all the rest of
20 the events when it comes to the criteria of abnormal occurrence. This
21 actually was the opinion of the previous ACMUI AO Subcommittee position
22 dating back several years.

23 Our current AO Subcommittee didn't -- although
24 understood that opinion, didn't feel strongly that that change was needed
25 and embraced the notion that embryo/fetal is so sensitive that it would be
26 reasonable to have a very low dose threshold for that consideration of an

1 abnormal occurrence.

2 Next slide.

3 And this just continues what I just said. And Mr. Sheetz's
4 opinion that it should also be unintended radiation causing permanent
5 impairment or damage should be the criteria rather than dose.

6 And these are my acronyms. And with that concludes my
7 presentation. Thank you for your time.

8 CHAIR HANSON: Thank you, Dr. Ennis. Appreciate that
9 discussion.

10 Next, we'll hear from Dr. Hossein Jadvar on the emerging
11 radiopharmaceutical therapy knowledge requirements and theranostics.

12 Dr. Jadvar?

13 DR. JADVAR: Thank you, Chairman Hanson. And good
14 morning to you and Commissioner Wright and Commissioner Baran. For
15 me, it's also an honor to be able to present here today.

16 Can I have my slides, please?

17 So this is the agenda. I will go over the membership, our
18 charge, give some background, and then present to you some of the current
19 and emerging theranostic agents, some of the challenges that we face in the
20 field, and then talk about the knowledge requirements and show you a
21 picture or a sample of what a theranostic room setup could look like.

22 May I have the next slide, please?

23 This is the membership. I chaired the Subcommittee.
24 The other members included Dr. Vasken Dilsizian, Dr. Ennis, Dr. O'Hara, Mr.
25 Zoubir Ouhib, Mr. Mailman, and our NRC Staff Resource was Maryann
26 Ayoade. I want to thank all of them for contributing to this effort. Also want

1 to acknowledge Ms. Lisa Dimmick, who was very helpful from NRC as we
2 discussed and deliberated on this particular issue.

3 May I have the next slide, please?

4 So our Subcommittee charge was to outline the knowledge
5 in the specific or specialized practice of policy requirements that is needed
6 for the safe use and handling of the emerging radiopharmaceuticals in the
7 field of theranostics, and also provide consideration and recommendation to
8 the NRC staff.

9 May I have the next slide, please?

10 So just on to the definition, what is theranostics?
11 Theranostics is essentially a systemic integration of diagnostic tools which
12 could include imaging. Does not have to be imaging per se, but in this
13 case, we focus on nuclear imaging, and it's paired with therapeutic agents.
14 And again, this does not have to be radioactive, but again, in this particular
15 topic here, we are focusing on radiopharmaceuticals.

16 These are targeted through the same biomolecules, or in a
17 broader definition of theranostics, to a similar parameter, a physiological
18 parameter. And theranostics, although it has been around for a long time --
19 but it has advanced dramatically the past few years, and it is very much
20 aligned with the concept of precision or personalized medicine.

21 It was probably started in the early 1940s by Dr. Saul Hertz
22 at Mass General Hospital, who realized that radioiodine can be used for
23 treatment of thyroid diseases, although he did not perform imaging.
24 However, this was the basic concept for targeted radiopharmaceutical
25 therapy and the basis of theranostics.

26 May I have the next slide, please?

1 So these are some of the currently approved theranostic
2 agents that are being used in the clinics. The first one is the oldest one,
3 which I just talked about, started by -- essentially, it started with Dr. Saul
4 Hertz back in 1941 in relation to treatment of thyroid diseases, particularly
5 thyroid cancer, with the target being the sodium iodide symporter.

6 We also had anti-CD20 theranostic pair, which is used for
7 the treatment of patients with lymphoma. This is called Zevalin and was
8 approved in 2002. In a broader term, bone scanning with sodium fluoride or
9 technetium-99 MDP and treatment with radium-223 dichloride for treatment
10 of osteoblastic metastases in patients with metastatic cancer, resistant
11 prostate cancer is also considered a broader term for theranostic
12 companion. Radium was approved by the FDA in 2013.

13 The next one also fits under that broader definition, the
14 technetium-99m MAA and the Y90 microspheres, which basically looks at
15 the physiological parameter of the hyperperfusion for treatment of patients
16 who have liver tumors, either metastatic or primary.

17 The next one is MIBG, and the target here is
18 norepinephrine transporter, and this is commercialized with the name of
19 Azedra. That was FDA approved in 2018 for treatment of patients with
20 pheochromocytoma and paraganglioma.

21 And finally, there's gallium-68 or copper-64 dotatate. The
22 gallium-68 dotatate is commercialized as Netspot, which was approved in
23 2016. The copper-64 version of it is called Detectnet, and that was
24 approved in 2020. These are for imaging of patients with neuroendocrine
25 tumors who express somatostatin receptors. Gallium-68 dotatoc is also a
26 similar agent for imaging, and that was approved in 2019. And finally, the

1 therapy pair is lutetium-177 dotatate, which is commercialized as Lutathera,
2 and that was published -- I'm sorry, that was FDA approved in 2018.

3 Next slide, please.

4 What's within the near future? We are very excited that
5 theranostic agents are being rolled out very soon for targeting
6 prostate-specific membrane antigens, which are applicable to patients with
7 prostate cancer.

8 The imaging agent, the gallium-68 PSMA-11, was
9 approved for local use at UCLA and UCSF in 2020. And then, very
10 recently, in May of 2021, the F-18 label of PSMA, which is commercialized
11 as Pylarify, was also approved by the FDA for imaging.

12 The lutetium-177 PSMA theranostic pair for -- or
13 companion for treatment is not approved yet, but the approval is anticipated
14 very soon, within the next several months, based on the positive results of
15 the VISION trial that was just published in the New England Journal of
16 Medicine in June of 2021.

17 What's on the horizon? There are a number of other
18 things that we think that may be coming to clinics within the next five to
19 seven years. One is related to alpha therapy for targeting PSMA. There
20 are theranostic companions that target chemokine receptors, primarily
21 applicable to multiple myeloma but also other cancers.

22 Next one is targeted to gastrin-releasing peptide receptors.
23 That is applicable to multiple tumors, including prostate cancer. And finally,
24 a very exciting molecule or agent, which is an inhibitor for the fibroblast
25 activation protein that targets the stromal microenvironment of the tumor --
26 not the tumor itself but the microenvironment of the tumor -- applicable to

1 multiple cancers for imaging and treatment.

2 Next slide, please.

3 These are additional agents that are on the horizon, some
4 targeted to the renal cell carcinoma, some targeted to glioblastoma
5 multiforme. And finally, another one which targets the DNA repair enzyme,
6 and that's applicable to multiple cancers.

7 Next slide, please.

8 So there are a number of challenges in theranostics that I
9 just want to briefly overview. Some of them are technical, and that's related
10 to the need for standardization and development of efficient protocols and
11 development of interdisciplinary teams that will work together in the clinic.

12 These new imaging agents need to be incorporated into
13 clinical guidelines, such as the NCCN Guidelines. And, of course,
14 education and training is also extremely important in this case.

15 As far as economic challenges, it's related to supply chain
16 for a study pipeline of some of these radioisotopes that will become more
17 common in the clinic, and also the issue of sufficient reimbursement for
18 these type of new treatments, doing a cost utility analysis to compare the
19 utility and cost of these new agents or emerging agents in comparison to the
20 current available treatment. And, of course, there's always need for R&D
21 funding.

22 Biomedical challenges may be -- can I have the next slide,
23 please? In the biomedical challenges, we always need to identify new
24 biological targets and then, of course, perform the preclinical animal studies,
25 first in-human studies, and large perspective or randomized studies to
26 decipher the place of these new emerging theranostics in the clinic.

1 And then, of course, after those are being approved or
2 available, then a number of other clinical trials need to be done to see what
3 is the best approach to treatment of patients under the banner of precision
4 medicine. Is it single treatment with theranostics, or should it be in tandem?

5 Should it be modified or adapted depending upon some imaging or other
6 diagnostic tool and how it can be combined with other available treatment?

7 And, of course, we focus on cancer, but theranostics is not only related to
8 cancer and can be applied to other non-oncologic diseases.

9 Can I have the next slide, please?

10 So what are the knowledge requirements? The makeup
11 of the healthcare team at the time of administration -- our Subcommittee
12 discussed that it may consist of the authorized user, of course with the
13 appropriate training in this very fast-moving emerging field of theranostics;
14 also a certified nuclear medicine technologist; radiation safety officer; a
15 registered nurse, which can help with non-radioactive parts of the
16 preparation of the patient for treatment; and a medical physicist if that
17 person is available or applicable, especially as dosimetry becomes routine in
18 the clinic. It is not now, but it may become.

19 Also, we discussed that AU should be present. It's not
20 must; it's should be present, either virtually or in person at the time of the
21 dose administration to supervise this type of treatment.

22 Next slide, please.

23 Therapy should be done in a dedicated and regulatory
24 approved room appropriate for radioisotope administration. I'll show you an
25 example of that. If in this interdisciplinary team there may be non-radiation
26 workers, for example a nurse, oncology nurse, which may be participating in

1 preparation of the patient, they may need to wear a radiation badge, and this
2 can be determined by the RSO.

3 Next slide, please.

4 There is, of course, an issue of the extravasation and
5 patient release criteria that is pertinent in theranostics, and those are being
6 addressed by the other ACMUI Subcommittees.

7 The radioactive waste management, again, this has to be
8 referred to the facility-established guidelines and regulation.

9 The AU is responsible for the patient concerns which are
10 directly related to the radiopharmaceutical therapy, including
11 radiation-induced injuries, within that interdisciplinary team that we talked
12 about.

13 And also, we have to make sure that the emerging
14 theranostics -- again, this is a very fast-moving field -- are within the
15 regulatory guidelines. And we have to watch for that.

16 Next slide, please.

17 The authorized user is encouraged to avail themselves of
18 all the newest training information in each new theranostics as they emerge,
19 and this can be done through CME or through the medical organization and
20 credentialing through the medical center where the AU is active.

21 Patient dosimetry is an important topic, and this is related
22 to patient-specific dose versus fixed activity, although patient-specific
23 dosimetry plays a relatively minor role at this time. But this is anticipated to
24 be more prevalent in the future. There are a number of challenges in this
25 area. We still don't have a randomized clinical trial that compares dosimetry
26 patients, dosimetry-based versus (inaudible) activity-based treatment to see

1 if there is an outcome benefit for the patient with, of course, minimization of
2 toxic effects to the normal tissue.

3 There are other issues with regard to standardization that
4 need to be addressed. With regard to alpha particles, dosimetry, to my
5 understanding, is more challenging, and the microscale radiation effect and
6 daughter distribution needs to be taken into account.

7 And finally, it has to be a cost utility analysis to see if the
8 potential patient benefit versus the cost and complexity of the logistics that is
9 involved with the patient-specific dosimetry. And then the next item is to
10 outreach to patients to help the providers and also the AUs to make sure
11 that the correct information and the newest information is available to
12 everyone.

13 And next slide, please.

14 This is an example or illustration of a possible room that
15 can be used for treatment of patients. This is, in fact, from our center at the
16 University of Southern California. We use this room that is prepared for
17 treatment of patients with Lutathera. There is also a bathroom attached to
18 this room to the left of this picture, which is not shown. But I just wanted to
19 show an example of this.

20 And the next slide, which I think is my acronyms.

21 And thank you again for your time.

22 CHAIRMAN HANSON: Thank you, Dr. Jadvar. And next
23 we'll hear from Mr. Josh Mailman, the ACMUI patients' rights advocate. Mr.
24 Mailman.

25 MR. MAILMAN: The thing is remembering to take
26 yourself off mute before you talk. Thank you very much, Commissioner

1 Hanson. And thank you to the fellow Commissioners as well for inviting me
2 to give this talk on patient advocacy and how we bring about change for
3 patients.

4 I'll go to the next slide please. So briefly, the agenda is
5 perspective on the role of patient advocates and patient advocates here on
6 the ACMUI. And before I do that, I also would like to thank the, as a new
7 member of the ACMUI, I want to really thank the, my fellow Committee
8 Members for being so welcoming to me in my role here as a patient
9 advocate on the subcommittees that I'm part of and working to embrace the
10 patient view in the subcommittee roles. And also to the NRC Staff for their
11 onboarding. And also, helping me through this early phases of my term on
12 the ACMUI.

13 So, next slide please. So in most of these stories, when
14 you talk about patient advocates, in reality we are a patient first for many of
15 us who are advocates, we are patients. And I'm a patient who has been,
16 has several dozen at this point, nuclear medicine diagnostic scans. And
17 some, as well as (inaudible) therapies.

18 And I have benefitted by these things. And while I was in
19 a good phase of my health early on after my diagnosis in 2009, I did the
20 thing of asking my oncologist how can I help. And that's how my start into
21 patient advocacy really started because my oncologist suggested places for
22 me to go and work to help raise awareness, and one thing led to another.
23 And I ended up working with the NCI as part of my background in
24 onboarding as a patient advocate. And I'll talk about that in a second.

25 Next slide. So as I said, how can I help. So, as well as
26 talking to my oncologist, I ended up talking to my, next slide please, I ended

1 up talking to my nuclear medicine physician. And this was before Lutathera
2 or Lu-177 dotatate was approved in the U.S., when I needed therapy. And I
3 ended up in Europe for my first steps of therapies, and imaging, with
4 gallium-68. And I ended up invited to the First World Congress of
5 gallium-68 and receptor radionuclide therapy.

6 And I didn't know exactly what I was thinking, but by the
7 time the third one rolled around in 2015 in Washington, D.C., I had really
8 thought that the emerging field, as Dr. Jadvar had said, was really going to
9 explode.

10 And when I saw this particular slide where all the different
11 gallium-68 compounds that might be used in the future for patients, I realized
12 this was something that I would be working a lot with. I also had the honor
13 of meeting Dr. Henry Vanbrocklin from the UCSF, who invited me to be part
14 of the advocacy at the SNMMI.

15 The next slide please. But I think one of the challenges of
16 being a patient advocate is, well, what exactly is a patient advocate.
17 Depending on who you talk to and where you are, patient advocacy can be
18 described in, just so many ways. And this is one definition of health care
19 concerns with advocacy for patients, survivors and caregivers.

20 Next slide please. That really is one phrase but many
21 hats. We can be part of raising awareness, we can be part of doing patient
22 rights. We can work for institutions that, in the medical care provisioning,
23 help institutes where we can help give a voice to a patient during their
24 patient care.

25 Next slide please. And these are the typical advocate
26 activities. We have patient rights, as we're talking about here in many

1 different forms. Both rights in the hospital when we're under care, matters
2 of privacy, informed consent and patient representation, awareness building
3 and support of education survivors and their caregivers.

4 Next slide. And we do help bring voice to the patients.
5 But what I really want to like go is to the next slide as well.

6 I like to look at this, because I think we get caught up in,
7 with patient advocates as just being, raising awareness or giving support in
8 fund-raising. But I take this from a friend of mine who runs an organization
9 called, Patient Advocates and Research.

10 And really, advocacy is a jigsaw puzzle. And it covers,
11 and not all advocates cover every aspect of this jigsaw puzzle. And some
12 of us do our, bring support and awareness, some of us bring fund-raising.
13 Some of us cover all the pieces.

14 And what I'd like to, next slide please, I think research and
15 policy advocacy is different than awareness advocacy and fund-raising.
16 And I was lucky to be onboarded at the NCI when I started my advocacy for
17 doing more scientific work.

18 They have an onboarding that allows you to learn a bit
19 about the language of research and the language of working through
20 conflicts of interest. And one of the books that really help me understand
21 my role as an advocate past the awareness point of being an advocate is,
22 When Science Offers Salvation, by Rebecca Dresser, which is a fantastic
23 book for advocates to understand their role in acting and bringing forth better
24 science to patients.

25 Next slide please. So as I said, there's many multi-facets.
26 When I started writing this particular presentation, I had just come off a

1 week of one of the things that I do, which is being teaching staff at the Vail
2 workshop which is a workshop to teach young investigators about how to
3 manage or run a clinical trial.

4 And we can make impacts in the science field, in
5 guidelines and trial designs, in the regulatory world. But I have 18 students
6 and I actually asked them afterwards how did they think differently about
7 patient advocacy once they've worked with one. And it was really
8 interesting to see how they change their view on the value of the patient
9 advocate. And I'll leave their words up there just because that describes it.

10 I'll go to the next slide. So as Dr. Metter talked earlier in
11 the presentation about where, how we get education as committee
12 members, also, how I get my education as a patient advocate and where I
13 learn from, and I wanted to go where I spend my time and where I learn
14 information for, to give you a little bit of background of the perspective I
15 bring, because we all bring different perspectives.

16 Next slide please. So I am a president of one of the
17 largest neuroendocrine tumor communities, support communities in the U.S.,
18 based here in northern California. We annually run conferences of about
19 400 people talking about neuroendocrine tumors and the emerging therapies
20 that can help us and which has been dominated recently by nuclear
21 medicine as well.

22 I'm the inaugural chair of the Society of Nuclear medicines
23 patient advocacy group. I also do the awareness with, and raise funds for
24 research with the neuroendocrine tumor research foundation.

25 Next slide please. On the research side, I do sit on the GI
26 steering committee for the National Cancer Institute. I was also recently

1 appointed to the scientific research community, or ASCO. And as I
2 mentioned, I'm the member of the faculty for ASCO-AACR.

3 All these things help me learn more about my craft of being
4 a patient advocate, and to bring the voice of the patient. But most
5 importantly, next slide please, not most importantly, but regulatory, I am, on
6 top of sitting here with you, the advisory committee for the medical use of
7 isotope, I'm also an FDA patient rep.

8 Next slide please. But mostly I listen to fellow patients,
9 their journeys and their challenges when I talk to patients. And daily, I work
10 on forums that help, where I can listen to patients, understand their
11 concerns, get some feedback on things that are going on in the various other
12 work that I do.

13 And with that, I want to thank you. Next slide please.
14 This is my group. We usually use a running person for a running festival,
15 but as we all are doing now, was virtual this year and so we took virtual
16 shots and put them altogether.

17 And next slide for my acronyms. And I will turn this back
18 over to Dr. Metter for the close for the, for our committee.

19 DR. METTER: And, Chairman Hanson, that is our
20 presentation from the ACMUI, and I turn it back to you. Thank you.

21 CHAIRMAN HANSON: Thank you, Dr. Metter. And
22 thank you, Mr. Mailman, for your presentation. And thanks to all the
23 members of the ACMUI who are here this morning. Thank you for your
24 service to the Agency, and certainly to the public.

25 We'll start with questions this morning with Commissioner
26 Baran.

1 COMMISSIONER BARAN: Well, thank you all for your
2 presentations and for your work on the Committee. I'd like to continue the
3 conversation about whether extravasation should be reported as medical
4 events.

5 As you all know, in 1980, the Commission established a
6 policy that extravasation should not be considered in its administrations.
7 The NRC staff is currently evaluating a range of options for making a
8 change.

9 In its July 2021 report, ACMUI subcommittee on
10 extravasations stated that it supports the NRC staff's draft option to make
11 extravasations that require medical attention, reportable medical events.

12 As I understand it, the idea is that a dose assessment
13 wouldn't be required; instead, these events would be reportable if there was
14 skin damage near the administration site that requires medical care. So this
15 was be a qualitative rather than a dose-based approach.

16 Could someone walk us through the Committee's views on
17 the pros and cons of this kind of qualitative approach?

18 DR. METTER: Yes, Commissioner, this is Darlene
19 Metter. And thank you for the question.

20 And at this point I believe I would like to go ahead and
21 have this topic addressed by the subcommittee, who has also extensively
22 evaluated this on extravasation. I would like to call on the Extravasation
23 Subcommittee Chair, Melissa Martin, and members of her subcommittee, to
24 respond.

25 MS. MARTIN: Thank you, very much, Commissioner
26 Hanson, for the opportunity to present to you guys today.

1 We spent a lot of time, and I want to make a couple of
2 points, and then I'm going to have Dr. Dilsizian give the medical view from
3 this. I am the physicist on this committee.

4 I think one of the questions that has come up many times
5 is the dose question. We keep talking about, the dose options. Realize, I
6 want you guys to realize that the medical physics community is working on
7 developing the dose methodology.

8 We had a presentation earlier this week from one of the
9 leading researchers from Johns Hopkins on methodologies for dose. We
10 are trying to put a summer school together for the summer of 2023 on how to
11 do these dose calculations.

12 That gives you a clue that dose calculations for all of the
13 isotopes that are available is not decided, it is not optimized. And I think we
14 have to be very aware of that fact that just because you can see a number,
15 does not mean that number is accurate.

16 So we took it as a subcommittee that we would put the
17 evaluation of extravasations in the hands of the experienced medical staff
18 that would know how to evaluate these evaluations. And again, we really
19 emphasize that these extravasations need to be evaluated by experienced
20 and qualified medical physicians. Not just any physician but one that has
21 experience on evaluating these. Because we don't feel like the ability to
22 come up with a magic number right now, is available.

23 COMMISSIONER BARAN: So it sounds like --

24 MS. MARTIN: And --

25 COMMISSIONER BARAN: Sorry, I didn't want to
26 interrupt.

1 MS. MARTIN: No, go ahead.

2 COMMISSIONER BARAN: So it sounds like, one of the
3 driving factors for a more qualitative approach are the practical challenges of
4 determining whether a particular dose threshold is crossed, is that right?

5 MS. MARTIN: That would be correct, sir.

6 COMMISSIONER BARAN: Okay. And then were there
7 others you wanted to hand off the question to on just kind of a general
8 discussion of pros and cons of the qualitative approach?

9 MS. MARTIN: I was going to ask Dr. Dilsizian, who is an
10 expert physician that was part of our committee, to give the medical
11 physician's position on this and why we came up with this approach.

12 DR. DILSIZIAN: Thank you very much for the opportunity
13 to speak with you. I just want to give you my background. As you all know,
14 I'm a cardiologist, as well as a fully trained nuclear medicine physician and
15 board certified in telemedicine, cardiology and nuclear medicine. I spent 13
16 years of my life at the NIH where I did a lot of the exercise treadmill studies
17 that required IV injections of radiotracers. I was the Director for about
18 seven years of that period. And currently the chief of nuclear medicine at
19 the University of Maryland School of Medicine. And I've been in this
20 position for 20 years.

21 So, I've had about 30 years of clinical experience in this
22 area. And the question is, what is the problem that we are trying to solve.
23 I guess the first problem is that we want to define the incidents and
24 prevalence of extravasation, and second, does its merit change in
25 regulation.

26 And so, extravasation was excluded, as you know, from

1 the medical event reporting. And the question is, why not just have it back
2 in to determine what is the current prevalence of this problem.

3 So, as a cardiologist, if I'm trying to address a problem, we
4 have solid endpoints that are indisputable clinical endpoints. For example,
5 the sudden cardiac death is an endpoint. A heart attack or heart failure is
6 solid endpoints. And so, first we define what are the clinical endpoints and
7 then look for root causes and technical issues that can address and assess
8 those problems to prevent them.

9 So when it comes to extravasation, we are looking for
10 tissue injury that is a patient harm caused by the extravasation. Which as
11 we all know, is exceedingly rare. And second, we are also trying to say, if
12 the extravasation occurred, did it cause poor quality images that required
13 that the patient come another day and be injected with a second dose to
14 repeat the study.

15 So for me, those are clinical endpoints. (Inaudible) tissue
16 injury or repeating the study because the extravasation did not allow us to
17 have high quality images. And so, my recommendation therefore would be
18 to gather the information, as we did as a subcommittee, and the entire
19 ACMUI agreed, first to define the problem. And we would do that by option
20 4, trying to see how often and how common is the extravasation occurring
21 and causing tissue injury. And I also would recommend, which is not part of
22 our recommendation, to actually gather information, of repeating the study
23 another day, to see how many times the extravasation has resulted in poor
24 quality images requiring the second dose.

25 Once we get that data, then obviously we'd come up with
26 some objective indices, which would be some dose-based approach to

1 assess and solve the problem. Thank you very much for your attention.

2 COMMISSIONER BARAN: Well, thank you, that's very
3 interesting. When you talk about tissue damage, is that exclusively skin
4 damage or are there other types of injuries or conditions we would be
5 thinking about that might require medical attention in what sounds like the
6 rare case of an extravasation where that's necessary?

7 DR. DILSIZIAN: Well, again, the most common obvious
8 cause is, if the dose is extravasated at the site of the injection. As we all
9 know, we get leakage of blood when we get our blood drawn by a
10 phlebotomist. It's more common than uncommon. And a lot times that's
11 part of the practice of medicine.

12 And so, when we talk about extravasation publications, we
13 need to keep in mind that a lot of these publications have commented about
14 any leakage at the site, which is something that we all get from the
15 phlebotomist as extravasation. Obviously that would not be a correct way of
16 approaching this. The correct way of approaching this would be, if the
17 extravasation itself caused local tissue inflammation or injury that would
18 require medical attention, which would be the option 4.

19 And so, again, once we start gathering this data we can
20 define further how extensive is this damage or how rapidly it recovered.
21 And then we can attack the problem clinically.

22 COMMISSIONER BARAN: Okay. And if there is tissue
23 damage, if we're kind of thinking about the category of tissue damage from
24 extravasation radiation that would require medical attention, is this
25 something that's basically, can be detected with the naked eye?

26 Is it something that's seen right away? You would look at

1 it, or the patient would look at it and know, well, this is a case where medical
2 attention is needed or is it less obvious than that?

3 DR. DILSIZIAN: Well, what we are doing, and what the
4 SNMMI has recommended, is to encourage patients to report back any sight
5 of redness or inflammation at the site of the injection, back to the authorized
6 user.

7 And so we obviously would be looking at other causes of
8 redness, which would be allergy to latex, for example, or the band-aid that
9 was used. So, as professionals we should be able to differentiate what is
10 the actual radiation induced tissue injury from that of allergy from latex.

11 So once we gather that data and report it back to the NRC,
12 I think we'll have a very good idea of the extent and the prevalence of this
13 condition. And then subsequently, obviously we can come up with these
14 indices that can define what is a threshold and how we can prevent it.

15 COMMISSIONER BARAN: Well, thank you for this
16 discussion. Thank you all for your perspectives on this. It gives us a lot to
17 think about as we review the upcoming staff paper down the road. Thanks
18 so much.

19 DR. DILSIZIAN: Sure. Thank you.

20 CHAIRMAN HANSON: Thank you, Commissioner Baran.
21 Commissioner Wright.

22 COMMISSIONER WRIGHT: Thank you very much and
23 good morning.

24 I really appreciate the presentations, as well as the
25 important work that you, all of you, do on the committee. And I think I'll just
26 echo what I said last year, giving you the same thanks that I gave you last

1 year which is, really thank you for the work that you do outside of the
2 committee as medical professionals.

3 There is really no way to overstate just the importance of,
4 and the sacrifices that you make and have made, especially during COVID in
5 the last year and a half. So you try to help keep us safe and as healthy as
6 possible. And it does come at the expense of your time and energy, so
7 thank you.

8 And to Josh Mailman, first I want to, I don't have a question
9 for you, but I do want to welcome you and say that as a cancer survivor
10 myself who has benefitted from radiopharmaceuticals, I think that your role is
11 very important and I'm pleased to have you as part of the committee. I think
12 I share a little bit of your history in a way that mine was, I started mine in, my
13 journey, in 2008. And my daughter, who was 27 at the time, started her
14 journey in 2009, along with, about the time you did.

15 So, I've been an advocate, not a patient advocate, but I've
16 been an advocate, especially in the area of education and awareness. And
17 even today I will talk to patients, talk to, as they face surgery and go through
18 surgery, have come out of surgery or starting treatment, just to give them
19 that hope. So thank you for what you do because what, you have a critical
20 role to play and I wanted you to know that personally, that it strikes a chord
21 with me.

22 And Commissioner Baran has already started off with
23 some good questions, and I will get into some of that in a minute, too. But,
24 Dr. Ennis, I think I'm going to start with you. I appreciate the staff and
25 ACMUI looking, re-looking, at the AO criteria. I really do view this effort as a
26 better, as an opportunity to better align with our agency and the statutory

1 requirements to report.

2 We've gone through what that really means and how
3 important it is to Congress and to the public, especially from the area of
4 significant events. I think sometimes it might get confusing, and I think you
5 alluded to that, when there is little or no adverse health effects.

6 So, I guess the question I want to get to, can you expand a
7 little bit on how the NRC and Agreement States will determine that an event
8 resulted in patient harm? I mean, who is going to perform that review?
9 And if it was approved, how would we ensure a consistent application of the
10 patient harm criteria?

11 DR. ENNIS: All right. Yes, that's obviously an insightful
12 question. And thank you for it. And there is no doubt this type of thing is
13 inherently going to be somewhat subjective. That doesn't mean it's not
14 better, but it does mean it might be a little less objective.

15 I do think it's likely, obviously this is really up to NRC, but I
16 would imagine how likely that the staff will feel the need to engage with a
17 medical consultant to help them assess these events and determine whether
18 indeed there is this threshold of actual medical harm from the event.

19 It's a relatively small number, so from a very practical and
20 financial perspective, I don't think that would be a barrier. But again, it's
21 more of an internal NRC question, I think, about how to implement it.
22 Certainly it would be much more concerning to me from a practical point of
23 view if we were talking about hundreds and hundreds of events that needed
24 to be reviewed every year.

25 But the whole point of the AO is a subjective thing as well.
26 It's what rises to the level of meeting Congress and public's awareness. So

1 that inherently is subjective. And while it would be wonderful if it was
2 something very nice and objective. I mean, we're all scientist, doctors,
3 physicists, people, we're very quantitative people. And we all like those
4 solutions and they're always a lot easier when we can add them. But
5 sometimes it's quantitative and objective are less good, and in this situation I
6 think that that's the case.

7 COMMISSIONER WRIGHT: Thank you. So, I'm going to
8 come back to Dr. Metter. And you had the conversation with Commissioner
9 Baran a little bit. I think he talked a little bit about option 4 and what that
10 was about. And did I understand that the committee is looking at how to
11 maybe define medical attention or radiation injuries? Am I correct to
12 understand that, or if not, what do you understand those terms to mean?

13 DR. METTER: Well, thank you, Commissioner Wright. I
14 would like to go ahead and, again, turn it back to the committee, the
15 subcommittee that reviewed that, to Melissa Martin, regarding their
16 perspectives on medical attention.

17 COMMISSIONER WRIGHT: Sure. You're on mute.

18 MS. MARTIN: Excuse me. We did look, spend a
19 significant amount of time trying to evaluate this and set some criteria. And
20 again, what we felt most comfortable with at this point was the decision to
21 have an experienced physician evaluate whether there would be potentially
22 medical harm from these, if an extravasation occurred.

23 One thing that was very difficult to assess is the idea that
24 there is different definitions of extravasation. And the criteria to define what
25 is called significant extravasation is not consistent.

26 One of the recommendations was that the patient by

1 imaged, both at the injection site and at the target. So in other words, if you
2 were trying to study the kidneys you would be doing an imaging study of the
3 arm where the patient was injected, as well as the kidney. So the patient
4 would have two views every study.

5 That would also, and then the idea was to define an
6 extravasation. If you picked up any isotope at the injection site, and as was
7 alluded to before, it is not uncommon to have, when you have your blood
8 drawn, to have a slight extravasation.

9 We certainly are, and the blood leaking out. That would
10 show up on an image as a positive extravasation if you do that for every
11 isotope that was injected.

12 The other problem is, there are many isotopes that are
13 injected that are not visible using imaging techniques. So we have over 45
14 different pharmaceuticals that are injected. We do not have imaging
15 techniques for all 45 isotopes.

16 So to define what is a, in a quantitative way, is a major
17 challenge at this point that we're not ready to determine, we aren't capable of
18 determining that. So that's when we went with the medical evaluation by
19 the experienced physician. I don't know if, Dr. Dilsizian, do you have
20 anything else to add?

21 DR. DILSIZIAN: No. Thanks so much, no, not really.
22 Again, I think that the, as a Commission scientist, the thought would be first
23 to define a clinical endpoints, what is the problem. Define the prevalence of
24 the occurrence of tissue injury and repeating the study, requiring the second
25 dose. And then subsequently find techniques to assess it.

26 I think that at this point we don't have the data, the

1 prevalence. And I can tell you that in my 30 years of experience, both as a
2 cardiologist and nuclear medicine physician, while I've had patients come
3 back for repeat studies because of the poor quality images from
4 extravasation, I have not had a patient being harmed from the extravasation
5 at the site of the injection.

6 COMMISSIONER WRIGHT: Okay, thank you. Mr.
7 Chairman, I have one more question I'm going to try to get in here in the time
8 I have left --

9 CHAIRMAN HANSON: Please go ahead.

10 COMMISSIONER WRIGHT: -- if that's okay?

11 CHAIRMAN HANSON: Yes.

12 COMMISSIONER WRIGHT: And I'm going to stay again
13 with the committee. I guess they'll have to answer this one here the same, I
14 think it's Ms. Martin, is that right?

15 So, in the petition, and some of the comments, public
16 comments on the commission, that it's been suggested that additional
17 actions beyond event reporting should be taken to address extravasations.
18 Such as developing vascular access protocols or treatment protocols for
19 extravasations and worksheets, as I think you mentioned earlier, to calculate
20 dose.

21 In your view, are these additional actions within the NRC's
22 regulatory authority or do they encroach on the practice of medicine? And I
23 guess if I could follow-up very quickly, are these actions being performed
24 now, how difficult would they be to implement? And then finally, has the
25 staff in ACMUI considered methods of communicating best practices?

26 If you can expand a little bit on that in treating

1 extravasations of radio, of preventing the extravasations of
2 radiopharmaceuticals?

3 MS. MARTIN: I will give you a little bit of history. And
4 again, I've also been involved for well over 30 years with these procedures
5 now.

6 At this point I think it's a very comfortable saying, if an
7 extravasation has occurred, then calculations would probably be done, and
8 certainly could be done, to assess as best as possible the actual dose
9 delivered. The actual occurrence of extravasations is so small --

10 COMMISSIONER WRIGHT: Right.

11 MS. MARTIN: -- that it's rarely done. But the
12 methodology is there. That if a significant extravasation occurred, the dose
13 could be calculated.

14 To turn that around and say, that should be done for every
15 injection is a real waste of time, to a certain extent. Because if the
16 extravasation hasn't occurred, the procedure moves forward. Again, you're
17 just asking for a lot of calculations to be done that really would not add to the
18 study or add information to the patient.

19 COMMISSIONER WRIGHT: Thank you. Thank you, Mr.
20 Chairman.

21 CHAIRMAN HANSON: Thank you, Commissioner Wright.
22 Dr. Ennis, I think I'll start with you. Thank you again for your presentation.

23 I had a couple of questions I think for you about medical
24 events and medical event reporting. Your subcommittee noted that, noted
25 timeout as a way to mitigate some medical events.

26 And at the ACMUI's recommendation, the NRC put out an

1 information notice to inform licensees about the subcommittee's findings.

2 And I guess I have kind of a two-part question for you.

3 So, while a timeout procedure should be a standard
4 practice that helps prevent medical events, has, or will your subcommittee
5 analyze further kind of the root causes of medical events?

6 And then I guess the second part of that question is, is
7 there a nexus between some medical events and radiation safety
8 competence considering the training experience requirements for authorized
9 user physicians that are in place, and given that those requirements are in
10 place to ensure physicians are able to independently fulfill radiation safety
11 related duties in which they're authorized? So that's kind of a two-parter.
12 Could you kind of comment on the timeout and the confidence of radiation
13 safety professionals?

14 DR. ENNIS: Sure. Sure, absolutely. So I'll try tackling
15 them in order. So in terms of the first question, the subcommittee is a
16 standing subcommittee and will continue to evaluate events. We are limited
17 by the availability of whatever information is in NMED.

18 We don't have the authority or the ability to interview
19 people at the site for particular events, even for selective incidents, there is
20 no mechanism for that. So really don't have the ability to do a formal root
21 cause analysis of our own, but rely on information that has been collected by
22 the states, or by the NRC, and reported in the NMED system.

23 As I alluded to, we actually have a subcommittee that has
24 made a recommendation about strengthening that process and making that
25 information more robust to allow us to do a better job. If we wanted to
26 entertain the possibility of having the ability to do root causes analyses, that

1 would be a whole different subject.

2 But short of that, we are continuing, and will continue, to
3 look for trends, look for issues that we think are important. There is some
4 limitation of the data that we have and therefore there is some subjectivity in
5 interpreting it.

6 As was alluded to, in attributing exactly whether alleged or
7 a timeout would affect it, whether there is an issue of intention or
8 inexperience, these are interpretations as best we can with our expertise on
9 what's happening to help inform the future. But is literally the only kind of
10 information that we have available.

11 But we do think we can make some reasonable
12 assessments of these things. I don't think these are completely random
13 thoughts, but are supported by the information that we have in enough
14 cases. And see enough transient, we think the recommendations are
15 sensible and worthwhile.

16 In terms of the issue about whether there is a competency
17 issue about radiation safety issues per say, it's an interesting one. And
18 again, it would be very difficult to really assess. I mean, we have not, I
19 guess I would say a few things. First, I'm fairly familiar with the training
20 experience requirements to a common authorized user, and I feel like those
21 requirements are very good, having gone through them personally. And
22 colleagues in the field, I do feel like if you come through the process and
23 achieve the level of AU, as it is currently written, you are knowledgeable in
24 radiation safety.

25 Then the question is, do you maintain that throughout your
26 career. And I think that's where the infrequency type of issues may come

1 into play.

2 Is infrequency another way of saying a lack of knowledge,
3 current knowledge of radiation safety? Perhaps that's what it is. I think
4 that's complex. Is it related to a procedure itself, is it related to radiation
5 safety aspect, I don't think I can say. And I sense in our view that we can
6 really dissect that difference.

7 But I would leave open the possibility that in some of the
8 ones that we are calling infrequent user inattention that there could be a
9 layer of a radiation safety need for tutorial catching up type of thing. But I
10 can't say with any confidence that that's a problem that we really should
11 specifically address.

12 CHAIRMAN HANSON: Okay, thank you. I think you
13 raise a number of interesting issues there about kind of ongoing training and
14 experience.

15 I was really interested in your discussion about Y90
16 microspheres. You know, they represent a significant portion, at least it
17 appeared to me, of medical event reportings. And it seems like they have
18 gone up, or at least the absolute number has gone up over the last few
19 years, but I was wondering if you could kind of provide some context for that.

20 I wasn't sure if Y90 microsphere administrations had also
21 gone up so that maybe there was an increase in both the numerator or the
22 denominator there. And I just was kind of wondering also, given that the
23 absolute number does go up, if you have some insights about what might be
24 attributed in terms of the causes for that increase?

25 DR. ENNIS: So, with respect, I don't think the numbers
26 over the last few years have gone up. I don't know if we have the slides

1 available. But I believe the numbers are pretty stable. They are larger
2 than any other of our groups. But I don't see an upward trend beyond
3 random fluctuations. Oh, great, thank you.

4 CHAIRMAN HANSON: Ah.

5 DR. ENNIS: So here, 15, 15, 14, 14, so the
6 TheraSpheres have been stable over four years. The next slide would be
7 SirSpheres.

8 CHAIRMAN HANSON: I may have been thinking, like, if
9 you go back to kind of 2013. I think if you go back --

10 DR. ENNIS: Ah, yes.

11 CHAIRMAN HANSON: -- a little farther than the slide has,
12 there has been an increase there.

13 DR. ENNIS: Yes. No, I think that that going back further,
14 I think that that's true. And again, I think a subcommittee who evaluates this
15 could address it better. My sense is, yes, there has been a growth in their
16 use over the decades, if you will. And that that may be partly responsible
17 for it.

18 But I do think as proposed, the subcommittee to get some
19 numbers about how often this has been used, what's the true denominator,
20 what's the numerator, over time would be a very informative part of that
21 analysis.

22 CHAIRMAN HANSON: Yes. Okay. Thank you. I had
23 a question about abnormal occurrences I think primarily for you, Dr. Ennis,
24 but really anybody who wanted to jump in.

25 I'm interested in this idea of kind of a medical
26 consequence, a shift to focus on medical consequences for abnormal

1 events. And I guess, do you see that as a paradigm shift for how the NRC
2 would regard events of public health and safety significance reported to
3 Congress?

4 And I guess, I'll be more explicit. Do you see it as a
5 departure from kind of the linear no-threshold based regulatory model that
6 the NRC adheres to?

7 DR. ENNIS: So, we were not proposing to completely
8 eliminate those, but only to modify the definition to add the high dose
9 component. And the second component now, not just be essentially
10 medical events.

11 So, right, obtains current dose thresholds. But instead of
12 the second component being more or less the definition of a medical event,
13 instead raise the bar and have that second component be, not just that there
14 was a medical event, but that it was a medical event of significant
15 consequence and that because, again, it's reported to Congress, things that
16 are important for public health.

17 So a better, we thought it better, hardly perfect for sure,
18 but a better way to kind of really give Congress, and the public, okay, these
19 are things to be aware of that happen across the country. We think that that
20 combination would do a much better job.

21 CHAIRMAN HANSON: Thank you. Yes, I really
22 appreciate that clarification. As we wrap-up today, Mr. Mailman, I kind of
23 just wanted to give you the last word. And particularly as the patient rights
24 advocate. I know you're new to the committee, but you've been in this
25 space for a long time. And of course, you've been, I'm sure, exposed to the
26 activities of the NRC.

1 I just wanted to ask you if there are additional areas where
2 the NRC should be focusing activities or tasks that you think we should be
3 undertaking or expanding upon, or if you think there are areas where maybe
4 we're focusing and you don't think that those are necessarily productive?

5 You're on mute, I think, Mr. Mailman.

6 MR. MAILMAN: The unmute thing. I will unmute myself.
7 Thank you for the opportunity to address the Commission as well.

8 So, when I talk to patients about nuclear medicine, the
9 things, and especially dovetailing off of Dr. Jadvar's conversation on
10 emerging theranostic possibilities, patients are concerned that they're, the
11 people that are treating them are knowledgeable in what they're doing and
12 that they have the training to actually administer these new
13 radiopharmaceuticals that are coming out and that they have the expertise to
14 do that.

15 We do talk, even when Facebook is down for 16 hours, we
16 do seem to still have conversations with each other. And we see things that
17 they're concerned about. They want to make sure people have adequate
18 training, whether they're administering the drug, reading the images that
19 come from it.

20 One thing that we didn't talk about here, but the release
21 criteria. I spend tons of time probably second to where patients want to
22 make sure their physicians are trained, or those who care for them are
23 trained. I spend a lot of time going over release criteria and understanding
24 that in laymen's terms so that people who, I feel for when patients are
25 separated from their families are doing things that aren't necessarily required
26 for the isotope that they have administered to them. And so, that obviously

1 dovetails into patient education where it, the more that we can educate
2 patients about the uses and benefits, and even some of the challenges that,
3 knowing what to report and when to report it. These things are important to
4 patients.

5 I was looking, there is a Facebook group that I monitor that
6 has 2,000 members that have been going since 2017. So several thousand
7 posts. And really, the posts that are most dominant are, is this treatment
8 right for me, what are the next steps of developments that are coming down
9 the pike, or what might be available, and how do I tolerate this treatment and
10 live with my family post-therapy.

11 So these are the types of things the patients are
12 concerned about, that really are focused about. And while no patient wants
13 to be having extravasation, and this is not something we all look for, it is not
14 contrary to what you may see in the public comments.

15 It may not be the top of mind thing that patients are
16 concerned about because looking through, just actually while we were on
17 this call I looked over, did a search for it in over 3,000 messages, and there
18 wasn't one that wasn't one that I brought up asking for comments.

19 So, all of these things are important. But making sure that
20 our physicians understand what's coming and that they're applying this
21 correctly to us is probably the most important.

22 CHAIRMAN HANSON: Thank you very much, Mr.
23 Mailman. I think that's a good way to wrap-up and keep the patients in
24 mind.

25 Dr. Metter, thank you for your leadership on the ACMUI.
26 Thank you to all the members who are on today. We've got a set of

1 complex, but not intractable issues in front of us. We appreciate your
2 advice and your thoughtfulness in advising the Commission.

3 And thank you particularly to my colleagues for their
4 comments and questions as well this morning. And with that, we are
5 adjourned.

6 (Whereupon, the above-entitled matter went off the record
7 at 11:33 a.m.)

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